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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/608,183	09/01/2020	10758652	130670-08002	7286

86738 7590 08/12/2020

MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 539 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Michael Ragusa, Hingham, MA;
Haemonetics Corporation, Braintree, MA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0001

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~1611/C80~~ 130670-08002
	Application Number	15/608,183
Title of Invention	System and Method for Collecting Plasma	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Michael		Ragusa	

Residence Information (Select One) ● US Residency ○ Non US Residency ○ Active US Military Service

City	Hingham	State/Province	US	Country of Residence	MA

Mailing Address of Inventor:

Address 1	4 Willow Circle
Address 2	

City	Hingham	State/Province	MA
Postal Code	02043	Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	~~32401~~ 86738		
Email Address	~~usptomail@sunsteinlaw.com~~ docket@mccarter.com	Add Email	Remove Email

Application Information:

Title of the Invention	System and Method for Collecting Plasma		
Attorney Docket Number	~~1611/C80~~ 130670-08002	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	4	Suggested Figure for Publication (if any)	

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0002

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~1611/C80~~ 130670-08002
	Application Number	15/608,183
Title of Invention	System and Method for Collecting Plasma	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	~~32494~~ 86738		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0003

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~1611/C80~~ 130670-08002
	Application Number	15/608,183
Title of Invention	System and Method for Collecting Plasma	

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[j] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0004

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~1611/C80~~ 130670-08002
	Application Number	15/608,183
Title of Invention	System and Method for Collecting Plasma	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0005

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~1611/C80~~ 130670-08002
	Application Number	15/608,183
Title of Invention	System and Method for Collecting Plasma	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name: Haemonetics Corporation

Mailing Address Information For Applicant:

Address 1	~~400 Wood Road~~ 125 Summer Street		
Address 2			
City	~~Braintree~~ Boston	**State/Province**	MA
Country	US	Postal Code	~~02184~~ 02110
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0006

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~1611/080~~ 130670-08002
	Application Number	15/608,183

Title of Invention	System and Method for Collecting Plasma

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Jonathan C. Lovely, #60,821/			Date (YYYY-MM-DD)	2020-08-11
First Name	Jonathan C.	Last Name	Lovely	Registration Number	60,821

Additional Signature may be generated within this form by selecting the Add button. Add

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0007

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~1611/C80~~
	Application Number	130670-08002
Title of Invention	System and Method for Collecting Plasma	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0008

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0009

Electronic Acknowledgement Receipt

EFS ID:	40249126
Application Number:	15608183
International Application Number:	
Confirmation Number:	7286
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Customer Number:	86738
Filer:	Jonathan Lovely
Filer Authorized By:	
Attorney Docket Number:	130670-08002
Receipt Date:	11-AUG-2020
Filing Date:	30-MAY-2017
Time Stamp:	13:29:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	Request_to_Update_the_Address_of_the_Applicant_and_Request_for_Corrected_Filing_Receipt_.pdf	22456 9af6eb8e651c53970fb04dfe7ed5ea42f88e45db	no	2

Warnings:

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0010

Information:					
2	Application Data Sheet	Corrected_ADS_.PDF	842917 bbccc2d1537afd5dfc207bef5db1788c0c9bc089	no	8
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Miscellaneous Incoming Letter	Marked_Filing_Receipt_.PDF	354253 de831121728f950d548206e6998b25e821d0bb48	no	3
Warnings:					
Information:					
			Total Files Size (in bytes):	1219626	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: 130670-08002
(PATENT)

In re Utility Application of:
Haemonetics Corporation

Application No.: 15/608,183 | Confirmation No.: 7286

Filed: May 30, 2017 | Art Unit: 3799

For: SYSTEM AND METHOD FOR COLLECTING PLASMA | Examiner: Deak, Leslie R.

REQUEST TO UPDATE THE ADDRESS OF THE APPLICANT AND REQUEST FOR CORRECTED FILING RECEIPT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The Applicant hereby requests that the Applicant's address be updated and made of record and a corrected Filing Receipt be issued in the above-identified U.S. Utility Patent Application. The Application Data Sheet filed on May 30, 2017 and the Official Filing Receipt dated June 8, 2017, a copy of which is attached hereto, has an error in the Applicant(s) section.

Please correct the **address of the Applicant, Haemonetics Corporation** to read: **125 Summer Street, Boston, MA 02110** instead of 400 Wood Road, Braintree, MA 02184.

Applicant additionally requests that all pertinent U.S. Patent and Trademark Office records relating to the subject application be changed to reflect this correction.

Concurrent with the filing of this request, the following documents are submitted herewith:

- A Corrected Application Data Sheet (CADS) to correct the address of the Applicant as shown by underlining the correct address and removing the incorrect address as shown by a strikethrough; and

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0012

- A marked copy of the Official Filing Receipt to correct the city of the Applicant as shown by underlining the correct city and removing the incorrect city as shown by a strikethrough.

The Applicant believes no fee is due with this request. However, if a fee is due, please charge our Deposit Account No. 50-4876, under Order No. 130670-08002 from which the undersigned is authorized to draw.

Dated: August 11, 2010

Respectfully submitted,

Electronic signature: /Jonathan C. Lovely, Reg. No. 60,821/
Jonathan C. Lovely
Registration No.: 60,821
MCCARTER & ENGLISH, LLP
265 Franklin Street
Boston, Massachusetts 02110
(617) 449-6500
(617) 607-9200 (Fax)
Attorney/Agent For Applicant

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0013

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/608,183	05/30/2017	3761	1740	~~1611/C80~~ 130670-08002	20	2

CONFIRMATION NO. 7286

FILING RECEIPT

~~2101~~
~~Sunstein Kann Murphy & Timbers LLP~~
~~125 SUMMER STREET~~
~~BOSTON, MA 02110-1618~~

86738
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

OC000000091875350

Date Mailed: 06/08/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Michael Ragusa, Hingham, MA;

Applicant(s)

Haemonetics Corporation, ~~Braintree, MA;~~ Boston, MA;

Power of Attorney: The patent practitioners associated with Customer Number ~~02101~~ 86738

Domestic Applications for which benefit is claimed - None.
A proper domestic benefit claim must be provided in an Application Data Sheet in order to constitute a claim for domestic benefit. See 37 CFR 1.76 and 1.78.

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 06/06/2017
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/608,183**

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0014

Projected Publication Date: 12/06/2018

Non-Publication Request: No

Early Publication Request: No

Title

System and Method for Collecting Plasma

Preliminary Class

604

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0015

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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NOT GRANTED

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Petitioner Terumo Exhibit 1021-0016

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/608,183	05/30/2017	Michael Ragusa	130670-08002	7286

86738 7590 07/28/2020
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER	
DEAK, LESLIE R	

ART UNIT	PAPER NUMBER
3799	

NOTIFICATION DATE	DELIVERY MODE
07/28/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@mccarter.com

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0017

Response to Rule 312 Communication	Application No.	Applicant(s)	
	15/608,183	Ragusa, Michael	
	Examiner	Art Unit	AIA (FITF) Status
	LESLIE R DEAK	3799	Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☑ The amendment filed on 15 July 2020 under 37 CFR 1.312 has been considered, and has been:
   a) ☑ entered.
   b) ☐ entered as directed to matters of form not affecting the scope of the invention.
   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
      Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.
   d) ☐ disapproved. See explanation below.
   e) ☐ entered in part. See explanation below.

/LESLIE R DEAK/
Primary Examiner, Art Unit 3799

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0018

Docket No.: 130670-08002
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Haemonetics Corporation

Application No.: 15/608,183 | Confirmation No.: 7286

Filed: May 30, 2017 | Art Unit: 3799

For: SYSTEM AND METHOD FOR COLLECTING PLASMA | Examiner: L. R. Deak

MS Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

OK to enter.

/LRD/
22 July 2020

AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. § 1.312

Prior to issuance of the patent, Applicant respectfully requests entry of this amendment under 37 C.F.R. § 1.312 for the above-captured patent application.

Amendments to the Claims may be found on page 2.

Remarks may be found on page 7.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0019

Doc Code: IFEE PTOL/85B-EFS

Document Description: Issue Fee Payment (PTO-85B)

Issue Fee Transmittal Form

Application Number	Filing Date	First Named Inventor	Atty. Docket No.	Confirmation No.
15608183	30-May-2017	Michael Ragusa	130670-08002	7286

TITLE OF INVENTION :

System and Method for Collecting Plasma

Entity Status	Application Type	Art Unit	Class - Subclass	EXAMINER
Regular Undiscounted	Utility under 35 USC 111(a)	3799	006040	LESLIE DEAK

Issue Fee Due	Publication Due	Total Fee(s) Due	Date Due	Prev. Paid Fee
$1000	$0	$1000	10-Aug-2020	$0

1.Change of Correspondence Address and/or Indication Of Fee Address (37 CFR 1.33 & 1.363)

Current Correspondence Address:	Current Indicated Fee Address :
86738 MCCARTER & ENGLISH, LLP BOSTON 265 Franklin Street Boston MA 02110 UNITED STATES 617-449-6500 docket@mccarter.com	
☐ Change of correspondence address requested, system generated AIA/122-EFS form attached	☐ Fee Address indication requested, system generated SB/47-EFS form attached

2.Entity Status

Change in Entity Status

○ Applicant certifying micro entity status; system generated Micro Entity certification form attached. See 37 CFR 1.29.
Note: Absent a valid certification of micro entity status, issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. If this box is checked, you will be prompted to choose a micro entity status on the gross income basis (37 CFR 1.29(a)) or the institution of higher education basis (37 CFR 1.29(d)), and make the applicable certification online.

○ Applicant asserting small entity status. See 37 CFR 1.27.
Note: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

◉ Applicant changing to regular undiscounted fee status.
Note: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0020

Doc Code: IFEE PTOL/85B-EFS

Document Description: Issue Fee Payment (PTO-85B)

3.The Following Fee(s) Are Submitted:

☒ Issue Fee

☐ I authorize USPTO to apply my previously paid issue fee to the current fees due

☐ Publication Fee

☐ The Director is hereby authorized to apply my previously paid issue fee to the current fee due and to charge deficient fees to Deposit Account Number _____

☐ Advance Order - # of copies _____

☒ If i**n addition to** the payment of the issue fee amount submitted with this form, there are any discrepancies in any amount(s) due, the Director is authorized to charge any deficiency or credit any overpayment, to Deposit Account Number 504876 . The **issue fee must be submitted** with this form. **If payment of the issue fee does not accompany this form, checking this box and providing a deposit account number will NOT be effective to satisfy full payment of the fee(s) due.**

4.Firm and/or Attorney Names To Be Printed

NOTE: If no name is listed, no name will be printed
For printing on the patent front page, list to be displayed as entered

1. McCarter & English LLP
2. Jonathan C. Lovely
3.

5.Assignee Name(s) and Residence Data To Be Printed

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

Name	City	State	Country	Category
Haemonetics Corporation	Boston	MASSACHUSETTS	united states	corporation

6.Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am an attorney or agent registered to practice before the Patent and Trademark Office who has filed and has been granted power of attorney in this application. I also certify that this Fee(s) Transmittal form is being transmitted to the USPTO via EFS-WEB on the date indicated below.

Signature	/Jonathan C. Lovely/	**Date**	07-15-2020
Name	Jonathan Lovely	**Registration Number**	60821

WEB IFEE 1.0

Electronic Patent Application Fee Transmittal

Application Number:	15608183
Filing Date:	30-May-2017
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Filer:	Jonathan Lovely
Attorney Docket Number:	130670-08002

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1000**

Electronic Acknowledgement Receipt	
EFS ID:	40002547
Application Number:	15608183
International Application Number:	
Confirmation Number:	7286
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Customer Number:	86738
Filer:	Jonathan Lovely
Filer Authorized By:	
Attorney Docket Number:	130670-08002
Receipt Date:	15-JUL-2020
Filing Date:	30-MAY-2017
Time Stamp:	15:37:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1000
RAM confirmation Number	E20207EF37551906
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment after Notice of Allowance (Rule 312)	312_Amendment.pdf	35583 4dfe59157e204bfd1029c018da7695aebfc724fc	no	8
Warnings:					
Information:					
2	Issue Fee Payment (PTO-85B)	Web85b.pdf	46243 09d84ac496131b4cbc42ef2f8ba050c751315362	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	31764 cc0f703cf5ec2f577aaaa48e0fefbe6042d4583a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	113590		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: 130670-08002
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Haemonetics Corporation

Application No.: 15/608,183	Confirmation No.: 7286
Filed: May 30, 2017	Art Unit: 3799
For: SYSTEM AND METHOD FOR COLLECTING PLASMA	Examiner: L. R. Deak

MS Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. § 1.312

Prior to issuance of the patent, Applicant respectfully requests entry of this amendment under 37 C.F.R. § 1.312 for the above-captured patent application.

Amendments to the Claims may be found on page 2.

Remarks may be found on page 7.

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Petitioner Terumo Exhibit 1021-0026

AMENDMENTS TO THE CLAIMS

The following **Listing of Claims** will replace all prior versions, and listing, of claims in the application.

Listing of Claims

1. (Previously Presented) A method for collecting plasma comprising:

(a) determining a weight of a donor;

(b) determining a hematocrit of the donor;

(c) inserting a venous-access device into the donor;

(d) withdrawing whole blood from the donor through the venous-access device and a draw line, the draw line connected to a blood component separation device;

(e) introducing anticoagulant into the withdrawn whole blood through an anticoagulant line;

(f) separating the withdrawn whole blood into a plasma component and at least a second blood component using the blood component separation device;

(g) collecting the plasma component from the blood component separation device and into a plasma collection container;

(h) calculating a volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma collection container;

(i) calculating a volume of pure plasma collected within the plasma collection container based, at least in part, on the calculated volume of anticoagulant in the collected plasma component; and

(j) continuing steps (d) through (i) until a target volume of pure plasma is collected within the plasma collection container.

2. (Currently Amended) A method according to claim 1, further comprising:

determining a change in volume within an anticoagulant container, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the change in volume within the anticoagulant container.

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3. (Currently Amended) A method according to claim 1, further comprising:

determining a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the number of rotations of the anticoagulant pump.

4. (Currently Amended) A method according to claim 1, further comprising:

determining a volume of anticoagulant within the blood component separation device, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the volume of anticoagulant within the blood component separation device.

5. (Currently Amended) A method according to claim 1, further comprising:

monitoring a volume of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection container ~~device~~ based, at least in part, on the monitored volume of collected plasma component.

6. (Currently Amended) A method according to claim 1, further comprising:

monitoring a weight of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection container ~~device~~ based, at least in part, on the monitored weight of collected plasma component.

7. (Currently Amended) A method according to claim 1, wherein step (b) includes monitoring a volume of red blood cells collected within the blood component separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood component separation device and a volume of whole blood withdrawn from the donor.

8. (Original) A method according to claim 1, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

9. (Previously Presented) A method according to claim 1, wherein the volume of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into

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Petitioner Terumo Exhibit 1021-0028

the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

10. (Original) A method according to claim 1, further comprising:

returning, after collecting at least a portion of the target volume of pure plasma, the second blood component to the donor through a return line.

11. (Currently Amended) A system for collecting plasma comprising:

a venous-access device for drawing whole blood from a subject and returning blood components to the subject;

a blood component separation device for separating the drawn blood into a plasma component and a second blood component, the blood component separation device having an outlet and being configured to send the plasma component to a plasma container;

a blood draw line fluidly connected to the venous-access device and configured to transport drawn whole blood to the blood component separation device, the flow through the blood draw line being controlled by a blood draw pump;

an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood; and

a controller configured to control the operation of the blood component separation device and the blood draw pump, the controller configured to calculate (1) a volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma ~~collection~~ container, and (2) a volume of pure plasma collected within the plasma container based, at least in part, upon the volume of anticoagulant in the collected plasma component, the controller configured to stop the blood draw pump when a target volume of pure plasma is collected within the plasma container.

12. (Previously Presented) A system according to claim 11, wherein the volume of anticoagulant in the collected plasma component is based, at least in part, on a volume of anticoagulant added to the drawn whole blood and the subject's hematocrit.

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13. (Currently Amended) A system according to claim 11, further comprising:

an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant ~~container~~ source based on the measured weight of the anticoagulant source, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the change in volume within the anticoagulant source.

14. (Currently Amended) A system according to claim 11, wherein the controller is configured to monitor a number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the number of rotations of the anticoagulant pump.

15. (Currently Amended) A system according to claim 11, further comprising:

an optical sensor located on the blood component separation device and configured to monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the volume of anticoagulant within the blood component separation device.

16. (Currently Amended) A system according to claim 11, further comprising:

a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma container ~~collection device~~ based, at least in part, on the monitored volume of collected plasma component.

17. (Currently Amended) A system according to claim 11, further comprising:

a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma container ~~collection device~~ based, at least in part, on the monitored weight of collected plasma component.

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Petitioner Terumo Exhibit 1021-0030

18. (Currently Amended) A system according to claim 11, further comprising:

an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood component separation device, the controller configured to determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood component separation device and a volume of whole blood withdrawn from the ~~donor~~ subject.

19. (Currently Amended) A system according to claim 11, wherein the target volume of pure plasma is based, at least in part, on the weight of the ~~donor~~ subject.

20. (Previously Presented) A system according to claim 11, wherein the volume of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

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Petitioner Terumo Exhibit 1021-0031

REMARKS

Applicant would like to thank the examiner for the Notice of Allowance dated May 8, 2020 and for finding claims 1-20 to be allowable. In the present paper, Applicant requests amendments to claims 2-7, 11 and 13-19 be entered. The amendments to the claims do not include new matter and the claims have not been amended for reasons related to patentability.

Amendments to the Claims

Claims 2-7, 11 and 13-19 have been amended herein for language consistency. In particular, the following amendments have been made:

- Claims 2-4 and 14-15 have been amended such that "collected plasma" now reads "collected plasma component"
- Claim 3 has also been amended to add "to" after "a method according…"
- Claims 5-6 have been amended such that "plasma collection device" now reads "plasma collection container"
- Claim 7 has been amended such that "blood separation device" now reads "blood component separation device"
- Claim 11 has been amended such that "plasma collection container" now reads "plasma container"
- Claim 13 has been amended such that "collected plasma" now reads "collected plasma component" and "anticoagulant container" now reads "anticoagulant source"
- Claims 16 and 17 have been amended such that "plasma collection device" now reads "plasma container".
- Claim 18 has been amended such that "blood separation device" now reads "blood component separation device" and "donor" now reads "subject"

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Petitioner Terumo Exhibit 1021-0032

- Claim 19 has been amended such that "donor" now reads "subject"

Applicant respectfully requests that the Examiner enter the amendments presented herein pursuant to 37 C.F.R. § 1.312. The amendments to the claims merely correct obvious typographical errors and language inconsistency. The amendments do not change the scope of the claims and, therefore, are patentable for at least those reasons given in the Notice of Allowance. Applicant believes that the amended claims do not require additional search or examination. Applicant therefore respectfully requests that the amendments be approved and entered, and the application proceed to issuance.

CONCLUSION

It is believed that the application remains in order for allowance. This amendment is submitted with payment of the issue fee. The director is hereby authorized to charge any additional fees which may be required with respect to this communication or credit any overpayment to deposit account No. 50-4876, under order No. 130670-08002. Applicants also request that the examiner contact applicants' attorney, Jonathan Lovely, if it will assist in processing this application through issuance.

Dated: July 15, 2020

Respectfully submitted,
Electronic signature: /Jonathan C. Lovely, Reg. No. 60,821/
Jonathan C. Lovely
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Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0033

UNITED STATES PATENT AND TRADEMARK OFFICE

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NOTICE OF ALLOWANCE AND FEE(S) DUE

86738 7590 05/08/2020
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER
DEAK, LESLIE R

ART UNIT	PAPER NUMBER
3799	

DATE MAILED: 05/08/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/608,183	05/30/2017	Michael Ragusa	130670-08002	7286

TITLE OF INVENTION: System and Method for Collecting Plasma

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	08/10/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0034

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

86738 7590 05/08/2020
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/608,183	05/30/2017	Michael Ragusa	130670-08002	7286

TITLE OF INVENTION: System and Method for Collecting Plasma

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	08/10/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
DEAK, LESLIE R	3799	604-006040

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0035

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/608,183	05/30/2017	Michael Ragusa	130670-08002	7286

86738 7590 05/08/2020

MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER	
DEAK, LESLIE R	

ART UNIT	PAPER NUMBER
3799	

DATE MAILED: 05/08/2020

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0036

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0037

Notice of Allowability	Application No. 15/608,183	Applicant(s) Ragusa, Michael	
	Examiner LESLIE R DEAK	Art Unit 3799	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to AFCP filing submitted 1 May 2020.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-20 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☑ Other AFCP form.

/LESLIE R DEAK/
Primary Examiner, Art Unit 3799

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0038

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Allowable Subject Matter

2. Claims 1-20 are allowed.

3. The following is an examiner's statement of reasons for allowance: The prior art fails to disclose or suggest the method and system as claimed by Applicant. In particular, the prior art fails to disclose a method of collecting blood plasma wherein a volume of anticoagulant in the collected plasma component is calculated in real time, as the plasma is being collected (such as by counting anticoagulant pump revolutions), along with the other steps and limitations of the claims. The prior art systems rely on calculations prepared in advance.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LESLIE R DEAK whose telephone number is (571)272-4943. The examiner can normally be reached on Monday-Friday, 9am to 5:30pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tom Sweet can be reached on 571-272-4761. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LESLIE R DEAK/
Primary Examiner, Art Unit 3799
5 May 2020

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/608,183	Ragusa, Michael
	Examiner	**Art Unit**
	LESLIE R DEAK	3799

CPC						
Symbol					**Type**	**Version**
A61M	/	1	/	024	F	2013-01-01
A61M	/	1	/	029	I	2013-01-01
A61M	/	1	/	3672	I	2013-01-01
A61M	/	1	/	38	I	2013-01-01
G01N	/	15	/	05	A	2013-01-01
G01N	/	2015	/	055	A	2013-01-01
A61M	/	2230	/	207	A	2013-01-01
A61M	/	2202	/	0415	A	2013-01-01
A61M	/	1	/	3693	A	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	20	
/LESLIE R DEAK/ Primary Examiner, Art Unit 3799	05 May 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	4

U.S. Patent and Trademark Office — Part of Paper No.: 20200505

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0041

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/608,183	Ragusa, Michael
	Examiner	**Art Unit**
	LESLIE R DEAK	3799

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61M1/02	/	1	/	02
A61M1/36	/	1	/	36
A61M1/38	/	1	/	38

NON-CLAIMED				
G01N15/05	/	15	/	05

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 20	
/LESLIE R DEAK/ Primary Examiner, Art Unit 3799 (Primary Examiner)	05 May 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 4

U.S. Patent and Trademark Office

Part of Paper No.: 20200505

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0042

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/608,183	Ragusa, Michael
	Examiner	**Art Unit**
	LESLIE R DEAK	3799

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	20	
/LESLIE R DEAK/ Primary Examiner, Art Unit 3799	05 May 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	4

U.S. Patent and Trademark Office — Part of Paper No.: 20200505

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0043

AFCP 2.0 Decision	Application No.	Applicant(s)	
	15/608,183	Ragusa, Michael	
	Examiner	Art Unit	AIA (FITF) Status
	LESLIE R DEAK	3799	Yes

This is in response to the After Final Consideration Pilot request filed 01 May 2020.

1. **Improper Request** – The AFCP 2.0 request is improper for the following reason(s) and the after final amendment submitted with the request will be treated under pre-pilot procedure.

   ☐ An AFCP 2.0 request form PTO/SB/434 (or equivalent document) was not submitted.

   ☐ A non-broadening amendment to at least one independent claim was not submitted.

   ☐ The request is not the first proper AFCP 2.0 request submitted in response to the most recent final rejection.

   ☐ Other: _____

2. **Proper Request**

   A. After final amendment submitted with the request will not be treated under AFCP 2.0.
   The after final amendment cannot be reviewed and a search conducted within the guidelines of the pilot program.

   ☐ The after final amendment will be treated under pre-pilot procedure.

   B. Updated search and/or completed additional consideration.
   The examiner performed an updated search and/or completed additional consideration of the after final amendment within the time authorized for the pilot program. The result(s) of the updated search and/or completed additional consideration are:

   ☑ 1. All of the rejections in the most recent final Office action are overcome and a Notice of Allowance is issued herewith.

   ☐ 2. The after final amendment would not overcome all of the rejections in the most recent final Office action . See attached interview summary for further details.

   ☐ 3. The after final amendment was reviewed, and it raises a new issue(s). See attached interview summary for further details.

   ☐ 4. The after final amendment raises new issues, but would overcome all of the rejections in the most recent final Office action. A decision on determining allowability could not be made within the guidelines of the pilot. See attached interview summary for further details, including any newly discovered prior art.

   ☐ 5. Other: _____

   Examiner Note: Please attach an interview summary when necessary as described above.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0044

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/608,183	Ragusa, Michael
	Examiner	**Art Unit**
	LESLIE R DEAK	3799

CPC - Searched*		
Symbol	**Date**	**Examiner**
(A61M1/024 OR A61M1/029 OR A61M1/3672 OR A61M1/3693 OR A61M1/38 OR A61M2202/0415 OR A61M2230/207 OR G01N15/05 OR G01N2015/055 OR G01N15/042 OR G01N33/86).CPC.	10/28/2019	LRD

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
inventor name search, EAST BRS search, consulted foreign search report	10/28/2019	LRD
updated prior searches, consulted primary examiners	02/27/2020	LRD
updated prior searches	05/05/2020	LRD

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	N/A	05/05/2020	LRD

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0045

Bibliographic Data

Application No: 15/608,183

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /LESLIE R DEAK/ (Examiner's Signature) ____ (Initials)

Title: System and Method for Collecting Plasma

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
05/30/2017	604	3799	130670-08002
RULE			

APPLICANTS

Haemonetics Corporation, Braintree, MA, UNITED STATES

INVENTORS

Michael Ragusa Hingham, MA, UNITED STATES

CONTINUING DATA

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

06/06/2017

STATE OR COUNTRY

UNITED STATES

ADDRESS

MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110
UNITED STATES

FILING FEE RECEIVED

$1,740

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	3	"l15" and (hematocrit same anticoagulant)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2020/05/05 13:39
S1	2	("20180344910").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 11:36
S2	1	((A61M1/029 and A61M1/3672 and A61M1/3693 and A61M1/38 and A61M2202/0415 and A61M2230/207).CPC.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 11:37
S3	1	((A61M1/029 and A61M1/3672 and A61M1/3693 and A61M1/38 and A61M2202/0415).CPC.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 11:37
S4	20	((A61M1/3672 and A61M1/3693 and A61M1/38 and A61M2202/0415).CPC.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 11:37
S5	3	"20120175313"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:01
S6	2	"20030125881"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:16
S7	27	2009/0215602	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:17

S8	3	"20090215602"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:18
S9	2	S1 AND ((A61M1/024 OR A61M1/029 OR A61M1/3672 OR A61M1/3693 OR A61M1/38 OR A61M2202/0415 OR A61M2230/207 OR G01N15/05 OR G01N2015/055 OR G01N15/042 OR G01N33/86).CPC.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:25
S10	8637	((A61M1/024 OR A61M1/029 OR A61M1/3672 OR A61M1/3693 OR A61M1/38 OR A61M2202/0415 OR A61M2230/207 OR G01N15/05 OR G01N2015/055 OR G01N15/042 OR G01N33/86).CPC.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:25
S11	1805	S10 and hematocrit	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:26
S12	1	"l11" and (hematocrit with anticoagulant)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:26
S13	1	"l10" and (hematocrit with anticoagulant)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:30
S14	2	"l10" and (hematocrit same anticoagulant)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:30
S15	44	((("RAGUSA") near3 ("Michael"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/28 12:31
S16	2	"l15" and (hematocrit same anticoagulant)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:31

S17	183	("20010000185" | "20020062100" | "1025059" | "1611725" | "20010027156" | "20020043492" | "20020120227" | "20030055375" | "20030066807" | "20030125881" | "20030175150" | "20040186409" | "20050209522" | "20050235733" | "20060058167" | "20060155236" | "20070112289" | "20080146993" | "20120175313" | "20140039373" | "20140356851" | "20180344921" | "2087778" | "2661150" | "2750107" | "2792172" | "3096283" | "3145713" | "3239136" | "3244362" | "3244363" | "3409213" | "3456875" | "3489145" | "3565330" | "3655058" | "3737096" | "3774840" | "3987961" | "4007871" | "4010894" | "4014497" | "4040965" | "4056224" | "4082217" | "4086924" | "4140268" | "4142670" | "4151844" | "4197847" | "4285464" | "4300717" | "4303193" | "4321921" | "4387848" | "4425114" | "4430072" | "4447221" | "4457747" | "4464167" | "4466888" | "4482342" | "4490135" | "4530691" | "4534863" | "4643714" | "4647279" | "4655742" | "4680025" | "4684361" | "4692136" | "4708712" | "4713176" | "4734089" | "4740202" | "4740313" | "4755300" | "4767396" | "4795419" | "4795448" | "4806247" | "4806252" | "4808307" | "4850995" | "4869812" | "4871462" | "4876013" | "4889524" | "4911833" | "4934995" | "4940543" | "4943273" | "4968295" | "4983156" | "4983158" | "4985153" | "4994188" | "5039401" | "5045048" | "5098372" | "5098373" | "5100372" | "5100564" | "5112298" | "5114396" | "5135667" | "5141486" | "5147290" | "5154716" | "5174894" | "5194145" | "5217426" | "5217427" | "5234403" | "5254248" | "5273517" | "5277701" | "5298016" | "5298171" | "5300060" | "5316540" | "5318511" | "5318512" | "5348533" | "5368542" | "5368555" | "5386734" | "5387174" | "5387187" | "5403272" | "5405308" | "5417650" | "5431814" | "5437598" | "5437624" | "5462667" | "5470483" | "5484396" |	US-PGPUB; USPAT	OR	OFF	2019/10/28 12:37

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S18	2	("20180344910").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2020/02/27 09:46

EAST Search History (Interference)

<This search history is empty>

5/5/2020 1:51:45 PM
C:\Users\ldeak\Documents\EAST\Workspaces\15608183.wsp

OK to enter.
/LRD/
5 May 2020

AMENDMENTS TO THE CLAIMS

The following **Listing of Claims** will replace all prior versions, and listing, of claims in the application.

Listing of Claims

1. (Currently Amended) A method for collecting plasma comprising:

(a) determining a weight of a donor;

(b) determining a hematocrit of the donor;

(c) inserting a venous-access device into the donor;

(d) withdrawing whole blood from the donor through the venous-access device and a draw line, the draw line connected to a blood component separation device;

(e) introducing anticoagulant into the withdrawn whole blood through an anticoagulant line;

(f) separating the withdrawn whole blood into a plasma component and at least a second blood component using the blood component separation device;

(g) collecting the plasma component from the blood component separation device and into a plasma collection container;

(h) calculating a ~~percentage~~ volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma collection container;

(i) calculating a volume of pure plasma collected within the plasma collection container based, at least in part, on the calculated ~~percentage~~ volume of anticoagulant in the collected plasma component; and

(j) continuing steps (d) through (i) until a target volume of pure plasma is collected within the plasma collection container.

2. (Currently Amended) A method according to claim 1, further comprising:

determining a change in volume within an anticoagulant container, the calculated volume ~~percentage~~ of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant container.

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3. (Currently Amended) A method according claim 1, further comprising:

determining a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump, the calculated volume ~~percentage~~ of anticoagulant in the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump.

4. (Currently Amended) A method according to claim 1, further comprising:

determining a volume of anticoagulant within the blood component separation device, the calculated volume ~~percentage~~ of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.

5. (Original) A method according to claim 1, further comprising:

monitoring a volume of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component.

6. (Original) A method according to claim 1, further comprising:

monitoring a weight of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component.

7. (Currently Amended) A method according to claim 1, wherein step (b) includes monitoring a volume of red blood cells ~~collection~~ collected within the blood separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor.

8. (Original) A method according to claim 1, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

9. (Currently Amended) A method according to claim 1, wherein the volume ~~percentage~~ of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

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10. (Original) A method according to claim 1, further comprising:

returning, after collecting at least a portion of the target volume of pure plasma, the second blood component to the donor through a return line.

11. (Currently Amended) A system for collecting plasma comprising:

a venous-access device for drawing whole blood from a subject and returning blood components to the subject;

a blood component separation device for separating the drawn blood into a plasma component and a second blood component, the blood component separation device having an outlet and being configured to send the plasma component to a plasma container;

a blood draw line fluidly connected to the venous-access device and configured to transport drawn whole blood to the blood component separation device, the flow through the blood draw line being controlled by a blood draw pump;

an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood; and

a controller configured to control the operation of the ~~centrifuge bowl~~ blood component separation device and the blood draw pump, the controller configured to calculate (1) a ~~percentage~~ volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma collection container, and (2) a volume of pure plasma collected within the plasma container based, at least in part, upon the ~~percentage~~ volume of anticoagulant in the collected plasma component, the controller configured to stop the blood draw pump when a target volume of pure plasma is collected within the plasma container.

12. (Currently Amended) A system according to claim 11, wherein the ~~percentage~~ volume of anticoagulant in the collected plasma component is based, at least in part, on a volume of anticoagulant added to the drawn whole blood and the subject's hematocrit.

13. (Currently Amended) A system according to claim 11, further comprising:

an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant

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container based on the measured weight of the anticoagulant source, the calculated ~~percentage~~ volume of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant source.

14. (Currently Amended) A system according to claim 11, wherein the controller is configured to monitor a number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood, the calculated ~~percentage~~ volume of anticoagulant in the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump.

15. (Currently Amended) A system according to claim 11, further comprising:

an optical sensor located on the blood component separation device and configured to monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device, the calculated ~~percentage~~ volume of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.

16. (Original) A system according to claim 11, further comprising:

a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component.

17. (Original) A system according to claim 11, further comprising:

a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component.

18. (Original) A system according to claim 11, further comprising:

an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood separation device, the controller

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configured to determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor

19. (Original) A system according to claim 11, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

20. (Currently Amended) A system according to claim 11, wherein the ~~percentage~~ volume of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

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Petitioner Terumo Exhibit 1021-0055

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/608,183	Filing Date 05/30/2017	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $80 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $420 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	05/01/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/LASHAWN R MORGAN/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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Petitioner Terumo Exhibit 1021-0056

Doc Code: A.NE.AFCP
Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Practitioner Docket No.:	Application No.:	Filing Date:
130670-08002	15/608,183	May 30, 2017

First Named Inventor:	Title:
Michael Ragusa	SYSTEM AND METHOD FOR COLLECTING PLASMA

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).

2. The above-identified application contains an outstanding final rejection.

3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.

4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.

5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.

6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).

7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]

8. By filing this certification and request, applicant acknowledges the following:

- Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
- The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
  - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
  - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
    - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
    - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

Signature	/Jonathan C. Lovely, Reg. No. 60,821/	Date	May 1, 2020
Name (Print/Typed)	Jonathan C. Lovely	Practitioner Registration No.	60,821

***Note**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

☐ * Total of 1 forms are submitted.

ME1 33253731v.1

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Petitioner Terumo Exhibit 1021-0057

Docket No.: 130670-08002
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Haemonetics Corporation

Application No.: 15/608,183 | Confirmation No.: 7286

Filed: May 30, 2017 | Art Unit: 3799

For: SYSTEM AND METHOD FOR COLLECTING PLASMA | Examiner: L. R. Deak

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE UNDER 37 CFR 1.116 REQUESTING CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM (AFCP 2.0)

Dear Sir:

INTRODUCTORY COMMENTS

In response to the Final Office Action dated March 3, 2020, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 7 of this paper.

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Petitioner Terumo Exhibit 1021-0058

AMENDMENTS TO THE CLAIMS

The following **Listing of Claims** will replace all prior versions, and listing, of claims in the application.

Listing of Claims

1. (Currently Amended) A method for collecting plasma comprising:

(a) determining a weight of a donor;

(b) determining a hematocrit of the donor;

(c) inserting a venous-access device into the donor;

(d) withdrawing whole blood from the donor through the venous-access device and a draw line, the draw line connected to a blood component separation device;

(e) introducing anticoagulant into the withdrawn whole blood through an anticoagulant line;

(f) separating the withdrawn whole blood into a plasma component and at least a second blood component using the blood component separation device;

(g) collecting the plasma component from the blood component separation device and into a plasma collection container;

(h) calculating a ~~percentage~~ volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma collection container;

(i) calculating a volume of pure plasma collected within the plasma collection container based, at least in part, on the calculated ~~percentage~~ volume of anticoagulant in the collected plasma component; and

(j) continuing steps (d) through (i) until a target volume of pure plasma is collected within the plasma collection container.

2. (Currently Amended) A method according to claim 1, further comprising:

determining a change in volume within an anticoagulant container, the calculated volume ~~percentage~~ of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant container.

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Petitioner Terumo Exhibit 1021-0059

3. (Currently Amended) A method according claim 1, further comprising:

determining a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump, the calculated volume ~~percentage~~ of anticoagulant in the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump.

4. (Currently Amended) A method according to claim 1, further comprising:

determining a volume of anticoagulant within the blood component separation device, the calculated volume ~~percentage~~ of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.

5. (Original) A method according to claim 1, further comprising:

monitoring a volume of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component.

6. (Original) A method according to claim 1, further comprising:

monitoring a weight of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component.

7. (Currently Amended) A method according to claim 1, wherein step (b) includes monitoring a volume of red blood cells ~~collection~~ collected within the blood separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor.

8. (Original) A method according to claim 1, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

9. (Currently Amended) A method according to claim 1, wherein the volume ~~percentage~~ of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

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Petitioner Terumo Exhibit 1021-0060

10. (Original) A method according to claim 1, further comprising:

returning, after collecting at least a portion of the target volume of pure plasma, the second blood component to the donor through a return line.

11. (Currently Amended) A system for collecting plasma comprising:

a venous-access device for drawing whole blood from a subject and returning blood components to the subject;

a blood component separation device for separating the drawn blood into a plasma component and a second blood component, the blood component separation device having an outlet and being configured to send the plasma component to a plasma container;

a blood draw line fluidly connected to the venous-access device and configured to transport drawn whole blood to the blood component separation device, the flow through the blood draw line being controlled by a blood draw pump;

an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood; and

a controller configured to control the operation of the ~~centrifuge bowl~~ blood component separation device and the blood draw pump, the controller configured to calculate (1) a ~~percentage~~ volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma collection container, and (2) a volume of pure plasma collected within the plasma container based, at least in part, upon the ~~percentage~~ volume of anticoagulant in the collected plasma component, the controller configured to stop the blood draw pump when a target volume of pure plasma is collected within the plasma container.

12. (Currently Amended) A system according to claim 11, wherein the ~~percentage~~ volume of anticoagulant in the collected plasma component is based, at least in part, on a volume of anticoagulant added to the drawn whole blood and the subject's hematocrit.

13. (Currently Amended) A system according to claim 11, further comprising:

an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant

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container based on the measured weight of the anticoagulant source, the calculated ~~percentage~~ volume of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant source.

14. (Currently Amended) A system according to claim 11, wherein the controller is configured to monitor a number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood, the calculated ~~percentage~~ volume of anticoagulant in the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump.

15. (Currently Amended) A system according to claim 11, further comprising:

an optical sensor located on the blood component separation device and configured to monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device, the calculated ~~percentage~~ volume of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.

16. (Original) A system according to claim 11, further comprising:

a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component.

17. (Original) A system according to claim 11, further comprising:

a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component.

18. (Original) A system according to claim 11, further comprising:

an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood separation device, the controller

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configured to determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor

19. (Original) A system according to claim 11, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

20. (Currently Amended) A system according to claim 11, wherein the ~~percentage~~ volume of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

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REMARKS

Applicants would like to thank the examiner for the review of the present application. Applicants request reconsideration of the pending claims in view of the following remarks. Applicant has amended claims 1-4, 7, 9, 11-15 and 20 herewith. Claims 1-20 are currently pending in the application.

Examiner Interview Summary

Applicant would like to thank Examiner Deak for the telephone interview on March 25, 2020. During the interview, Examiner Deak, Applicant's counsel and Michael Ragusa (the inventor) discussed the pending claims, the Office Action dated March 3, 2020 and the cited prior art (e.g., U.S. Application No. 2003/012881 to Ryan, hereinafter "Ryan"). In particular, Applicant's counsel and Mr. Ragusa explained that Ryan does not calculate a volume of pure plasma and calculates the volume of anticoagulant in the plasma component in a different manner. Examiner Deak proposed adding a temporal component to the independent claims to specify when the volume of anticoagulant in the collected plasma component is calculated. To expedite prosecution, Applicant's counsel and Mr. Ragusa suggested the possibility of amending the claims to specify that the anticoagulant in the plasms component is calculated "as the plasma component is being collected in the plasma collection container." Examiner Deak indicated that such an amendment should overcome the cited prior art.

35 USC § 102

Claims 11, 12, 16, 17, 19 and 20 are rejected under 35 U.S.C. 102(a)(1) and (a)(2) as being anticipated by U.S. 2003/0125881 to Ryan.

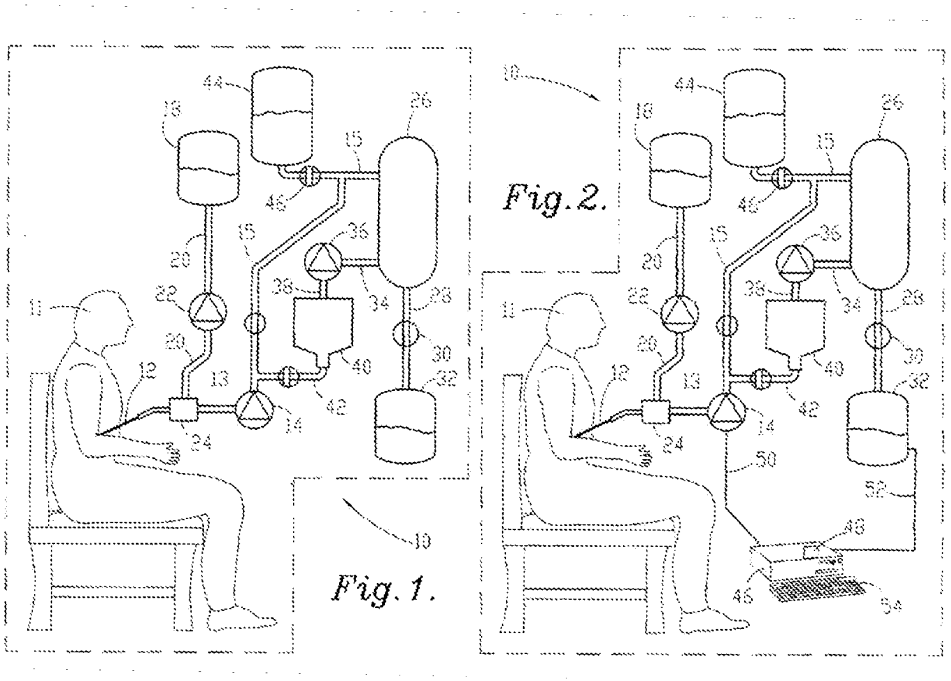
Amended claim 11 defines, in relevant part, a system for collecting plasma that includes (1) a venous-access device for drawing whole blood from a subject and returning blood components to the subject, and (2) a blood component separation device for separating the drawn blood into a plasma component and a second blood component. The blood component separation device may have an outlet and may send the plasma component to a plasma container. A blood draw line fluidly

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connected to the venous-access device transports the drawn whole blood to the blood component separation device, and the flow through the blood draw line is controlled by a blood draw pump. An anticoagulant line is connected to an anticoagulant source and introduces anticoagulant into the drawn whole blood. The system also has a controller that controls the operation of the centrifuge bowl and the blood draw pump. The controller may calculate (1) a volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma collection container, and (2) a volume of pure plasma collected within the plasma container based, at least in part, upon the volume of anticoagulant in the collected plasma component. The controller may stop the blood draw pump when a target volume of pure plasma is collected within the plasma container.

Ryan fails to teach or suggest the claimed system. Rather, Ryan teaches a method and apparatus for collecting a plasma portion and that withdraws donor-weight specific plasma and blood volumes. Ryan's plasmapheresis system 10 includes a controller 46 that is in communicative control of a whole blood pump 14 as a function of either the volume of blood pumped by pump 14 or the volume of plasma contained in plasma reservoir 32 (e.g., as determined by the weight of the plasma reservoir 32 or by volume using optical sensors). The data from the scale or from the optical sensor is transmitted to the controller 46 and a processor 48 which monitor the amount of plasma collected. During operation, a donor 11 is weighed on a conventional scale, and the donor-specific body weight is obtained. Ryan then provides the processor 48 with the donor-specific body weight and the processor 48 calculates a particular plasma volume to be extracted from the donor based upon the donor-specific body weight and a selected standard of milliliters of plasma per pound of body weight. Ryan continues processing whole blood and collecting plasma until the calculated plasma volume is collected as determined by the number of revolutions of the pump 14 or the "actual" volume of plasma collected in the plasma reservoir 32 as measured by the weight of the reservoir 32 or the optical sensor. The "actual" volume of plasma is a combination of plasma and anticoagulant.

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The office action suggests that Ryan's controller/processor 46/48 constitutes the claimed controller and that Ryan's controller/processor 46/48 calculate a percentage of anticoagulant in the collected plasma, a volume of plasma collected, and an appropriate time to stop the blood pump 14. As noted above, Applicant has amended claim 11 to specify that the controller calculates a volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma collection container. Ryan fails to teach or suggest such an anticoagulant calculation. Rather, at best, Ryan calculates a total collection volume (plasma and anticoagulant) prospectively prior to the start of the blood processing. In particular, as discussed within Ryan (e.g., see paragraph s [0024], [0025] and [0032] to [0036]), Ryan determines the donor's body weight and then multiplies the weight by a collection volume per pound (e.g., 5.8 milliliters per pound of donor body weight) to determine a volume of plasma and anticoagulant to collect. Ryan does not calculate the volume of anticoagulant in the collected plasma as the plasma component is collected in the container, as required by amended claim 11.

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Furthermore, Ryan does not calculate a volume of pure plasma (plasma only without anticoagulant) collected within the plasma collection container and then stop the processing once a target of pure plasma is collected. Rather, as evidenced by the equation provided in paragraphs [0032] and [0033] of Ryan (e.g., "Vpac=DW x CV") and the comparison in Table 3 of Ryan, Ryan calculates and stops based on a volume that includes both plasma and anticoagulant, not just pure plasma as required by amended claim 11. Additionally, Ryan specifically teaches using a scale to measure the weight of the bag 32 (the plasma collection container) or an optical sensor to measure the volume within the bag 32 and stopping when this measurement reaches the target. However, both the scale and the optical sensor measure the volume of the plasma and anticoagulant collected in the bag. Accordingly, Ryan does not teach or suggest calculating the volume of anticoagulant in the collected plasma component as the plasma component is collected and does not compensate for this volume of anticoagulant obtain/calculate a volume of "pure plasma," as required by claim 11.

Therefore, claim 11 is allowable over Ryan. Moreover, claims 12, 16, 17, 19 and 20 which depend from claim 11 are also allowable over Ryan

35 USC § 103

Claims 1, 5, 6, 8-10 are rejected under 35 U.S.C. 103 as being unpatentable over U.S. 2003/0125881 to Ryan.

In a manner similar to claim 11, claim 1 defines, in relevant part, a method for collecting plasma that includes (1) determining the weight and hematocrit of a donor, (2) calculating a volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma container, (3) calculating a volume of pure plasma collected within the plasma collection container, and (4) collecting plasma until a target volume of pure plasma is collected within the plasma collection container. Accordingly, claim 1 is allowable over Ryan for at least the same reasons as discussed above for claim 11. For example, as discussed above, Ryan fails to teach or suggest calculating the volume of anticoagulant in the collected plasma component as the plasma component is collected and does not compensate for this volume of anticoagulant to obtain/calculate a volume of "pure plasma" – Ryan sets a total volume of plasma and anticoagulant to collect prior

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to the start of processing and looks at the volume of plasma and anticoagulant combined. Therefore, amended claim 1 is allowable over Ryan. Moreover, claims 5, 6, and 8-10 are allowable over Ryan for at least the same reasons.

Claims 2-4, 13 and 14 are rejected under 35 U.S.C. 103 as being unpatentable over U.S. 2003/0125881 to Ryan in view of U.S. 2012/0175313 to Barry et al.

As dependent claims of claims 1 and 11, claims 2-4 and 13-14 include all of the limitations of the base claim from which they depend. Therefore, claims 2-4 and 13-14 are allowable over the cited prior art for at least the reasons discussed above for claims 1 and 11.

Comments Regarding Claim Amendments

As discussed above, Applicant has amended the pending claims to specify that the volume of anticoagulant in the plasma component is calculated as the plasma component is being collected in the plasma collection container. Applicant would like to note that these amendments are being made to expedite prosecution and is not meant to be an agreement that the cited prior art teaches the claims as originally filed. Additionally, Applicant would like to note that other embodiments disclosed within the present application may calculate the anticoagulant within the plasma collection container in a different manner. For example, other disclosed embodiments may calculate the percentage of anticoagulant in the container and/or may calculate it at a different time (e.g., before blood processing begins). The amendments made herein are not intended to limit Applicant's ability to pursue such alternative embodiments in the future and are not intended to be a disclaimer of these alternative embodiments or any other subject matter supported by the disclosure of the present application, including the originally filed claims.

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CONCLUSION

It is believed that the application is now in order for allowance and Applicants respectfully request that a notice of allowance be issued. Applicant believes no fee is due with this response. Applicants also request that the examiner contact applicants' attorney, Jonathan Lovely, if it will assist in processing this application through issuance.

Dated: May 1, 2020

Respectfully submitted,

Electronic signature: /Jonathan C. Lovely, Reg. No. 60,821/
Jonathan C. Lovely
Registration No.: 60,821
MCCARTER & ENGLISH, LLP
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Boston, Massachusetts 02110
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Attorney/Agent For Applicant

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0069

Electronic Acknowledgement Receipt

EFS ID:	39323624
Application Number:	15608183
International Application Number:	
Confirmation Number:	7286
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Customer Number:	86738
Filer:	Jonathan Lovely
Filer Authorized By:	
Attorney Docket Number:	130670-08002
Receipt Date:	01-MAY-2020
Filing Date:	30-MAY-2017
Time Stamp:	15:20:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	After Final Consideration Program Request	After_Final_Consideration_Pilot_Program_Request_.pdf	34877 984da5c6f99984161b9e53d91b650619b325bf8e	no	1

Warnings:

Information:					
2		Response_to_Final_Office_Action_.pdf	577219 8cf77d023f39b22711145f94b5d35b715baac6e2	yes	12

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response After Final Action	1	1
	Claims	2	6
	Applicant Arguments/Remarks Made in an Amendment	7	12

Warnings:	
Information:	
Total Files Size (in bytes):	612096

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/608,183	05/30/2017	Michael Ragusa	130670-08002	7286

86738 7590 03/30/2020
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER
DEAK, LESLIE R

ART UNIT	PAPER NUMBER
3781	

NOTIFICATION DATE	DELIVERY MODE
03/30/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@mccarter.com

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Petitioner Terumo Exhibit 1021-0072

Applicant-Initiated Interview Summary	**Application No.** 15/608,183	**Applicant(s)** Ragusa, Michael	
	Examiner LESLIE R DEAK	**Art Unit** 3781	**AIA (FITF) Status** Yes

All participants (applicant, applicants representative, PTO personnel):

(1) LESLIE R. DEAK.

(3) Michael Ragusa, Inventor.

(2) Jonathan Lovely, Counsel.

(4) _____.

Date of Interview: 25 March 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☑102 ☑103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1 and 11.

Identification of prior art discussed: US 2003/0125881 to Ryan.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/LESLIE R DEAK/ Primary Examiner, Art Unit 3781	

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Petitioner Terumo Exhibit 1021-0073

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

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Petitioner Terumo Exhibit 1021-0074

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Steps h, I, j are the meat here. Prior art systems, when they collect plasma, FDA provides a nomogram based on weight of the patient, sets out how much volume you can pull out of each of the weight groups. Prior art systems collect plasma and AC, and base measurements off of the combined volume. In the instant case, if we tailor calculations to the donor, it's more accurate. Calculate the percentage of AC in the container, and from that, calculate the amount of pure plasma. Ryan doesn't follow FDA nomogram directly, but uses individual weights to figure out how much plasma to pull out. Ryan's calculations of collections are that of plasma and AC. AC percentage calculations done by Ryan are at the beginning of separation, and there's no teaching of how to calculate the AC in the actual collection bag.

How does this invention make the calculation of how much AC is in the collection bag? Fxn of donor hct and AC ratio. Based on weight or pump strokes.

Ryan calculates how much AC is going into the separator. Here, we're seeing how much AC is in the plasma after separation. Ryan lacks any ability to track how much AC is going to the product, and how much is being returned to the donor.

Examiner suggested adding "real-time" measurements of AC volume in steps h and i of the claimed method. Applicant will review the claim language and make formal amendments. Applicant's suggested claim language appears to overcome the Ryan reference.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/608,183	05/30/2017	Michael Ragusa	130670-08002	7286

86738 7590 03/03/2020

MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER	
DEAK, LESLIE R	

ART UNIT	PAPER NUMBER
3781	

NOTIFICATION DATE	DELIVERY MODE
03/03/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0076

Office Action Summary	Application No. 15/608,183	Applicant(s) Ragusa, Michael	
	Examiner LESLIE R DEAK	Art Unit 3781	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 31 January 2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-20 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-20 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 24 August 2017 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☑ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☑ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

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Petitioner Terumo Exhibit 1021-0077

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Response to Arguments

2. Applicant's arguments filed 31 January 2020 have been fully considered but they are not persuasive.

3. Applicant argues that Ryan fails to calculate a volume of “pure plasma” (plasma without anticoagulant) in the plasma container, the value of which is used to control the blood draw pump. Applicant alleges that Ryan calculates only the amount of fluid in the plasma container, which is a combination of pure plasma and anticoagulant. While Ryan focuses on total volume collection in Table 1, the following paragraphs go deeper. Ryan clearly discloses in paragraph 0022 that the apparatus and method can calculate a plasma volume of (such as 625mL) based on a total collection volume of plasma and anticoagulant (such as 690mL), and this information may be used to control the pumping of blood from the donor (see Table 2, ¶0022). As such, Ryan reasonably discloses the calculation of a pure plasma volume as claimed by Applicant.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.

> (a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

5. Claims 11, 12, 16, 17, 19, and 20 are rejected under 35 U.S.C. 102(a)(1) and (a)(2) as being anticipated by US 2003/0125881 to Ryan.

In the specification and figures, Ryan teaches the apparatus as claimed by Applicant. With regard to claim 11, Ryan discloses a venous access device 12, a blood component separation device 26, plasma container 32, a blood draw line connected to venous access 12, a blood pump 14, an anticoagulant line 20, and a controller 46/48 that calculates a percentage of anticoagulant in the collected plasma, and a volume of plasma collected, and an appropriate time to stop blood pump 14 (see FIG 2, Table 2, ¶0022).

With regard to claims 12, 19, 20, Ryan teaches using a patient's weight, hematocrit, and amount of anticoagulant used to determine a target amount of collected plasma with a determined amount of anticoagulant (see ¶0014).

With regard to claims 15-17, Ryan discloses a plasma container weight sensor as well as an optical sensor (see ¶0031).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1, 5, 6, and 8-10 are rejected under 35 U.S.C. 103 as being unpatentable over US 2003/0125881 to Ryan.

In the specification and figures, Ryan teaches the method as claimed by Applicant. With regard to claims 1, 8, 9, Ryan teaches a method for collecting plasma comprising the steps of using donor weight, donor hematocrit and amount of anticoagulant used to determine a target amount of plasma that can be collected from a patient (see ¶0014). Once that determination is made, the method includes the steps of drawing blood from a patient, adding anticoagulant, separating the blood, collecting the plasma, and repeating those steps until a target plasma volume is reached (see ¶0011, 0012, 0022, 0023). Ryan does not teach that the steps of the method are performed in the same order as set forth by Applicant, but does teach using all of the same variables as those used by Applicant (donor weight, hematocrit, amount of anticoagulant) to generate the same result (target plasma volume), generally suggesting the claimed method to a person having ordinary skill in the art.

With regard to claims 5, 6, Ryan teaches that the volume of plasma collected is monitored throughout the procedure via weight or light transmission (see ¶0031, 0044).

With regard to claim 10, Ryan discloses that a second, cellular blood component may be returned to the patient (see ¶0012).

8. Claims 2-4, 7, 13, 14, and 18 are rejected under 35 U.S.C. 103 as being unpatentable over US 2003/0125881 to Ryan in view of US 2012/0175313 to Barry et al.

In the specification and figures, Ryan discloses the method and apparatus substantially as claimed by Applicant. With regard to claims 2-4, 13, 14, Ryan fails to disclose the step of determining a change in the volume of anticoagulant to determine the amount of anticoagulant in the system. However, Barry discloses monitoring pump strokes and, as a backup, weight of the anticoagulant container to determine the amount of anticoagulant in the extracorporeal system (see ¶0057). The monitoring of the pumps and weight sensor help ensure an accurate metering of anticoagulant within the separation circuit (see ¶0057). It would have been obvious to a person having ordinary skill in the art at the time of filing to add the monitoring system and steps disclosed by Barry to the apparatus and method disclosed by Ryan in order to provide accurate metering of anticoagulant within the separation circuit, as taught by Barry.

With regard to claims 7 and 18, Ryan is silent as to an optical hematocrit sensor. However, Barry discloses an apheresis apparatus and method that uses an optical hematocrit sensor to accurately set and monitor target collection volumes in order to more accurately control the collection procedure (see US 2009/0215602 ¶0327, incorporated by reference in '313. ¶0035, 0058, 0084). It would have been obvious to a person having ordinary skill in the art at the time of filing to add the optical monitoring system and steps disclosed by Barry to the apparatus and method disclosed by Ryan in order to provide accurate setting and monitoring of target collection values within the separation circuit, as taught by Barry.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LESLIE R DEAK whose telephone number is (571)272-4943. The examiner can normally be reached on Monday-Friday, 9am to 5:30pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tatyana Zalukaeva can be reached on 571-272-1115. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LESLIE R DEAK/
Primary Examiner, Art Unit 3781
27 February 2020

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/608,183	Ragusa, Michael
	Examiner	Art Unit
	LESLIE R DEAK	3781

CPC - Searched*		
Symbol	Date	Examiner
(A61M1/024 OR A61M1/029 OR A61M1/3672 OR A61M1/3693 OR A61M1/38 OR A61M2202/0415 OR A61M2230/207 OR G01N15/05 OR G01N2015/055 OR G01N15/042 OR G01N33/86).CPC.	10/28/2019	LRD

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
inventor name search, EAST BRS search, consulted foreign search report	10/28/2019	LRD
updated prior searches, consulted primary examiners	02/27/2020	LRD

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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Petitioner Terumo Exhibit 1021-0084

Docket No.: 130670-08002
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Michael Ragusa

Application No.: 15/608,183 Confirmation No.: 7286

Filed: May 30, 2017 Art Unit: 3781

For: SYSTEM AND METHOD FOR COLLECTING PLASMA Examiner: L. R. Deak

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

In response to the Office Action dated November 1, 2019, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 7 of this paper.

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AMENDMENTS TO THE CLAIMS

The following **Listing of Claims** will replace all prior versions, and listing, of claims in the application.

Listing of Claims

1. (Original) A method for collecting plasma comprising:

(a) determining a weight of a donor;

(b) determining a hematocrit of the donor;

(c) inserting a venous-access device into the donor;

(d) withdrawing whole blood from the donor through the venous-access device and a draw line, the draw line connected to a blood component separation device;

(e) introducing anticoagulant into the withdrawn whole blood through an anticoagulant line;

(f) separating the withdrawn whole blood into a plasma component and at least a second blood component using the blood component separation device;

(g) collecting the plasma component from the blood component separation device and into a plasma collection container;

(h) calculating a percentage of anticoagulant in the collected plasma component;

(i) calculating a volume of pure plasma collected within the plasma collection container based, at least in part, on the calculated percentage of anticoagulant in the collected plasma component; and

(j) continuing steps (d) through (i) until a target volume of pure plasma is collected within the plasma collection container.

2. (Original) A method according to claim 1, further comprising:

determining a change in volume within an anticoagulant container, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant container.

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3. (Original) A method according claim 1, further comprising:

determining a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump.

4. (Original) A method according to claim 1, further comprising:

determining a volume of anticoagulant within the blood component separation device, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.

5. (Original) A method according to claim 1, further comprising:

monitoring a volume of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component.

6. (Original) A method according to claim 1, further comprising:

monitoring a weight of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component.

7. (Original) A method according to claim 1, wherein step (b) includes monitoring a volume of red blood cells collection within the blood separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor.

8. (Original) A method according to claim 1, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

9. (Original) A method according to claim 1, wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

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10. (Original) A method according to claim 1, further comprising:

returning, after collecting at least a portion of the target volume of pure plasma, the second blood component to the donor through a return line.

11. (Original) A system for collecting plasma comprising:

a venous-access device for drawing whole blood from a subject and returning blood components to the subject;

a blood component separation device for separating the drawn blood into a plasma component and a second blood component, the blood component separation device having an outlet and being configured to send the plasma component to a plasma container;

a blood draw line fluidly connected to the venous-access device and configured to transport drawn whole blood to the blood component separation device, the flow through the blood draw line being controlled by a blood draw pump;

an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood; and

a controller configured to control the operation of the centrifuge bowl and the blood draw pump, the controller configured to calculate (1) a percentage of anticoagulant in the collected plasma component, and (2) a volume of pure plasma collected within the plasma container based, at least in part, upon the percentage of anticoagulant in the collected plasma component, the controller configured to stop the blood draw pump when a target volume of pure plasma is collected within the plasma container.

12. (Original) A system according to claim 11, wherein the percentage of anticoagulant in the collected plasma component is based, at least in part, on a volume of anticoagulant added to the drawn whole blood and the subject's hematocrit.

13. (Original) A system according to claim 11, further comprising:

an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant container based on the measured weight of the anticoagulant source, the calculated percentage of

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anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant source.

14. (Original) A system according to claim 11, wherein the controller is configured to monitor a number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump.

15. (Original) A system according to claim 11, further comprising:

an optical sensor located on the blood component separation device and configured to monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.

16. (Original) A system according to claim 11, further comprising:

a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component.

17. (Original) A system according to claim 11, further comprising:

a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component.

18. (Original) A system according to claim 11, further comprising:

an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood separation device, the controller configured to determine the subject's hematocrit based, at least in part, upon on the monitored

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volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor

19. (Original) A system according to claim 11, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

20. (Original) A system according to claim 11, wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

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REMARKS

Applicants would like to thank the examiner for the review of the present application. Applicants request reconsideration of the pending claims in view of the following remarks. Claims 1-20 are currently pending in the application.

35 USC § 102

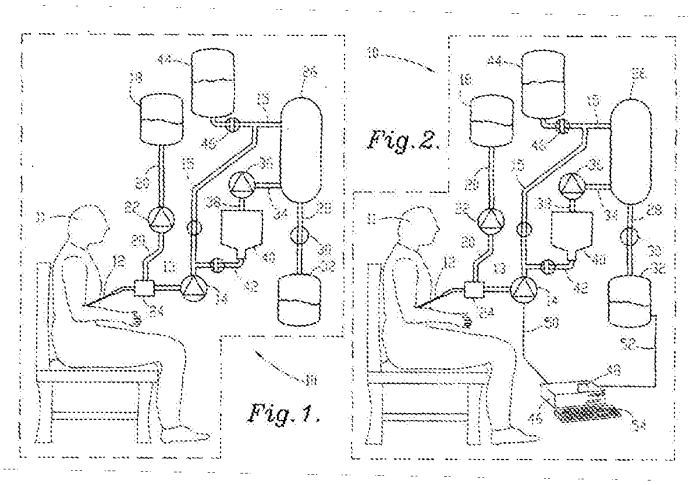
Claims 11, 12, 16, 17, 19 and 20 are rejected under 35 U.S.C. 102(a)(1) and (a)(2) as being anticipated by U.S. 2003/0125881 to Ryan.

Claim 11 defines, in relevant part, a system for collecting plasma that includes (1) a venous-access device for drawing whole blood from a subject and returning blood components to the subject, and (2) a blood component separation device for separating the drawn blood into a plasma component and a second blood component. The blood component separation device may have an outlet and may send the plasma component to a plasma container. A blood draw line fluidly connected to the venous-access device transports the drawn whole blood to the blood component separation device, and the flow through the blood draw line is controlled by a blood draw pump. An anticoagulant line is connected to an anticoagulant source and introduces anticoagulant into the drawn whole blood. The system also has a controller that controls the operation of the centrifuge bowl and the blood draw pump. The controller may calculate (1) a percentage of anticoagulant in the collected plasma component, and (2) a volume of pure plasma collected within the plasma container based, at least in part, upon the percentage of anticoagulant in the collected plasma component. The controller may stop the blood draw pump when a target volume of pure plasma is collected within the plasma container.

Ryan fails to teach or suggest the claimed system. Rather, Ryan teaches a method and apparatus for collecting the plasma portion and that withdraws donor-weight specific plasma and blood volumes. Ryan's plasmapheresis system 10 includes a controller 46 that is in communicative control of a whole blood pump 14 as a function of either the volume of blood pumped by pump 14 or the volume of plasma contained in plasma reservoir 32 (e.g., as determined by the weight of the

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plasma reservoir 32 or by volume using optical sensors). The data from the scale or from the optical sensor is transmitted to the controller 46 and a processor 48 which monitor the amount of plasma collected. During operation, a donor 11 is weighed on a conventional scale, and the donor-specific body weight of the donor is obtained. Ryan then provides the processor 48 with the donor-specific body weight and the processor 48 calculates a particular plasma volume to be extracted from the donor based upon the donor-specific body weight and a selected standard of milliliters of plasma per pound of body weight. Ryan continues processing whole blood and collecting plasma until the calculated plasma volume is collected as determined by the number of revolutions of the pump 14 or the "actual" volume of plasma collected in the plasma reservoir 32 as measured by the weight of the reservoir 32 or the optical sensor.



The office action suggests that Ryan's controller/processor 46/48 constitutes the claimed controller and that Ryan's controller/processor 46/48 calculate a percentage of anticoagulant in the collected plasma and a volume of plasma collected, and an appropriate time to stop the blood pump 14. Applicant respectfully disagrees and would like to note that nowhere does Ryan teach or suggest calculating and/or collecting a volume of "pure plasma," as required by claim 11. As discussed within the present application, the volume of "pure plasma" is the volume of plasma only…it is <u>not</u> the volume of the plasma and anticoagulant mixed together (see paragraphs [0018] and [0035] of the present application. Additionally, as also discussed within the present application, the osmolarity

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of the red blood cells prevents the added anticoagulant to remain with the red blood cells, and the anticoagulant mixes with the plasma component and is collected within the plasma collection container along with the plasma. Ryan does not calculate the volume of pure plasma collected within the plasma container and then stop when a target volume of pure plasma is collected in the container. Rather, as discussed above, Ryan either stops based on a volume of whole blood drawn from the subject (based on a number of pump rotations; see paragraph [0038] of Ryan) or the total volume of fluid (i.e., both plasma and anticoagulant) collected within the reservoir bag 32. For example, for embodiments that stop based on the fluid volume within the bag 32, Ryan may use a scale to measure the weight of the bag 32 or an optical sensor to measure the volume within the bag. However, both the scale and the optical sensor measure the volume of the plasma and anticoagulant collected in the bag…Ryan does not teach or suggest compensating for the volume of anticoagulant that is mixed with the plasma to obtain/calculate a volume of "pure plasma," as required by claim 11.

Applicant would also like to note that, although Ryan refers to the volume of plasma measured by the scale and/or optical sensor as the "actual volume of plasma," as discussed above this volume is actually a mixture of plasma and anticoagulant (e.g., because the added anticoagulant mixes with and is collected with the plasma). This is further evidenced by the equations provided within Ryan. In particular, Ryan provides the equation "Vpac=DW x CV" to determine the volume of plasma to collect. However, Ryan also specifically states that Vpac, which is the volume of plasma to be collected, is the "plasma and anticoagulant collection volume in milliliters" (emphasis added). Additionally, as shown in Table 3 of Ryan, Ryan is basing the amount of plasma on the FDA guidelines which specifically state that the values are "with anticoagulant." In other words, Ryan does not calculate a volume of pure plasma and/or stop based on a volume of pure plasma – Ryan specifically teaches using a volume of plasma and anticoagulant.

Accordingly, claim 11 is allowable over Ryan. Moreover, claims 12, 16, 17, 19 and 20 which depend from claim 11 are also allowable over Ryan

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35 USC § 103

Claims 1, 5, 6, 8-10 are rejected under 35 U.S.C. 103 as being unpatentable over U.S. 2003/0125881 to Ryan.

In a manner similar to claim 11, claim 1 defines, in relevant part, a method for collecting plasma that includes (1) determining the weight and hematocrit of a donor, (2) calculating a percentage of anticoagulant in the collected plasma component and a volume of pure plasma collected within the plasma collection container, and (3) collecting plasma until a target volume of pure plasma is collected within the plasma collection container. Accordingly, claim 1 is allowable over Ryan for at least the same reasons as discussed above for claim 11. For example, as discussed above, Ryan fails to teach or suggest calculating a volume of pure plasma and collecting plasma until a target volume of pure plasma is collected – Ryan looks at the volume of plasma and anticoagulant combined. Moreover, claims 5, 6, and 8-10 are allowable over Ryan for at least the same reasons.

Claims 2-4, 13 and 14 are rejected under 35 U.S.C. 103 as being unpatentable over U.S. 2003/0125881 to Ryan in view of U.S. 2012/0175313 to Barry et al.

As dependent claims of claims 1 and 11, claims 2-4 and 13-14 include all of the limitations of the base claim from which they depend. Therefore, claims 2-4 and 13-14 are allowable over the cited prior art for at least the reasons discussed above for claims 1 and 11.

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CONCLUSION

It is believed that the application is now in order for allowance and Applicants respectfully request that a notice of allowance be issued. Applicant believes no fee is due with this response. Applicants also request that the examiner contact applicants' attorney, Jonathan Lovely, if it will assist in processing this application through issuance.

Dated: January 31, 2020

Respectfully submitted,

Electronic signature: /Jonathan C. Lovely, Reg. No. 60,821/
Jonathan C. Lovely
Registration No.: 60,821
MCCARTER & ENGLISH, LLP
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Attorney/Agent For Applicant

Terumo v. Haemonetics - PGR2025-00077
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Electronic Acknowledgement Receipt

EFS ID:	38456160
Application Number:	15608183
International Application Number:	
Confirmation Number:	7286
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Customer Number:	86738
Filer:	Jonathan Lovely
Filer Authorized By:	
Attorney Docket Number:	130670-08002
Receipt Date:	31-JAN-2020
Filing Date:	30-MAY-2017
Time Stamp:	13:53:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		15608183_Response_to_Non-Final_OA.pdf	482877 9c20e8cfe0758f1fa605c6022a4c979dfefcdefd	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	6
	Applicant Arguments/Remarks Made in an Amendment	7	11
Warnings:			
Information:			
	Total Files Size (in bytes):	482877	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/608,183	Filing Date 05/30/2017	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $80 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $420 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	01/31/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARCUS D MONROE/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/608,183	05/30/2017	Michael Ragusa	130670-08002	7286

86738 7590 11/01/2019

MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER
DEAK, LESLIE R

ART UNIT	PAPER NUMBER
3781	

NOTIFICATION DATE	DELIVERY MODE
11/01/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@mccarter.com

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0099

Office Action Summary	**Application No.** 15/608,183	**Applicant(s)** Ragusa, Michael	
	Examiner LESLIE R DEAK	**Art Unit** 3781	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 30 May 2017.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-20 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-20 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 24 August 2017 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☑ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☑ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0100

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.
>
> (a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

3. Claims 11, 12, 16, 17, 19, and 20 are rejected under 35 U.S.C. 102(a)(1) and (a)(2) as being anticipated by US 2003/0125881 to Ryan.

In the specification and figures, Ryan teaches the apparatus as claimed by Applicant. With regard to claim 11, Ryan discloses a venous access device 12, a blood component separation device 26, plasma container 32, a blood draw line connected to venous access 12, a blood pump 14, an anticoagulant line 20, and a controller 46/48 that calculates a percentage of anticoagulant in the collected plasma, and a volume of plasma collected, and an appropriate time to stop blood pump 14 (see FIG 2 and accompanying test).

With regard to claims 12, 19, 20, Ryan teaches using a patient's weight, hematocrit, and amount of anticoagulant used to determine a target amount of collected plasma with a determined amount of anticoagulant (see ¶0014).

With regard to claims 15-17, Ryan discloses a plasma container weight sensor as well as an optical sensor (see ¶0031).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1, 5, 6, 8-10 are rejected under 35 U.S.C. 103 as being unpatentable over US 2003/0125881 to Ryan.

In the specification and figures, Ryan teaches the method as claimed by Applicant. With regard to claims 1, 8, 9, Ryan teaches a method for collecting plasma comprising the steps of using donor weight, donor hematocrit and amount of anticoagulant used to determine a target amount of plasma that can be collected from a patient (see ¶0014). Once that determination is made, the method includes the steps of drawing blood from a patient, adding anticoagulant, separating the blood, collecting the plasma, and repeating those steps until a target plasma volume is reached (see ¶0011, 0012, 0023). Ryan does not teach that the steps of the method are performed in the same order as set forth by Applicant, but does teach using all of the same variables as

those used by Applicant (donor weight, hematocrit, amount of anticoagulant) to generate the same result (target plasma volume), generally suggesting the claimed method to a person having ordinary skill in the art.

With regard to claims 5, 6, Ryan teaches that the volume of plasma collected is monitored throughout the procedure via weight or light transmission (see ¶0031, 0044).

With regard to claim 10, Ryan discloses that a second, cellular blood component may be returned to the patient (see ¶0012).

6. Claims 1, 5, 6, 8-10 are rejected under 35 U.S.C. 103 as being unpatentable over US 2003/0125881 to Ryan in view of US 2012/0175313 to Barry et al.

In the specification and figures, Ryan discloses the method and apparatus substantially as claimed by Applicant. With regard to claims 2-4, 13, 14, Ryan fails to disclose the step of determining a change in the volume of anticoagulant to determine the amount of anticoagulant in the system. However, Barry discloses monitoring pump strokes and, as a backup, weight of the anticoagulant container to determine the amount of anticoagulant in the extracorporeal system (see ¶0057). The monitoring of the pumps and weight sensor help ensure an accurate metering of anticoagulant within the separation circuit (see ¶0057). It would have been obvious to a person having ordinary skill in the art at the time of filing to add the monitoring system and steps disclosed by Barry to the apparatus and method disclosed by Ryan in order to provide accurate metering of anticoagulant within the separation circuit, as taught by Barry.

With regard to claims 7 and 18, Ryan is silent as to an optical hematocrit sensor. However, Barry discloses an apheresis apparatus and method that uses an optical

hematocrit sensor to accurately set and monitor target collection volumes in order to more accurately control the collection procedure (see US 2009/0215602 ¶0327, incorporated by reference in '313. ¶0035, 0058, 0084). It would have been obvious to a person having ordinary skill in the art at the time of filing to add the optical monitoring system and steps disclosed by Barry to the apparatus and method disclosed by Ryan in order to provide accurate setting and monitoring of target collection values within the separation circuit, as taught by Barry.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LESLIE R DEAK whose telephone number is (571)272-4943. The examiner can normally be reached on Monday-Friday, 9am to 5:30pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tatyana Zalukaeva can be reached on 571-272-1115. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LESLIE R DEAK/
Primary Examiner, Art Unit 3781
28 October 2019

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/608,183	Ragusa, Michael
	Examiner	**Art Unit**
	LESLIE R DEAK	3781

CPC - Searched*		
Symbol	**Date**	**Examiner**
(A61M1/024 OR A61M1/029 OR A61M1/3672 OR A61M1/3693 OR A61M1/38 OR A61M2202/0415 OR A61M2230/207 OR G01N15/05 OR G01N2015/055 OR G01N15/042 OR G01N33/86).CPC.	10/28/2019	LRD

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
inventor name search, EAST BRS search, consulted foreign search report	10/28/2019	LRD

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0106

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2	("20180344910").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 11:36
L2	1	((A61M1/029 and A61M1/3672 and A61M1/3693 and A61M1/38 and A61M2202/0415 and A61M2230/207).CPC.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 11:37
L3	1	((A61M1/029 and A61M1/3672 and A61M1/3693 and A61M1/38 and A61M2202/0415).CPC.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 11:37
L4	20	((A61M1/3672 and A61M1/3693 and A61M1/38 and A61M2202/0415).CPC.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 11:37
L5	3	"20120175313"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:01
L6	2	"20030125881"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:16
L7	27	2009/0215602	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:17
L8	3	"20090215602"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:18
L9	2	1 AND ((A61M1/024 OR A61M1/029 OR A61M1/3672 OR A61M1/3693 OR A61M1/38 OR A61M2202/0415 OR A61M2230/207 OR G01N15/05 OR G01N2015/055 OR G01N15/042 OR G01N33/86).CPC.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:25
L10	8637	((A61M1/024 OR A61M1/029 OR A61M1/3672 OR A61M1/3693 OR A61M1/38 OR A61M2202/0415 OR A61M2230/207 OR G01N15/05 OR G01N2015/055 OR G01N15/042 OR G01N33/86).CPC.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:25
L11	1805	l10 and hematocrit	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:26
L12	1	"l11" and (hematocrit with anticoagulant)	US-PGPUB;	OR	OFF	2019/10/28

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0107

			USPAT; USOCR; DERWENT			12:26
L13	1	"I10" and (hematocrit with anticoagulant)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:30
L14	2	"I10" and (hematocrit same anticoagulant)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:30
L15	44	((("RAGUSA") near3 ("Michael"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/28 12:31
L16	2	"I15" and (hematocrit same anticoagulant)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:31

EAST Search History (Interference)

< This search history is empty>

10/28/2019 12:32:20 PM
C:\Users\ldeak\Documents\EAST\Workspaces\15608183.wsp

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0108

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(Based on PTO 10-07 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 6

Complete if Known	
Application Number	15/608,183
Filing Date	May 30, 2017
First Named Inventor	Michael Ragusa
Art Unit	3781
Examiner Name	T. Zalukaeva
Attorney Docket Number	130670-08002

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-1,025,059	04-30-1912	Hatton et al.	
	AB	US-1,611,725	12-21-1926	Degerth et al.	
	AC	US-2,087,778	07-20-1937	Nelin	
	AD	US-2,661,150	12-01-1953	Abbott, Jr.	
	AE	US-2,750,107	06-12-1956	More	
	AF	US-2,792,172	05-14-1957	Tait	
	AG	US-3,096,283	07-02-1963	Hein	
	AH	US-3,145,713	08-25-1964	Latham, Jr.	
	AI	US-3,239,136	03-08-1966	Hein	
	AJ	US-3,244,362	04-05-1966	Hein	
	AK	US-3,244,363	04-05-1966	Hein	
	AL	US-3,409,213	11-05-1968	Latham, Jr.	
	AM	US-3,456,875	07-22-1969	Hein	
	AN	US-3,489,145	01-13-1970	Judson et al.	
	AO	US-3,565,330	02-23-1971	Latham, Jr.	
	AP	US-3,655,058	04-11-1972	Novak	
	AQ	US-3,737,096	06-05-1973	Jones et al.	
	AR	US-3,774,840	11-27-1973	Boatright	
	AS	US-3,987,961	10-26-1976	Sinn et al.	
	AT	US-4,007,871	02-15-1977	Jones et al.	
	AU	US-4,010,894	03-08-1977	Kellogg et al.	
	AV	US-4,014,497	03-29-1977	Spiewok et al.	
	AW	US-4,040,965	08-09-1977	Kohlheb	
	AX	US-4,056,224	11-01-1977	Lolachi	
	AY	US-4,082,217	04-04-1978	Westberg	
	AZ	US-4,086,924	05-02-1978	Latham, Jr.	
	AA1	US-4,140,268	02-20-1979	Lacour	
	AB1	US-4,142,670	03-06-1979	Ishimaru et al.	
	AC1	US-4,151,844	05-01-1979	Cullis et al.	
	AD1	US-4,197,847	04-15-1980	Djerassi	
	AE1	US-4,285,464	08-25-1981	Latham, Jr.	
	AF1	US-4,300,717	11-17-1981	Latham, Jr.	
	AG1	US-4,303,193	12-01-1981	Latham, Jr.	
	AH1	US-4,321,921	03-30-1982	Laszczower	
	AI1	US-4,387,848	06-14-1983	Kellogg et al.	
	AJ1	US-4,425,114	01-10-1984	Schoendorfer et al.	
	AK1	US-4,430,072	02-07-1984	Kellogg et al.	
	AL1	US-4,447,221	05-08-1984	Mulzet	
	AM1	US-4,457,747	07-03-1984	Tu	
	AN1	US-4,464,167	08-07-1984	Schoendorfer et al.	
	AO1	US-4,466,888	08-21-1984	Verkaart	
	AP1	US-4,482,342	11-13-1984	Lueptow et al.	
	AQ1	US-4,490,135	12-25-1984	Troutner	
	AR1	US-4,530,691	07-23-1985	Brown	
	AS1	US-4,534,863	08-13-1985	Bacon et al.	

Examiner Signature	/LESLIE R DEAK/ (10/28/2019)	Date Considered	10/28/2019

ME1 28965507v.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /L.R.D/

Used in Lieu of PTO/SB/08A/B
(Based on PTO 10-07 version)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/608,183
				Filing Date	May 30, 2017
				First Named Inventor	Michael Ragusa
				Art Unit	3781
(Use as many sheets as necessary)				Examiner Name	T. Zalukaeva
Sheet	2	of	6	Attorney Docket Number	130670-08002

	AT1	US-4,643,714	02-17-1987	Brose	
	AU1	US-4,647,279	03-03-1987	Mulzet et al.	
	AV1	US-4,655,742	04-07-1987	Vantard	
	AW1	US-4,680,025	07-14-1987	Kruger et al.	
	AX1	US-4,684,361	08-04-1987	Feldman et al.	
	AY1	US-4,692,136	09-08-1987	Feldman et al.	
	AZ1	US-4,708,712	11-24-1987	Mulzet	
	AA2	US-4,713,176	12-15-1987	Schoendorfer et al.	
	AB2	US-4,734,089	03-29-1988	Cullis	
	AC2	US-4,740,202	04-26-1988	Stacey et al.	
	AD2	US-4,740,313	04-26-1988	Schoendorfer et al.	
	AE2	US-4,755,300	07-05-1988	Fischel et al.	
	AF2	US-4,767,396	08-30-1988	Powers	
	AG2	US-4,795,419	01-03-1989	Yawn et al.	
	AH2	US-4,795,448	01-03-1989	Stacey et al.	
	AI2	US-4,806,247	02-21-1989	Schoendorfer et al.	
	AJ2	US-4,806,252	02-21-1989	Brown et al.	
	AK2	US-4,808,307	02-28-1989	Fischel et al.	
	AL2	US-4,850,995	07-25-1989	Tie et al.	
	AM2	US-4,869,812	09-26-1989	Schoendorfer et al.	
	AN2	US-4,871,462	10-03-1989	Fischel et al.	
	AO2	US-4,876,013	10-24-1989	Shmidt et al.	
	AP2	US-4,889,524	12-26-1989	Fell et al.	
	AQ2	US-4,911,833	03-27-1990	Schoendorfer et al.	
	AR2	US-4,934,995	06-19-1990	Cullis	
	AS2	US-4,940,543	07-10-1990	Brown et al.	
	AT2	US-4,943,273	07-24-1990	Pages	
	AU2	US-4,968,295	11-06-1990	Neumann	
	AV2	US-4,983,156	01-08-1991	Knelson	
	AW2	US-4,983,158	01-08-1991	Headley	
	AX2	US-4,985,153	01-15-1991	Kuroda et al.	
	AY2	US-4,994,188	02-19-1991	Prince	
	AZ2	US-5,039,401	08-13-1991	Columbus et al.	
	AA3	US-5,045,048	09-03-1991	Kaleskas et al.	
	AB3	US-5,098,372	03-24-1992	Jonsson	
	AC3	US-5,098,373	03-24-1992	Polaschegg	
	AD3	US-5,100,372	03-31-1992	Headley	
	AE3	US-5,100,564	03-31-1992	Pall et al.	
	AF3	US-5,112,298	05-12-1992	Prince et al.	
	AG3	US-5,114,396	05-19-1992	Unger et al.	
	AH3	US-5,135,667	08-04-1992	Schoendorfer	
	AI3	US-5,141,486	08-25-1992	Antwiler	
	AJ3	US-5,147,290	09-15-1992	Jonsson	
	AK3	US-5,154,716	10-13-1992	Bauman et al.	
	AL3	US-5,174,894	12-29-1992	Ohsawa et al.	
	AM3	US-5,194,145	03-16-1993	Schoendorfer	
	AN3	US-5,217,426	06-08-1993	Bacehowski et al.	
	AO3	US-5,217,427	06-08-1993	Cullis	
	AP3	US-5,234,403	08-10-1993	Yoda et al.	

Examiner Signature	/LESLIE R DEAK/ (10/28/2019)	Date Considered	10/28/2019

ME1 28965507v.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /L.R.D/

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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/608,183
				Filing Date	May 30, 2017
				First Named Inventor	Michael Ragusa
				Art Unit	3781
(Use as many sheets as necessary)				Examiner Name	T. Zalukaeva
Sheet	3	of	6	Attorney Docket Number	130670-08002

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/608,183
				Filing Date	May 30, 2017
				First Named Inventor	Michael Ragusa
				Art Unit	3781
(Use as many sheets as necessary)				Examiner Name	T. Zalukaeva
Sheet	4	of	6	Attorney Docket Number	130670-08002

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 5 of 6

Complete if Known	
Application Number	15/608,183
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First Named Inventor	Michael Ragusa
Art Unit	3781
Examiner Name	T. Zalukaeva
Attorney Docket Number	130670-08002

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Examiner Signature	/LESLIE R DEAK/ (10/28/2019)	Date Considered	10/28/2019

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(Based on PTO 10-07 version)

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	15/608,183
				Filing Date	May 30, 2017
				First Named Inventor	Michael Ragusa
				Art Unit	3781
				Examiner Name	T. Zalukaeva
Sheet	6	of	6	Attorney Docket Number	130670-08002

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Haemonetics Nomogram - Male, 2 pages, May 1990.	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature	/LESLIE R DEAK/ (10/28/2019)	Date Considered	10/28/2019

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /L.R.D/

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	183	("20010000185" | "20020062100" | "1025059" | "1611725" | "20010027156" | "20020043492" | "20020120227" | "20030055375" | "20030066807" | "20030125881" | "20030175150" | "20040186409" | "20050209522" | "20050235733" | "20060058167" | "20060155236" | "20070112289" | "20080146993" | "20120175313" | "20140039373" | "20140356851" | "20180344921" | "2087778" | "2661150" | "2750107" | "2792172" | "3096283" | "3145713" | "3239136" | "3244362" | "3244363" | "3409213" | "3456875" | "3489145" | "3565330" | "3655058" | "3737096" | "3774840" | "3987961" | "4007871" | "4010894" | "4014497" | "4040965" | "4056224" | "4082217" | "4086924" | "4140268" | "4142670" | "4151844" | "4197847" | "4285464" | "4300717" | "4303193" | "4321921" | "4387848" | "4425114" | "4430072" | "4447221" | "4457747" | "4464167" | "4466888" | "4482342" | "4490135" | "4530691" | "4534863" | "4643714" | "4647279" | "4655742" | "4680025" | "4684361" | "4692136" | "4708712" | "4713176" | "4734089" | "4740202" | "4740313" | "4755300" | "4767396" | "4795419" | "4795448" | "4806247" | "4806252" | "4808307" | "4850995" | "4869812" | "4871462" | "4876013" | "4889524" | "4911833" | "4934995" | "4940543" | "4943273" | "4968295" | "4983156" | "4983158" | "4985153" | "4994188" | "5039401" | "5045048" | "5098372" | "5098373" | "5100372" | "5100564" | "5112298" | "5114396" | "5135667" | "5141486" | "5147290" | "5154716" | "5174894" | "5194145" | "5217426" | "5217427" | "5234403" | "5254248" | "5273517" | "5277701" | "5298016" | "5298171" | "5300060" | "5316540" | "5318511" | "5318512" | "5348533" | "5368542" | "5368555" | "5386734" | "5387174" | "5387187" | "5403272" | "5405308" | "5417650" | "5431814" | "5437598" | "5437624" | "5462667" | "5470483" | "5484396" | "5494592" | "5505685" | "5514070" | "5543062" | "5551941" | "5585007" | "5607579" | "5649903" | "5651766" | "5656163" | "5665061" | "5712798" |	US-PGPUB; USPAT	OR	OFF	2019/10/28 12:37

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Petitioner Terumo Exhibit 1021-0115

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Petitioner Terumo Exhibit 1021-0116

		A61M2230/207 OR G01N15/05 OR G01N2015/055 OR G01N15/042 OR G01N33/86).CPC.)	USOCR; DERWENT			
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S13	1	"I10" and (hematocrit with anticoagulant)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:30
S14	2	"I10" and (hematocrit same anticoagulant)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:30
S15	44	((("RAGUSA") near3 ("Michael"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/10/28 12:31
S16	2	"I15" and (hematocrit same anticoagulant)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2019/10/28 12:31

EAST Search History (Interference)

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Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0117

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	15608183
Filing Date	2017-05-30
First Named Inventor	Michael Ragusa
Art Unit	3781
Examiner Name	T. Zalukaeva
Attorney Docket Number	130670-08002

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Petitioner Terumo Exhibit 1021-0118

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15608183
	Filing Date	2017-05-30
	First Named Inventor	Michael Ragusa
	Art Unit	3781
	Examiner Name	T. Zalukaeva
	Attorney Docket Number	130670-08002

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		

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Examiner Signature	/LESLIE R DEAK/ (10/28/2019)	Date Considered	10/28/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /L.R.D/

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0119

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15608183
	Filing Date	2017-05-30
	First Named Inventor	Michael Ragusa
	Art Unit	3781
	Examiner Name	T. Zalukaeva
	Attorney Docket Number	130670-08002

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jonathan C. Lovely, Reg. No. 60,821/	Date (YYYY-MM-DD)	2019-02-01
Name/Print	Jonathan C. Lovely	Registration Number	60,821

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /L.R.D/

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0120

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /L.R.D/

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0121

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	15608183
	Filing Date	2017-05-30
	First Named Inventor	Michael Ragusa
	Art Unit	3781
	Examiner Name	T. Zalukaeva
	Attorney Docket Number	130670-08002

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20010000185	A1	2001-04-05	Keller et al.	
	2	20020062100	A1	2002-05-23	Pierce et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

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NON-PATENT LITERATURE DOCUMENTS Remove

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0122

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15608183
	Filing Date	2017-05-30
	First Named Inventor	Michael Ragusa
	Art Unit	3781
	Examiner Name	T. Zalukaeva
	Attorney Docket Number	130670-08002

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0123

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15608183
	Filing Date	2017-05-30
	First Named Inventor	Michael Ragusa
	Art Unit	3781
	Examiner Name	T. Zalukaeva
	Attorney Docket Number	130670-08002

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jonathan C. Lovely, Reg. No. 60,821/	Date (YYYY-MM-DD)	2019-02-01
Name/Print	Jonathan C. Lovely	Registration Number	60,821

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0124

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0125

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: February 1, 2019
Electronic Signature for Jonathan C. Lovely: /Jonathan C. Lovely, Reg. No. 60,821/

Docket No.: 130670-08002
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Michael Ragusa

Application No.: 15/608,183 | Confirmation No.: 7286

Filed: May 30, 2017 | Art Unit: 3781

For: SYSTEM AND METHOD FOR COLLECTING PLASMA | Examiner: T. Zalukaeva

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (SIDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Supplemental Information Disclosure Statement is filed before the mailing date of a first Office Action on the merits as far as is known to the undersigned (37 C.F.R. § 1.97(b)(3)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0126

37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Applicant believes no fee is due with this response.

Dated: February 1, 2019

Respectfully submitted,

Electronic signature: /Jonathan C. Lovely, Reg. No. 60,821/
Jonathan C. Lovely
Registration No.: 60,821
MCCARTER & ENGLISH, LLP
265 Franklin Street
Boston, Massachusetts 02110
(617) 449-6500
(617) 607-9200 (Fax)
Attorney/Agent For Applicant

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0127

Electronic Acknowledgement Receipt

EFS ID:	35033193
Application Number:	15608183
International Application Number:	
Confirmation Number:	7286
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Customer Number:	86738
Filer:	Jonathan Lovely
Filer Authorized By:	
Attorney Docket Number:	130670-08002
Receipt Date:	01-FEB-2019
Filing Date:	30-MAY-2017
Time Stamp:	14:24:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	130670-08002_-_Information_Disclosure_Statement_Fillable_PDF.pdf	1034413 6eb7692e7e4ad2775b186449c2e4e9491868e7e9	no	4

Warnings:

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0128

Information:					
2	Transmittal Letter	IDS_Letter.pdf	23024 7d8b81ccd002b7724875ff086967a02245bcb76f	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1057437	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Used in Lieu of PTO/SB/08A/B
(Based on PTO 10-07 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 6

Complete if Known	
Application Number	15/608,183
Filing Date	May 30, 2017
First Named Inventor	Michael Ragusa
Art Unit	3781
Examiner Name	T. Zalukaeva
Attorney Docket Number	130670-08002

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-1,025,059	04-30-1912	Hatton et al.	
	AB	US-1,611,725	12-21-1926	Degerth et al.	
	AC	US-2,087,778	07-20-1937	Nelin	
	AD	US-2,661,150	12-01-1953	Abbott, Jr.	
	AE	US-2,750,107	06-12-1956	More	
	AF	US-2,792,172	05-14-1957	Tait	
	AG	US-3,096,283	07-02-1963	Hein	
	AH	US-3,145,713	08-25-1964	Latham, Jr.	
	AI	US-3,239,136	03-08-1966	Hein	
	AJ	US-3,244,362	04-05-1966	Hein	
	AK	US-3,244,363	04-05-1966	Hein	
	AL	US-3,409,213	11-05-1968	Latham, Jr.	
	AM	US-3,456,875	07-22-1969	Hein	
	AN	US-3,489,145	01-13-1970	Judson et al.	
	AO	US-3,565,330	02-23-1971	Latham, Jr.	
	AP	US-3,655,058	04-11-1972	Novak	
	AQ	US-3,737,096	06-05-1973	Jones et al.	
	AR	US-3,774,840	11-27-1973	Boatright	
	AS	US-3,987,961	10-26-1976	Sinn et al.	
	AT	US-4,007,871	02-15-1977	Jones et al.	
	AU	US-4,010,894	03-08-1977	Kellogg et al.	
	AV	US-4,014,497	03-29-1977	Spiewok et al.	
	AW	US-4,040,965	08-09-1977	Kohlheb	
	AX	US-4,056,224	11-01-1977	Lolachi	
	AY	US-4,082,217	04-04-1978	Westberg	
	AZ	US-4,086,924	05-02-1978	Latham, Jr.	
	AA1	US-4,140,268	02-20-1979	Lacour	
	AB1	US-4,142,670	03-06-1979	Ishimaru et al.	
	AC1	US-4,151,844	05-01-1979	Cullis et al.	
	AD1	US-4,197,847	04-15-1980	Djerassi	
	AE1	US-4,285,464	08-25-1981	Latham, Jr.	
	AF1	US-4,300,717	11-17-1981	Latham, Jr.	
	AG1	US-4,303,193	12-01-1981	Latham, Jr.	
	AH1	US-4,321,921	03-30-1982	Laszczower	
	AI1	US-4,387,848	06-14-1983	Kellogg et al.	
	AJ1	US-4,425,114	01-10-1984	Schoendorfer et al.	
	AK1	US-4,430,072	02-07-1984	Kellogg et al.	
	AL1	US-4,447,221	05-08-1984	Mulzet	
	AM1	US-4,457,747	07-03-1984	Tu	
	AN1	US-4,464,167	08-07-1984	Schoendorfer et al.	
	AO1	US-4,466,888	08-21-1984	Verkaart	
	AP1	US-4,482,342	11-13-1984	Lueptow et al.	
	AQ1	US-4,490,135	12-25-1984	Troutner	
	AR1	US-4,530,691	07-23-1985	Brown	
	AS1	US-4,534,863	08-13-1985	Bacon et al.	

Examiner Signature		Date Considered	

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0130

Used in Lieu of PTO/SB/08A/B
(Based on PTO 10-07 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 6

Complete if Known	
Application Number	15/608,183
Filing Date	May 30, 2017
First Named Inventor	Michael Ragusa
Art Unit	3781
Examiner Name	T. Zalukaeva
Attorney Docket Number	130670-08002

	AT1	US-4,643,714	02-17-1987	Brose	
	AU1	US-4,647,279	03-03-1987	Mulzet et al.	
	AV1	US-4,655,742	04-07-1987	Vantard	
	AW1	US-4,680,025	07-14-1987	Kruger et al.	
	AX1	US-4,684,361	08-04-1987	Feldman et al.	
	AY1	US-4,692,136	09-08-1987	Feldman et al.	
	AZ1	US-4,708,712	11-24-1987	Mulzet	
	AA2	US-4,713,176	12-15-1987	Schoendorfer et al.	
	AB2	US-4,734,089	03-29-1988	Cullis	
	AC2	US-4,740,202	04-26-1988	Stacey et al.	
	AD2	US-4,740,313	04-26-1988	Schoendorfer et al.	
	AE2	US-4,755,300	07-05-1988	Fischel et al.	
	AF2	US-4,767,396	08-30-1988	Powers	
	AG2	US-4,795,419	01-03-1989	Yawn et al.	
	AH2	US-4,795,448	01-03-1989	Stacey et al.	
	AI2	US-4,806,247	02-21-1989	Schoendorfer et al.	
	AJ2	US-4,806,252	02-21-1989	Brown et al.	
	AK2	US-4,808,307	02-28-1989	Fischel et al.	
	AL2	US-4,850,995	07-25-1989	Tie et al.	
	AM2	US-4,869,812	09-26-1989	Schoendorfer et al.	
	AN2	US-4,871,462	10-03-1989	Fischel et al.	
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Examiner Signature		Date Considered	

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Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0131

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

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Complete if Known	
Application Number	15/608,183
Filing Date	May 30, 2017
First Named Inventor	Michael Ragusa
Art Unit	3781
Examiner Name	T. Zalukaeva
Attorney Docket Number	130670-08002

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Examiner Signature		Date Considered	

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0132

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet	4	of	6

Complete if Known	
Application Number	15/608,183
Filing Date	May 30, 2017
First Named Inventor	Michael Ragusa
Art Unit	3781
Examiner Name	T. Zalukaeva
Attorney Docket Number	130670-08002

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Petitioner Terumo Exhibit 1021-0133

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	15/608,183
				Filing Date	May 30, 2017
				First Named Inventor	Michael Ragusa
				Art Unit	3781
				Examiner Name	T. Zalukaeva
Sheet	5	of	6	Attorney Docket Number	130670-08002

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	15/608,183
				Filing Date	May 30, 2017
				First Named Inventor	Michael Ragusa
				Art Unit	3781
(Use as many sheets as necessary)				Examiner Name	T. Zalukaeva
Sheet	6	of	6	Attorney Docket Number	130670-08002

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Haemonetics Nomogram - Male, 2 pages, May 1990.	
	CB	LEMMENS et al., Estimating blood volume in obese and morbidly obese patients. Obes Surg. 2006 Jun;16(6):773-6.	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature		Date Considered	

ME1 28965507v.1

Docket No.: 130670-08002
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Michael Ragusa

Application No.: 15/608,183	Confirmation No.: 7286
Filed: May 30, 2017	Art Unit: 3781
For: SYSTEM AND METHOD FOR COLLECTING PLASMA	Examiner: T. Zalukaeva

INFORMATION DISCLOSURE STATEMENT (IDS)

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a first Office Action on the merits as far as is known to the undersigned (37 C.F.R. § 1.97(b)(3)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0136

The Examiner is advised that the following co-pending application contains subject matter that may be related to the present application:

U.S. Application	Filing Date	Publication No. / Patent No.	Status	Atty. Docket No.
15/793,339	October 25, 2017	2018-0344921	Published	130670-08003

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Applicant believes no fee is due with this response.

Dated: January 10, 2019

Respectfully submitted,
Electronic signature: /Jonathan C. Lovely, Reg. No. 60,821/
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Terumo v. Haemonetics - PGR2025-00077
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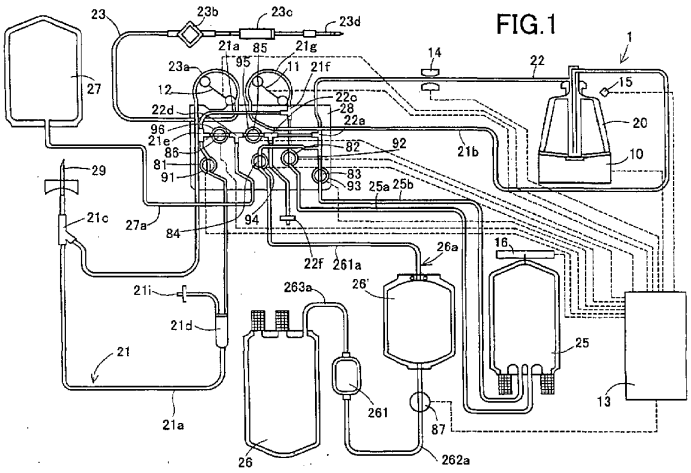
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(54) BLOOD COMPONENT COLLECTIG DEVICE

(57) An object is to provide a blood component collection system capable of collecting a desired blood component of high quality. A blood component collection system 1 comprises a centrifugal separator 20 centrifuging blood into a plurality of components, first line 21 for feeding the blood to the centrifugal separator 20, a second line 22 for releasing the blood component from the centrifugal separator 20, a temporary reservoir bag 26' for temporarily reserving the platelet concentrate, a leukoreduction filter 261 for separating and reducing leukocyte from the platelet concentrate, and a platelet collection bag 26 for reserving the platelet concentrate having passed through the leukoreduction filter 261. The blood component collection system 1 is constructed to feed the platelet concentrate in the temporary reservoir bag 26' to the platelet collection bag 26 through the leukoreduction filter 261, and then, feed plasma and collect the platelet remaining in the leukoreduction filter 261 (platelet concentrate from which leukocyte have been reduced) together with the plasma into the platelet collection bag 26.

FIG.1



EP 1 374 927 A1

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Description

Technical Field

[0001] The present invention relates to a blood component collection system for separating blood into a plurality of components and collecting any of the separated components.

Background Art

[0002] To collect blood, currently, blood component collection is adopted for the purposes of effectively utilizing blood and alleviating a burden a donor must incur. Namely, the collected blood is separated into components through centrifugation or the like, only a component needed for a patient to be transfused is collected, and the other components are restored to a donor.

[0003] In the component collection, for preparing a platelet product, blood collected from a donor is routed to a blood component collection circuit. A centrifugal separator called a centrifugal bowl included in the blood component collection circuit is used to separate the blood into components, that is, plasma, a buffy coat, and red blood cells. Platelets are separated from the buffy coat and collected into a container, whereby a platelet product is prepared. The remaining plasma, white blood cells, and red blood cells are returned to the donor.

[0004] However, according to the above method, when a large number of platelets is needed, the number of leukocyte (white blood cells) mixed in a platelet product increases. This leads to an increase in the risk of an attack of fever, alloimmunization, virus infection, or the like.

[0005] In efforts to cope with the above problem, proposals have been made of a method according to which collected platelets are passed through a leukoreduction filter (leukocyte removal filter) in order to separate or reduce leukocyte, and the platelets separated from the leukocyte are collected in order to prepare a leukocyte reduced platelet product. In this case, platelets remain in the leukoreduction filter. In order to improve the yield of platelets, the leukoreduction filter is cleansed using a cleanser such as physiological saline or an anticoagulant.

[0006] However, according to the above method, the cleanser is mixed in the platelet product. This poses a problem that the quality of the platelet product is degraded.

Disclosure of Invention

[0007] An object of the present invention is to provide a blood component collection system capable of collecting a desired blood component of high quality.

[0008] To achieve the above object, the present invention provides a blood component collection system comprising: a centrifugal separator including a rotor having a blood reservoir space therein and an inlet and an outlet which communicate with the blood reservoir space, and centrifuging blood introduced through the inlet by rotation of the rotor, into a plurality of components in the blood reservoir space; a first container for temporarily reserving therein a first blood component; a cell separating filter for separating or reducing a predetermined kind of cells from the first blood component; and a second container for reserving the first blood component having passed through the cell separating filter, wherein the blood component collection system further comprises: channel open/close means for opening or closing a channel linking the first container and the cell separating filter; and control means for controlling action of the channel open/close means, the channel open/close means is used to carry the first blood component in the first container to the second container through the cell separating filter, then supply a second blood component, and collect the first blood component, from which the predetermined kind of cells remaining in the cell separating filter have been separated or reduced, together with the second blood component into the second container.

[0009] According to another aspect, the present invention provides a blood component collection system comprising: a centrifugal separator including a rotor having a blood reservoir space therein and an inlet and an outlet which communicate with the blood reservoir space, and centrifuging blood introduced through the inlet by rotation of the rotor, into a plurality of components in the blood reservoir space; a first container for temporarily reserving therein a first blood component; a cell separating filter connected to the first container through a feed tube, and used to separate or reduce a predetermined kind of cells from the first blood component fed through the feed tube; and a second container which is connected to the cell separating filter through a release tube and used for reserving therein the first blood component having passed through the cell separating filter, wherein the blood component collection system further comprises: channel open/close means for opening or closing a channel of the feed tube; and control means for controlling action of the channel open/close means, the channel open/close means is used to carry the first blood component in the first container to the second container through the feed tube, cell separating filter, and release tube in response to a command sent from the control means, thereafter, a second blood component is fed, and the first blood component that remains in the cell separating filter and the channel of the release tube and that has the predetermined

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cells separated or reduced therefrom is collected together with the second blood component into the second container.

[0010] Preferably, in the blood component collection system according to the present invention, a full amount of a blood component to be collected into the second container is adjusted according to a fed amount of the second blood component. Specifically, the fed amount of the second blood component is determined based on a difference between a target full amount of the blood component to be collected into the second container and an amount of the first blood component to be carried to the second container.

[0011] More preferably, the blood component collection system according to the present invention further includes a third container for reserving the second blood component, wherein the second blood component is fed from the third container.

[0012] Preferably, in the blood component collection system according to the present invention, the second blood component is fed together with the first blood component which remains in the first container, to the cell separating filter.

[0013] More preferably, in the blood component collection system according to the present invention, the first blood component is plasma containing platelets, the second blood component is plasma, ant the cell separating filter is a leukoreduction filter.

Brief Description of the Drawings

[0014]

Fig. 1 is a plan view showing the configuration of a blood component collection system according to the present invention;

Fig. 2 is a partly cutaway sectional view showing a state in which a centrifugal separator drive is mounted on a centrifugal separator included in the blood component collection system;

Fig. 3 is a timing chart for explaining the operation of the blood component collection system according to the present invention;

Fig. 4 is a flowchart describing the operation of the blood component collection system according to the present invention;

Fig. 5 is a flowchart describing the operation of the blood component collection system according to the present invention;

Fig. 6 is a flowchart describing the operation of the blood component collection system according to the present invention;

Fig. 7 is a flowchart describing the operation of the blood component collection system according to the present invention; and

Fig. 8 is a flowchart describing actions to be performed for cleansing a line in the blood component collection system according to the present invention.

Best Mode for Carrying Out the Invention

[0015] A blood component collection system according to the present invention will be detailed in conjunction with a preferred embodiment shown in the drawings below.

[0016] Fig. 1 is a plan view showing the configuration of the blood component collection system according to the present invention. Fig. 2 is a partly cutaway sectional view showing a state in which a centrifugal separator drive is mounted on a centrifugal separator included in the blood component collection system. Fig. 3 is a timing chart for explaining the operation of the blood component collection system according to the present invention. Furthermore, Fig. 4 to Fig. 7 are flowcharts describing the operation of the blood component collection system according to the present invention. Fig. 8 is a flowchart describing the actions the blood component collection system according to the present invention performs for cleansing a line.

[0017] The blood component collection system 1 shown in Fig. 1 is a system for separating blood into a plurality of components and collecting any of the separated components (especially platelets). The blood component collection system 1 comprises a centrifugal separator 20 and a blood component collection circuit 2. The centrifugal separator 20 includes a rotor 142 having a blood reservoir space 146 therein and an inlet 143 and an outlet 144 which communicate with the blood reservoir space 146, and centrifuges the blood, which is introduced through the inlet 143 by rotation of the rotor 142, within the blood reservoir space 146. The blood component collection circuit 2 comprises: a first line 21 that links a blood collection needle 29 and the inlet 143 of the centrifugal separator 20; a second line 22 joined to the outlet 144 of the centrifugal separator 20; a third line 23 joined to the first line 21; a plasma collection bag 25 having a first tube 25a joined to the first line 21 and having a second tube 25b joined to the second line 22; a platelet collection bag 26 having a third tube 26a joined to the second line 22; and a buffy coat collection bag 27 having a fourth tube 27a joined to the second line 22.

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[0018] Furthermore, the blood component collection system 1 comprises: a centrifugal separator drive 10 which rotates the rotor 142 included in the centrifugal separator 20; a first fluid feeder pump 11 for the first line 21; a second fluid feeder pump 12 for the third line 23; a plurality of pieces of channel open/close means 81, 82, 83, 84, 85, 86, and 87 that is used to open or close the middle points of channels defined by the blood component collection circuit 2; a control unit (control means) 13 which controls the centrifugal separator drive 10, first fluid feeder pump 11, second fluid feeder pump 12, and plurality of pieces of channel open/close means 81 to 87; a turbidity sensor 14; an optical sensor 15; and a weight sensor 16.

[0019] To begin with, the blood component collection circuit 2 will be described below.

[0020] The blood component collection circuit 2 comprises: the first line (blood collection/return line) 21 that links the blood collection needle (blood collecting means) 29 used to collect blood and the inlet 143 of the centrifugal separator 20, and that includes a first pump tube 21g; the second line 22 that links the outlet 144 of the centrifugal separator 20 and the first line 21; the third line (anticoagulant injection line) 23 that is located near the blood collection needle 29 included in the first line 21 and that includes a second pump tube 23a; the plasma collection bag 25 that has the first tube 25a connected on the side of the blood component collection circuit 2 near the blood collection needle 29 beyond the pump tube 21g included in the first line 21, and has the second tube 25b joined to the second line 22; the platelet collection bag 26 that has the third tube 26a joined to the second line 22; and the buffy coat collection bag 27 that has a fourth tube 27a joined to the second line 22.

[0021] Incidentally, the blood collecting means is not limited to the blood collection needle 29. Alternatively, a connector (for example, a metallic or synthetic resin needle) coupled to a blood bag or any other blood pool will do.

[0022] As the blood collection needle 29, for example, a known metallic needle is adopted.

[0023] The first line 21 includes a first blood collection needle-side line 21a joined to the blood collection needle 29 and a first centrifugal separator-side line 21b joined to the inlet 143 of the centrifugal separator 20.

[0024] The first blood collection needle-side line 21a has a plurality of soft resin tubes concatenated. The first blood collection needle-side line 21a includes: orderly from the side thereof near the centrifugal separator 20, a branch connector 21c that joins the first blood collection needle-side line 21a and the third line 23; a chamber 21d used to remove bubbles or micro-aggregates; a branch connector 21e that joins the first blood collection needle-side line 21a and the second line 22; and a branch connector 21f that joins the first blood collection needle-side line 21a and the first tube 25a extending from the plasma collection bag 25.

[0025] Moreover, an air-permeable and bacteria-impermeable filter 21i is connected to the chamber 21d.

[0026] On the other hand, the first centrifugal separator-side line 21b is coupled to the branch connector 21f that joins the first blood collection needle-side line 21a and the first tube 25a, and includes the first pump tube 21g located near the connector.

[0027] The second line 22 that links the outlet 144 of the centrifugal separator 20 and the first line 21 has one end thereof coupled to the outlet 144 of the centrifugal separator 20 and the other end thereof coupled to the branch connector 21e of the first line 21.

[0028] The second line 22 includes: a branch connector 22a that joins the second line 22, the second tube 25b extending from the plasma collection bag 25, and the third tube 26a extending from the platelet collection bag 26; a branch connector 22c that joins the second line 22 and a tube including a bubble removing filter 22f; and a branch connector 22d that joins the second line 22 and the fourth tube 27a extending from the buffy coat collection bag 27.

[0029] The third line 23 has one end thereof coupled to the branch connector 21c included in the first line 21.

[0030] The third line 23 includes, orderly from the side thereof coupled to the branch connector 21c, the second pump tube 23a, a bacteria removal filter 23b, a bubble removing chamber 23c, and an anticoagulant container joint needle 23d.

[0031] The plasma collection bag (third container) 25 is a container into which plasma (second blood component) is collected (reserved). The plasma collection bag 25 has the first tube 25a coupled to the branch connector 21f which is located on the side of the blood component collection circuit near the blood collection needle 29 beyond the pump tube 21g included in the first line 21. The plasma collection bag 25 also has the second tube 25b coupled to the branch connector 22a included in the second line 22. Namely, the plasma collection bag 25 and second tube 25b constitute a plasma collection branch line used to collect plasma.

[0032] The platelet collection bag (second container) 26 is a container into which plasma containing platelets (first blood component) and having passed through a leukoreduction filter 261 that will be described later. The platelet collection bag 26 has the third tube 26a coupled to the branch connector 22a included in the second line 22. Hereinafter, plasma containing platelets (first blood component) shall be called "platelet concentrate (PC)", and the platelet concentrate (PC) collected (reserved) into the platelet collection bag 26 shall be called "a platelet product".

[0033] Moreover, a temporary reservoir bag (first container) 26' in which the platelet concentrate (first blood component) is temporarily reserved, and the leukoreduction filter (cell separating filter) 261 that separates or reduce leukocyte (predetermined kind of cells) from the platelet concentrate are inserted into the third tube 26a.

[0034] In short, the third tube 26a is composed of three tubes 261a, 262a, and 263a. The tube 261a links the branch

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connector 22a and the temporary reservoir bag 26'. The tube 262a links the temporary reservoir bag 26' and leukoreduction filter 261. The tube 263a links the leukoreduction filter 261 and the platelet (platelet product) collection bag 26.

[0035] The tube 262a serves as a feed tube that feeds platelet concentrate from the temporary reservoir bag 26' to the leukoreduction filter. The tube 263a serves as a release tube that releases the platelet concentrate, which has leukocyte reduced therefrom, from the leukoreduction filter 261 (feeds the platelet concentrate to the platelet collection bag 26).

[0036] In other words, the third tube 26 (composed of the tubes 261a, 262a, and 263a), temporary reservoir bag 26', leukoreduction filter 261, and platelet collection bag 26 constitute a platelet collection branch line that collects platelets (platelet product).

[0037] Moreover, the temporary reservoir bag 26', leukoreduction filter 261, and platelet collection bag 26 are positioned with the blood component collection system 1 constructed so that the leukoreduction filter 261 will be located at a lower position than the temporary reservoir bag 26' is and the platelet collection bag 26 will be located at a lower position than the leukoreduction filter 261 is.

[0038] Moreover, what is used as the leukoreduction filter 261 is, for example, a filter formed by inserting a filtration member into a casing having an inlet and an outlet formed at both ends thereof. The filtration member has one or two layers of a porous substance such as woven cloth, non-woven cloth, mesh, or foam made of a synthetic resin such as polypropylene, polyester, polyurethane, or polyamide.

[0039] The buffy coat collection bag 27 is a container into which a buffy coat is collected. The buffer coat bag 27 has the fourth tube 27a coupled to the branch connector 22d included in the second line 22. Namely, the buffy coat collection bag 27 and fourth tube 27a constitute a buffy coat collection branch line that collects buffy coat.

[0040] Preferably, the tubes used to form the first to third lines 21 to 23, pump tubes 21g and 23a, and the tubes 25a, 25b, 26a (composed of the tubes 261a, 262a, and 263a), and 27a coupled to the bags 25 to 27 are made of polyvinyl chloride.

[0041] When the tubes are made of polyvinyl chloride, satisfactory flexibility and softness are ensured. The tubes are therefore easy to handle. Moreover, the tubes can be readily blocked using a clamp or the like.

[0042] Moreover, the same material as the material made into the tubes can be adopted as the material to be made into the branch connectors 21c, 21e, 21f, 22a, 22c, and 22d.

[0043] What are used as the pump tubes 21g and 23a are tubes that are strong enough to remain undamaged even when pressurized by the fluid feeder pumps 11 and 12 (for example, roller pumps) to be described later.

[0044] What are used as the plasma collection bag 25, platelet collection bag 26, temporary reservoir bag 26', and buffy coat collection bag 27 are made by layering a flexible resin sheet material and fusing the margins of the layers (through heat fusion, high-frequency fusion, or ultrasonic fusion) in the form of a sac or bonding them using an adhesive in the form thereof.

[0045] The material to be made into the bags 25 to 27 and 26' is, for example, soft polyvinyl chloride.

[0046] Preferably, the sheet material used to make the platelet collection bag 26 is a material superb in gas permeability in terms of improvement of the ability to reserve platelets in good condition.

[0047] Preferably, the sheet material is made of, for example, polyolefin or DnDP flexible polyvinyl chloride. Otherwise, the above resin flexible sheet material may be adopted and made relatively thin (for example, the thickness ranges from about 0.1 mm to about 0.5 mm, or more particularly, from about 0.1 mm to about 0.3 mm).

[0048] Moreover, a platelet preservative, for example, GAC, PAS, or PSM-1 may be poured into the plasma collection bag 26 in advance.

[0049] The major elements of the blood component collection circuit 2 are, as shown in Fig. 1, provided as cassettes. Namely, the blood component collection circuit 2 has the lines (first line 21, second line 22, and third line 23) and the tubes (first tube 25a, second tube 25b, third tube 26a, and fourth tube 27a) partly stored and preserved, or in other words, partly locked in a cassette housing 28.

[0050] Both the ends of the first pump tube 21g and both the ends of the second pump tube 23a are locked in the cassette housing 28. The pump tubes 21g and 23a are projected from the cassette housing 28 in the form of a loop in line with the shape of the fluid feeder pumps (for example, roller pumps) 11 and 12. Consequently, the first and second pump tubes 21g and 23a can be easily attached to the fluid feeder pumps 11 and 12 respectively.

[0051] Furthermore, the cassette housing 28 has a plurality of openings 91 to 96 formed therein

[0052] The centrifugal separator 20 included in the blood component collection circuit 2 is generally called a centrifugal bowl, and designed to separate blood into a plurality of components by utilizing centrifugal force.

[0053] The centrifugal separator 20 comprises, as shown in Fig. 2, a pipe 141 extending vertically and having the inlet 143 formed at the upper end thereof, and a hollow rotor 142 that rotates about the pipe 141 and is sealed off from an upper part 145 in a fluid-tight manner.

[0054] The rotor 142 has the annular blood reservoir space 146 formed along the internal surface of the circumferential wall thereof. The blood reservoir space 146 is shaped (tapered) so that the inner and outer diameters thereof will gradually diminish from the lower part thereof shown in Fig. 2 to the upper part thereof. The lower part of the blood

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reservoir space 146 communicates with the lower-end opening of the pipe 141 by way of a substantially disk-like channel formed on the bottom of the rotor 142. The upper part of the blood reservoir space 146 communicates with the outlet 144. Moreover, the volume of the blood reservoir space 146 included in the rotor 142 ranges, for example, from about 100 mL to about 350 mL. The maximum inner diameter (maximum radius) of the blood reservoir space with the axis of rotation of the rotor 142 as a center ranges, for example, from about 55 mm to about 65 mm.

[0055] The rotor 142 is rotated under predetermined conditions for centrifugation (rotating speed and rotation time) predetermined by the centrifugal separator drive 10 included in the blood component collection system 1. Under the conditions for centrifugation, a blood separation pattern (for example, the number of blood components to be separated) can be determined for blood introduced into the rotor 142.

[0056] According to the present embodiment, the conditions for centrifugation are determined so that blood will be, as shown in Fig. 2, separated into, orderly from the innermost layer, a layer of plasma 131, a buffy coat layer 132, and a layer of red blood cells 133.

[0057] Next, the overall configuration of the blood component collection system 1 shown in Fig. 1 will be described below.

[0058] The blood component collection system 1 comprises: the centrifugal separator drive 10 that rotates the rotor 142 included in the centrifugal separator 20; the first fluid feeder pump 11 located in the middle of the first line 21; the second fluid feeder pump 12 located in the middle of the third line 23; the plurality of pieces of channel open/close means 81, 82, 83, 84, 85, 86, and 87 that can open or close the middles of the channels defined by (the first line 21, second line 22, first tube 25a, second tube 25b, and third tube 26a included in) the blood component collection circuit 2; and the control unit (control means) 13 that controls the centrifugal separator drive 10, first fluid feeder pump 11, second fluid feeder pump 12, and plurality of pieces of channel open/close means 81 to 87.

[0059] Furthermore, the blood component collection system 1 comprises: the turbidity sensor 14 attached to (included in) the second line 22 on the side of the second line near the centrifugal separator 20 (upstream) beyond the connector 22a that joins the second line 22 and the second tube 25b; the optical sensor 15 located near the centrifugal separator 20; and the weight sensor 16 that measures the weight of plasma together with the weight of the plasma collection bag 25.

[0060] The control unit 13 includes two pump controllers (not shown) that control the first fluid feeder pump 11 and second fluid feeder pump 12 respectively. The control unit 13 is electrically connected to the first fluid feeder pump 11 and second fluid feeder pump 12 via the respective pump controllers.

[0061] A driving controller (not shown) included in the centrifugal separator drive 10 is electrically connected to the control unit 13.

[0062] The pieces of channel open/close means 81 to 87 are electrically connected to the control unit 13.

[0063] The turbidity sensor 14, optical sensor 15, and weight sensor 16 are electrically connected to the control unit 13.

[0064] The control unit 13 is formed with, for example, a microcomputer, and receives detection signals from the turbidity sensor 14, optical sensor 15, and weight sensor 16 respectively at any time.

[0065] Based on the detection signals received from the turbidity sensor 14, optical sensor 15, and weight sensor 16 respectively, the control unit 13 activates the components of the blood component collection system 1 according to a pre-installed program. Specifically, the control unit 13 controls the start or stop of the rotations of the fluid feeder pumps 11 and 12, and the direction of rotation (forward rotation or reverse rotation). Moreover, if necessary, the control unit 13 controls the open or close of the pieces of channel open/close means 81 to 87 and the activation of the centrifugal separator drive 10.

[0066] The first channel open/close means 81 opens or closes the first line 21 while being located on the side of the blood component collection circuit near the blood collection needle 29 beyond the first pump tube 21g.

[0067] The second channel open/close means 82 opens or closes the first tube 25a extending from the plasma collection bag 25.

[0068] The third channel open/close means 83 opens or closes the second tube 25b extending from the plasma collection bag 25.

[0069] The fourth channel open/close means 84 opens or closes the third tube 26a (tube 261a) extending from the platelet collection bag 26.

[0070] The fifth channel open/close means 85 opens or closes the second line 22 while being located on the side (upstream) of the blood component collection circuit near the centrifugal separator 20 beyond the connector (branch connector 22d) that joins the second line 22 and the fourth tube 27a extending from the buffy coat collection bag 27.

[0071] The sixth channel open/close means 86 opens or closes the second line 22 while being interposed between the connector (branch connector 21e) that joins the first line 21 and second line 22, and the connector (branch connector 22d) that joins the second line 22 and the fourth tube 27a (downstream the connector that joins the second line 22 and fourth tube 27a).

[0072] Moreover, the seventh channel open/close means 87 opens or closes the third tube 26a (tube 262a).

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[0073] The pieces of channel open/close means 81 to 87 each have an insertion member into which the first line 21, second line 22, first tube 25a, second tube 25b, or third tube 26a (tube 261a or 262a) can be inserted. The insertion member includes a clamp that is actuated by a driving source, for example, a solenoid, an electric motor, or a (hydraulic or pneumatic) cylinder. More particularly, an electromagnetic clamp to be actuated by a solenoid is preferred.

[0074] The pieces of channel open/close means (clamps) 81 to 87 are actuated based on a signal sent from the control unit 13.

[0075] The centrifugal separator drive 10 comprises, as shown in Fig. 2, a housing 201 in which the centrifugal separator 20 is stored, legs 202, a motor 203 that is a driving source, and a disk-like locking base 205 that bears the centrifugal separator 20.

[0076] The housing 201 is placed on and fixed to the tops of the legs 202. Moreover, the motor 203 is fixed to the bottom of the housing 201 using a bolt 206 with a spacer 207 between them.

[0077] The locking base 205 is engaged with the distal part of a rotation shaft 204 of the motor 203 so that the locking base 205 will be rotated concentrically and together with the rotation shaft 204. A concave part in which the bottom of the rotor 142 is fitted is formed in the upper surface of the locking base 25.

[0078] Moreover, the upper part 145 of the centrifugal separator 20 is fixed to the housing 201 using a fixing member that is not shown.

[0079] In the centrifugal separator drive 10 having the foregoing components, when the motor 23 is driven, the locking base 205 and the rotor 142 fixed to the locking base 205 are rotated at, for example, a rotational frequency ranging from about 3000 rpm to about 6000 rpm.

[0080] The optical sensor 15 is located on the side (left side in Fig. 2) of the housing 201.

[0081] The optical sensor 15 is designed to irradiate light to the blood reservoir space 146 and receive light reflected therefrom.

[0082] In the optical sensor 15, light (for example, laser light) is irradiated from a floodlight 151. A light receiver 152 receives light reflected from the reflecting surface 147 of the rotor 142. The light receiver 152 converts the received light into an electric signal whose level is proportional to the amount of received light.

[0083] At this time, the irradiated light and reflected light pass through the blood components in the blood reservoir space 146. However, the abundance ratio of each blood component varies depending on the position of the interface between the blood component and an adjoining blood component (in the present embodiment, the interface B between the layer of plasma 131 and the buffy coat layer 132) through which the irradiated light or reflected light passes. For this reason, the transmittance of each blood component varies depending on the position. Accordingly, the amount of light received by the light receiver 152 varies (changes). The variation is detected as a change in output voltage sent from the light receiver 152.

[0084] In short, the optical sensor 15 can detect the position of the interface between adjoining blood components according to a change in the amount of light received by the light receiver 152.

[0085] The interface between adjoining blood components whose position is detected by the optical sensor 15 is not limited to the interface B but may be the interface between, for example, the buffy coat layer 132 and the layer of red blood cells 133.

[0086] Now, the layers 131 to 133 in the blood reservoir space 146 are different from one another in terms of color because of the difference among the blood components. In particular, the layer of red blood cells 133 is reddish because red blood cells are red. Consequently, from the viewpoint of improvement in precision to be offered by the optical sensor 15, light serving as irradiated light should preferably have a spectrum ranging, for example, from about 600 nm to about 900 nm, or more preferably, from about 750 nm to about 800 nm, though it is not limited to the range.

[0087] The turbidity sensor 14 senses the turbidity of a fluid flowing through the second line 22 and transmits a voltage inversely proportional to a degree of turbidity. Specifically, when the degree of turbidity is high, the turbidity sensor 14 transmits a low voltage. When the degree of turbidity is low, the turbidity sensor 14 transmits a high voltage.

[0088] Owing to the turbidity sensor 14, for example, a change of a fluid flowing through the second line 22 from air to plasma, a change in the concentration of platelets in plasma, or mixture of red blood cells in plasma can be detected.

[0089] As the first fluid feeder pump 11 to which the first pump tube 21g is attached and the second fluid feeder pump 12 to which the second pump tube 23a is attached, a non-blood contact pump, for example, a roller pump is adopted preferably.

[0090] Moreover, as the first fluid feeder pump (blood pump) 11, a pump capable of feeding blood in either directions is adopted. Specifically, a roller pump capable of rotating forward and reversely is adopted.

[0091] Next, referring to Fig. 1, Fig. 3, and Fig. 4 to Fig. 8 that are flowcharts, blood component collection to be performed using the blood component collection system 1 will be described by taking for instance a case where platelets are collected. Fig. 3 is a timing chart outlining a first cycle of blood component collection to be performed using the blood component collection system 1.

[0092] The blood component collection system 1 acts to execute platelet collection composed of, as shown in Fig. 3, a first plasma collection process (A), a constant-speed plasma circulation process (B), a second plasma collection

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process (C), an accelerated plasma circulation process (D), a third plasma collection process (E), a platelet collection step (F), and a blood return step.

[0093] Moreover, according to the present embodiment, the platelet collection is repeated three times (first cycle to third cycle). Furthermore, a buffy coat collection process (G) is executed prior to the blood return process after the completion of the platelet collection process (F) within each cycle other than the final (third) cycle. A buffy coat return process is executed prior to the first plasma collection process (A) within the next platelet collection.

[0094] According to the present invention, in the blood component collection system 1, concurrently with the final cycle of platelet collection, platelet concentrate temporarily collected (reserved) in the temporary reservoir bag 26' is fed to the leukoreduction filter 261, and filtered to have leukocyte separated or reduced therefrom (see S401 in Fig. 8). From the viewpoint of shortening the binding time during which a donor is bound, the filtration should preferably be started concurrently with the final cycle of platelet collection (in particular, in an early process within platelet collection). In the blood component collection system 1 of the present embodiment, the filtration is started nearly concurrently with the second plasma collection process (C) within the final cycle of platelet collection.

[0095] [0] First, the third line 23 and blood collection needle 29 are primed with an anticoagulant. Thereafter, a donor's vessel is punctured with the blood collection needle 29.

[1] First cycle of platelet collection (see Fig. 4 and Fig. 5)

[0096] [11] First, the blood component collection system 1 executes the first plasma collection (first PPP collection) process (A). In the first plasma collection process (A), blood is routed to the blood reservoir space 146 of the rotor 142, and centrifuged. Consequently, separated plasma (PPP) is collected into the plasma collection bag 25.

[0097] In the first plasma collection process (A), first, the control unit 13 executes plasma (second blood component) collection (step S101 in Fig. 4).

[0098] Specifically, the first channel open/close means 81 and fourth channel open/close means 84 are unblocked under the control of the control unit 13, but the other pieces of channel open/close means are left blocked. In this state, the first fluid feeder pump 11 is actuated (rotated forward) at a predetermined rotating speed (preferably, about 250 mL/min or less, or more preferably, from about 40 mL/min to about 150 mL/min, and in the present embodiment, 60 mL/min). Thus, blood is collected from the donor.

[0099] Concurrently with the blood collection, the second fluid feeder pump 12 is actuated under the control of the control unit 13. An anticoagulant, for example, an ACD-A solution is fed through the third line 23, and mixed in the collected blood.

[0100] At this time, the control unit 13 controls the rotating speed of the second fluid feeder pump 12 so that the anticoagulant will be mixed in the collected blood at a predetermined ratio (preferably, about 1/20 to about 1/6, for example, 1/10).

[0101] Consequently, the blood (anticoagulant-inclusive blood) is carried through the first line 21. The blood then enters the inlet 143 of the centrifugal separator 20, passes through the pipe 141, and is thus routed to the blood reservoir space 146 of the rotor 142.

[0102] At this time, the air (sterilized air) in the centrifugal separator 20 is fed to the temporary reservoir bag 26' by way of the second line 22 and third tube 26a.

[0103] Concurrently with the blood collection, or before or after the blood collection, the control unit 13 actuates the centrifugal separator drive 10 and rotates the rotor 142 at a predetermined rotational frequency.

[0104] With the rotation of the rotor 142, the blood introduced into the blood reservoir space 146 is separated into the layer of plasma (PPP) 131, buffy coat layer (BC) 132, and layer of red blood cells (CRC) 133 in that order from the innermost layer.

[0105] The rotational frequency of the rotor 142 ranges, preferably, from about 3000 rpm to about 6000 rpm, or more preferably, from about 4200 rpm to about 5800 rpm. Moreover, in the processes described below, the control unit 13 does not change the rotational frequency of the rotor 142 unless otherwise described.

[0106] Furthermore, the blood collection and the feed of an anticoagulant are continued. When an amount of blood (approx. 270 mL) exceeding the capacity of the blood reservoir space 146 is routed to the blood reservoir space 146, the blood reservoir space 146 is filled with blood, and plasma (PPP) overflows through the outlet 144 of the centrifugal separator 20.

[0107] At this time, the turbidity sensor 14 attached to the second line 22 detects that a fluid flowing through the second line 22 has changed from air to plasma. Based on the detection signal sent from the turbidity sensor 14, the control unit 13 blocks the fourth channel open/close means 84 and unblocks the third channel open/close means 83.

[0108] Consequently, plasma is routed or collected into the plasma collection bag (third container) 25 by way of the second line 22 and second tube 25b.

[0109] The weight sensor 16 measures the weight of the plasma collection bag 25. A weight signal representing the measured weight is transferred to the control unit 13.

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[0110] Thereafter, the control unit 13 judges from the information (weight signal) sent from the weight sensor 16 whether a predetermined amount of plasma has been collected into the plasma collection bag 25 (step S102 in Fig. 4).

[0111] The (predetermined) collected amount of plasma ranges, preferably, from about 10 g to about 150 g, or more preferably, from about 20 g to about 40 g.

[0112] If it is found at step S102 that the predetermined amount of plasma has not been collected into the plasma collection bag 25, the control unit 13 returns to step S101, and repeats step S101 and subsequent steps.

[0113] If it is found at step S102 that the predetermined amount of plasma has been collected into the plasma collection bag 25, the control unit 13 terminates the process [11] (first plasma collection process (A)), and proceeds to the constant-speed plasma circulation process (B).

[0114] [12] Thereafter, the blood component collection system 1 executes the constant-speed plasma circulation (constant-speed PPP circulation) process (B). In the constant-speed plasma circulation process (B), the plasma in the plasma collection bag 25 is circulated through the blood reservoir space 146 at a constant speed.

[0115] In the constant-speed plasma circulation process (B), first, the control unit 13 executes plasma circulation (step S103 in Fig. 4).

[0116] Specifically, under the control of the control unit 13, the first channel open/close means 81 is blocked and the second channel open/close means 82 is unblocked. Moreover, the second fluid feeder pump 12 is inactivated, and the first fluid feeder pump 11 is actuated (rotated forward) at a predetermined rotating speed (preferably, from about 60 mL/min to about 250 mL/min, and in the present embodiment, 200 mL/min).

[0117] Consequently, blood collection is suspended. The plasma in the plasma collection bag 25 is routed to the blood reservoir space 146 by way of the first tube 25a and first line 21 at a constant speed. Plasma flowing out of the outlet 144 of the centrifugal separator 20 is collected into the plasma collection bag 25 by way of the second line 22 and second tube 25b. In short, the plasma in the plasma collection bag 25 is circulated through the blood reservoir space 146 at the constant speed.

[0118] Thereafter, the control unit 13 judges whether a predetermined time (preferably, from about 10 sec to about 90 sec, for example, 30 sec) has elapsed since the start of the constant-speed plasma circulation (step S104 in Fig. 4).

[0119] If it is found at step S104 that the predetermined time has not elapsed since the start of the constant-speed plasma circulation, the control unit 13 returns to step S103, and repeats step S103 and subsequent steps.

[0120] If it is found at step S 104 that the predetermined time has elapsed since the start of the constant-speed plasma circulation, the control unit 13 terminates the process [12] (constant-speed plasma circulation process (B)), and proceeds to the second plasma collection process (C).

[0121] [13] Thereafter, the blood component collection system 1 executes the second plasma (PPP) collection process (C). In the second plasma collection process (C), blood is routed to the blood reservoir space 146 of the rotor 142 and centrifuged. Separated plasma is then collected into the plasma collection bag 25.

[0122] In the second plasma collection process (C), the same steps as those included in the process [11] (first plasma collection process (A)) are executed except the step of measuring a collected amount of plasma using the weight sensor 16. Instead of the step, the position of the interface between the layer of plasma 131 and the buffy coat layer 132 is detected.

[0123] In the second plasma collection process (C), first, the control unit 13 collects plasma (step S105 in Fig. 4).

[0124] At this time, the control unit 13 blocks the second channel open/close means 82 and unblocks the first channel open/close means 81.

[0125] Consequently, the number of red blood cells in the blood reservoir space 146 increases, that is, the thickness of the layer of red blood cells 133 increases. Accordingly, the interface B rises gradually (moves towards the axis of rotation of the rotor 142).

[0126] Thereafter, the control unit 13 judges from the detection signal sent from the optical sensor 15 (information of the detected interface position) whether the interface B has reached a predetermined level (first position) (step S106 in Fig. 4).

[0127] Incidentally, the first position of the interface B is a position at which the detection signal sent from the first optical sensor 15 (an output voltage sent from the light receiver 152) ranges, preferably, from about 1 V to about 2 V.

[0128] If it is found at step S106 that the interface B has not reached the first position, the control unit 13 returns to step S105, and repeats step S105 and subsequent steps.

[0129] Moreover, if it is found at step S 105 that the interface B has reached the first position, the control unit 13 terminates the present process [13] (second plasma collection process (C)) and proceeds to the accelerated plasma circulation process (D).

[0130] [14] Thereafter, the blood component collection system 1 executes the accelerated plasma (PPP) circulation process (D). In the accelerated plasma (PPP) circulation process (D), the plasma in the plasma collection bag 25 is circulated through the blood reservoir space 146 while being accelerated.

[0131] In the accelerated plasma (PPP) circulation process (D), first, the control unit 13 executes plasma circulation (step S107 in Fig. 4).

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[0132] Specifically, the first channel open/close means 81 is blocked under the control of the control unit 13, and the second channel open/close means 82 is unblocked thereunder. Moreover, the second fluid feeder pump 12 is inactivated, and the first fluid feeder pump 11 is activated (rotated forward) so that the rotating speed thereof will increase at a rate corresponding to a constant acceleration.

[0133] Consequently, blood collection is suspended. Moreover, the plasma in the plasma collection bag 25 is routed to the blood reservoir space 146 by way of the first tube 25a and first line 21 while being accelerated. Plasma flowing out of the outlet 144 of the centrifugal separator 20 is collected into the plasma collection bag 25 by way of the second line 22 and second tube 25b. In short, the plasma in the plasma collection bag 25 is circulated through the blood reservoir space 146 while being accelerated.

[0134] At this time, the control unit 13 extends control so that the rotating speed of the first fluid feeder pump 11 will increase at a rate corresponding to a constant acceleration from a speed lower than the speed attained during the constant-speed plasma circulation (initial speed is, in the present embodiment, 60 mL/min).

[0135] The condition for acceleration (acceleration) ranges, preferably, from about 1 mL/min/sec to 10 mL/min/sec, or more preferably, from about 3 mL/min/sec to about 6 mL/min/sec. In the present embodiment, the acceleration is set to a fixed value. Alternatively, the acceleration may be varied stepwise or continuously within the above range.

[0136] Thereafter, the control unit 13 judges whether the circulating speed at which plasma circulates through the blood reservoir space 146 has reached the maximum speed, that is, whether the rotating speed of the first fluid feeder pump 11 has reached the maximum speed (preferably, from about 130 mL/min to 250 mL/min, and in the present embodiment, 170 mL/min) (step S108 in Fig. 4).

[0137] The step S108 is continued until the circulating speed at which plasma circulates through the blood reservoir space 146 reaches the maximum speed.

[0138] If it is found at step S108 that the circulating speed at which plasma circulates through the blood reservoir space 146 has reached the maximum speed, the control unit 13 terminates the present process [14] (accelerated plasma circulation process (D)) and proceeds to the third plasma collection process (E).

[0139] [15] Thereafter, the blood component collection system 1 executes the third plasma (PPP) collection process (E). In the third plasma collection process (E), blood is routed to the blood reservoir space 146 of the rotor 142 and centrifuged. Separated plasma is collected into the plasma collection bag 25.

[0140] In the third plasma collection process (E), first, the control unit 13 executes plasma collection (step S109 in Fig. 4).

[0141] Thereafter, the control unit 13 judges from the information (weight signal) sent from the weight sensor 16 whether a predetermined amount of plasma has been collected into the plasma collection bag 25 (step S110 in Fig. 4).

[0142] The (predetermined) collected amount of plasma ranges, preferably, from about 2 g to about 30 g, or more preferably, from about 5 g to about 15 g.

[0143] If it is found at step S110 that the predetermined amount of plasma has been collected into the plasma collection bag 25, the control unit 13 terminates the present process [15] (third plasma collection process (E)) and proceeds to the plasma collection process (F) ⓘ in Fig. 5).

[0144] [16] Thereafter, the blood component collection system 1 executes the platelet (PC) collection process (F). In the platelet collection process (F), the plasma in the plasma collection bag 25 is circulated through the blood reservoir space 146 while being accelerated at a first acceleration. Thereafter, the first acceleration is changed to a second acceleration that is higher than the first acceleration. The plasma is circulated while being accelerated at the second acceleration. This causes platelets to flow out of the blood reservoir space 146. Consequently, platelet concentrate is collected (reserved) into the temporary reservoir bag 26'.

[0145] In the platelet collection process, first, the control unit 13 executes plasma (PPP) circulation at the first acceleration (first acceleration step in Fig. 3, step S111 in Fig. 5).

[0146] Specifically, the first channel open/close means 81 is blocked under the control of the control unit 13, and the second channel open/close means 82 is unblocked thereunder. The second fluid feeder pump 12 is inactivated, and the first fluid feeder pump 11 is activated (rotated forward) so that the rotating speed thereof will increase at a rate corresponding to the first acceleration.

[0147] Consequently, blood collection is suspended. Moreover, the plasma in the plasma collection bag 25 is routed to the blood reservoir space 146 by way of the first tube 25a and first line 21 while being accelerated at the first acceleration. Plasma flowing out of the outlet 144 of the centrifugal separator 20 is collected into the plasma collection bag 25 by way of the second line 22 and second tube 25b. In short, the plasma in the plasma collection bag 25 is circulated through the blood reservoir space 146 while being accelerated at the first acceleration.

[0148] At this time, when plasma is circulated through the blood reservoir space 146 while being accelerated at the first acceleration, the thickness of the layer of red blood cells 133 increases. Consequently, the interface B rises gradually (moves toward the axis of rotation of the rotor 142).

[0149] The first acceleration ranges, preferably, from about 0.5 mL/min/sec to about 10 mL/min/sec, or more preferably, from about 1.5 mL/min/sec to about 2.5 mL/min/sec. In the present embodiment, the first acceleration is set to

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a fixed value. Alternatively, the first acceleration may be varied stepwise or continuously within the above range.

[0150] Moreover, the initial rotating speed of the first fluid feeder pump 11 for circulating plasma at the first acceleration ranges, preferably, from about 40 mL/min to about 150 mL/min, or more preferably, from about 50 mL/min to about 80 mL/min. In the present embodiment, the initial rotating speed of the first fluid feeder pump 11 is set to 60 mL/min.

[0151] Thereafter, the control unit 13 continues step S111 until the circulating speed at which plasma circulates through the blood reservoir space 146 reaches a predetermined speed (step S112 in Fig. 5).

[0152] Incidentally, the circulating speed of plasma, that is, the rotating speed of the first fluid feeder pump 11 ranges, preferably, from about 100 mL/min to about 180 mL/min, or more preferably, from about 140 mL/min to about 160 mL/min. In the present embodiment, the rotating speed of the first fluid feeder pump 11 is set to 150 mL/min.

[0153] If it is found at step S112 that the circulating speed at which plasma circulates through the blood reservoir space 146 has reached the predetermined speed, the control unit 13 executes plasma (PPP) circulation at a second acceleration speed (first acceleration step in Fig. 3, step S113 in Fig. 5).

[0154] Specifically, the acceleration of the first fluid feeder pump 11 is changed from the first acceleration to the second acceleration under the control of the control unit 13. Moreover, the first fluid feeder pump 11 is activated (rotated forward) so that the rotating speed thereof will increase at a rate corresponding to the second acceleration. Consequently, the plasma in the plasma collection bag 25 is circulated through the blood reservoir space 146 while being accelerated at the second acceleration.

[0155] When the plasma is circulated through the blood reservoir space 146 while being accelerated at the second acceleration, the thickness of the layer of red blood cells 133 increases, and the interface B rises gradually (moves toward the axis of rotation of the rotor 142). Moreover, the platelets (PC) contained in the buffy coat layer 132 floats (goes up) against centrifugal force, and moves toward the outlet 144 of the rotor 142.

[0156] The second acceleration is determined to be higher than the first acceleration, and ranges, preferably, from about 3 mL/min/sec to about 20 mL/min/sec, or more preferably, from about 5 mL/min/sec to about 10 mL/min/sec. In the present embodiment, the second acceleration is set to a fixed value. Alternatively, the second acceleration may be varied stepwise or continuously within the range.

[0157] Thereafter, the control unit 13 judges whether the circulating speed at which plasma circulates through the blood reservoir space 146 has reached the maximum speed, that is, whether the rotating speed of the first fluid feeder pump 11 has reached the maximum speed (preferably, from about 120 mL/min to 300 mL/min, and in the present embodiment, 200 mL/min) (step S114 in Fig. 5).

[0158] If it is found at step S114 that the circulating speed at which plasma circulates through the blood reservoir space 146 has not reached the maximum speed, the control unit 13 returns to step S113, and repeats step S113 and subsequent steps.

[0159] If it is found at step S114 that the circulating speed at which plasma circulates through the blood reservoir space 146 has reached the maximum speed, the control unit 13 continues plasma (PPP) circulation (step S115 in Fig. 5).

[0160] Specifically, the control unit 13 extends control so that the rotating speed of the first fluid feeder pump 11 will be retained (held) at the maximum speed attained at step S115. Consequently, the circulating speed at which plasma circulates through the blood reservoir space 146 ranges, preferably, from about 120 mL/min to about 300 mL/min. In the present embodiment, the circulating speed is set to 200 mL/min.

[0161] Thereafter, the control unit 13 judges whether a predetermined time (preferably, from about 5 sec to about 15 sec, for example, 10 sec) has elapsed since the continuation of plasma circulation is determined (step S 116 in Fig. 5).

[0162] If it is found at step S116 that the predetermined time has not elapsed since the continuation of plasma circulation is determined, the control unit 13 judges whether the output voltage (PC concentration voltage) sent from the turbidity sensor 14 had dropped to a predetermined value (preferably, from about 2.5 V to about 3.5 V, for example, 3.0 V) or less (step S117 in Fig. 5).

[0163] If it is found at step S117 that the output voltage sent from the turbidity sensor 14 has not dropped to the predetermined value or less, the control unit 13 returns to step S115 and repeats step S115 and subsequent steps.

[0164] While steps S115 to S117 are repeated, if it is found at step S116 that the predetermined time has elapsed since the continuation of plasma circulation is determined, the control unit 13 terminates the present process [16] (platelet collection process (F)) and proceeds to the buffy coat collection process (G).

[0165] If it is found at step S117 that the output voltage sent from the turbidity sensor 14 has dropped to the predetermined value or less, that is, if the concentration of platelets contained in plasma which flows through the second line 22 along with the outflow of platelets from the outlet 144 of the rotor 142 has reached a predetermined value or more, the control unit 13 executes platelet (PC) collection (step S118 in Fig. 5).

[0166] Specifically, based on the detection signal sent from the turbidity sensor 14, the control unit 13 blocks the third channel open/close means 83 and unblocks the fourth channel open/close means 84.

[0167] Consequently, platelet concentrate is routed to the temporary reservoir bag 26' by way of the second line 22 and third tube 26a (tube 261a), and collected (reserved). At this time, since the seventh channel open/close means 87 is blocked, the platelet concentrate does not flow out of the temporary reservoir bag 26'.

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[0168] Moreover, the control unit 13 calculates the concentration of platelets (concentration of cumulative platelets) in the temporary reservoir bag 26' according to the output voltage (detection signal) sent from the turbidity sensor 14. The concentration of platelets keeps rising after the start of platelet collection. Once the concentration of platelets reaches the maximum value, it decreases.

[0169] Thereafter, the control unit 13 judges whether a predetermined time (preferably, from about 10 sec to about 25 sec, for example, 15 sec) has elapsed since the start of PC collection (step S119 in Fig. 5).

[0170] If it is found at step S119 that the predetermined time has not elapsed since the start of platelet collection, the control unit 13 judges whether the output voltage sent from the turbidity sensor 14 (platelet (PC) concentration voltage) has reached a predetermined value or less (step S 120 in Fig. 5).

[0171] The predetermined value of the output voltage sent from the turbidity sensor 14 is a value near the value of the output voltage transmitted when red blood cells (CRC) are mixed in plasma flowing through the second line 22, or preferably, about 0.5 V or less.

[0172] If it is found at step S120 that the output voltage sent from the turbidity sensor 14 has not reached the predetermined value or less, the control unit 13 judges whether the amount of platelet concentrate in the temporary reservoir bag 26' has reached a predetermined amount (step S121 in Fig. 5).

[0173] Incidentally, the collected (predetermined) amount of platelet concentrate ranges, preferably, about 20 mL to about 100 mL, or more preferably, from about 40 mL to about 70 mL.

[0174] If it is found at step S121 that the platelet concentrate in the temporary reservoir bag 26' has not reached the predetermined amount, the control unit 13 returns to step S118 and repeats step S118 and subsequent steps.

[0175] While steps S118 to S121 are repeated, if it is found at step S119 that the predetermined time has elapsed since the start of platelet collection, or if it is found at step S120 that the output voltage sent from the turbidity sensor 14 has reached the predetermined value or less, the control unit 13 terminates the present process [16] (platelet collection process (F)) and proceeds to the buffy coat collection process (G).

[0176] If it is found at step S121 that the platelet concentrate in the temporary reservoir bag 26' has reached the predetermined amount, the control unit 13 terminates the present process [16] (platelet collection process (F)) and proceeds to the buffy coat collection process (G).

[0177] [17] Thereafter, the blood component collection system 1 executes the buffy coat (BC) collection process (G). In the buffy coat (BC) collection process (G), a buffy coat is caused to flow out of the blood reservoir space 146 of the rotor 142 and collected.

[0178] In the buffy coat collection process (G), first, the control unit 13 executes buffy coat collection (step S122 in Fig. 5).

[0179] Specifically, the fourth channel open/close means 84 is blocked under the control of the control unit 13, and the fifth channel open/close means 85 is unblocked thereunder. The first fluid feeder pump 11 is activated (rotated forward) at the predetermined rotating speed (preferably, from about 60 mL/min to about 300 mL/min, and in the present embodiment, 200 mL/min).

[0180] Consequently, the plasma in the plasma collection bag 25 is routed to the blood reservoir space 146 at the predetermined speed by way of the first tube 25a and first line 21. The buffy coat flowing out of the outlet 144 of the rotor 142 is routed and collected into the buffy coat collection bag 27 by way of the second line 22 and fourth tube 27a.

[0181] In the buffy coat collection process (G), the control unit 13 changes the rotational frequency of the rotor 142.

[0182] The rotational frequency of the rotor 142 is set to be lower than the rotational frequency thereof set in the aforesaid processes [11] to [16] by, for example, a value ranging from about 100 rpm to about 300 rpm. Specifically, the rotational frequency ranging from about 4500 rpm to about 4600 rpm is preferred.

[0183] Thereafter, the control unit 13 judges whether a predetermined amount of a buffy coat has been collected into the buffy coat collection bag 27 (step S123 in Fig. 5).

[0184] Specifically, the control unit 13 calculates a collected (predetermined) amount of a buffy coat according to an amount of collected blood, a donor's hematocrit, and the number of platelets collected in the platelet collection process. The control unit 13 then determines the number of rotations, by which the first fluid feeder pump 11 should be rotated, on the basis of the calculated acquired amount. The control unit 13 then judges whether the first fluid feeder pump 11 has rotated by the number of rotations required to collect the calculated collected amount.

[0185] If it is found at step S123 that the predetermined amount of a buffy coat has not been collected into the buffy coat collection bag 27, that is, if the first fluid feeder pump 11 has not been rotated by the required number of rotations, the control unit 13 returns to step S122 and repeats step S122 and subsequent steps.

[0186] Moreover, if it is found at step S123 that the predetermined amount of a buffy coat has been collected into the buffy coat collection bag 27, that is, if the first fluid feeder pump 11 has been rotated by the required number of rotations, the control unit 13 blocks all the channel open/close means 81 to 87, inactivates the first fluid feeder pump 11, and terminates the present process [17] (buffy coat collection process (G)).

[0187] [18] Thereafter, the blood component collection system 1 executes a process of inactivating the centrifugal separator 20.

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[0188] In this process, first, the control unit 13 decelerates the centrifugal separator 20 (step S124 in Fig. 5).

[0189] Specifically, the rotational frequency of the centrifugal separator drive 10 is decreased under the control of the control unit 13. The rotor 142 is thus decelerated.

[0190] Furthermore, the control unit 13 inactivates the centrifugal separator 20 (step S125 in Fig. 5).

[0191] Specifically, the rotation of the centrifugal separator drive 10 is stopped in order to inactivate the rotor 142 under the control of the control unit 13.

[0192] [19] Thereafter, the blood component collection system 1 executes a blood return process. In the blood return process, the blood components in the blood reservoir space 146 of the rotor 142 are returned.

[0193] In the blood return process, the control unit 13 executes blood return (step S126 in Fig. 5).

[0194] Specifically, the first channel open/close means 81 is unblocked under the control of the control unit 13. Moreover, the first fluid feeder pump 11 is activated (rotated reversely) at a predetermined rotating speed (preferably, from about 20 mL/min to about 120 mL/min, for example, 90 mL/min).

[0195] Consequently, the blood components (mainly red blood cells) remaining in the blood reservoir space 146 of the rotor 142 are released from the outlet 144 of the centrifugal separator 20, and returned (restored) to the donor by way of the first line 21.

[0196] Incidentally, the full amount of the blood components (amount of returned blood) is calculated based on the amount of collected blood, the collected amount of plasma, and the collected amount of platelet concentrate.

[0197] The first fluid feeder pump 11 is rotated by the number of rotations required to restore the full amount of blood components (amount of returned blood) to the donor under the control of the control unit 13. Thereafter, the first channel open/close means 81 is blocked, the first fluid feeder pump 11 is inactivated, and the present process [19] (blood return process) is terminated.

[0198] Thus, the first cycle of platelet collection is completed.

[2] Second cycle of platelet collection (see Fig. 6 and Fig. 5)

[0199] Thereafter, the second cycle of platelet collection is executed.

[0200] The second cycle of platelet collection comprises the same processes as the first cycle of platelet collection except that a buffy coat restoration process precedes the first plasma collection process.

[0201] [20] First, the blood component collection system 1 executes the buffy coat (BC) restoration process. In the buffy coat restoration process, a collected buffy coat is restored to the blood reservoir space 146 of the rotor 142.

[0202] In the buffy coat restoration process, first, the control unit 13 executes buffy coat restoration (step S20X in Fig. 6).

[0203] Specifically, the fourth channel open/close means 84 and sixth channel open/close means 86 are unblocked under the control of the control unit 13. The other channel open/close means are left blocked. In this state, the first fluid feeder pump 11 is activated (rotated forward) at a predetermined rotating speed (preferably, from about 60 mL/min to about 250 mL/min, for example, 100 mL/min). Moreover, the centrifugal separator drive 10 is activated at a predetermined rotational frequency (for example, 4800 rpm).

[0204] Consequently, the buffy coat in the buffy coat collection bag 27 is fed to the pipe 141 through the inlet 143 of the centrifugal separator 20 by way of the fourth tube 27a and first line 21, and routed to the blood reservoir space 146 of the rotor 142. At this time, the air in the centrifugal separator 20 is fed to the temporary reservoir bag 26' through the second line 22.

[0205] Thereafter, the control unit 13 judges whether the buffy coat collection bag 27 has run out of a buffy coat to be restored (step S20Y in Fig. 6).

[0206] Specifically, the control unit 13 determines the number of rotations, by which the first fluid feeder pump 11 should be rotated, on the basis of the collected amount of a buffy coat. The control unit 13 then judges whether the first fluid feeder pump 11 has rotated by the number of rotations required to restore the buffy coat.

[0207] If it is found at step S20Y that the buffy coat to be restored is left, that is, if the first fluid feeder pump 11 has not rotated by the required number of rotations, the control unit 13 returns to step S20X and repeats the step S20X and subsequent steps.

[0208] If it is found at step S20Y that the buffy coat to be restored has run out, that is, the first fluid feeder pump 11 has rotated by the required number of rotations, the control unit 13 terminates the present process [20] (buffy coat restoration process) and proceeds to the first plasma collection process.

[0209] [21] to [29] The same processes as the processes [11] to [19] are executed.

[0210] Consequently, the second cycle of platelet collection is completed.

[3] Third (final) cycle of platelet collection (see Fig. 6 and Fig. 7).

[0211] Successively, the third cycle of platelet collection is executed.

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[0212] In the third cycle of platelet collection, the same processes as those included in the second cycle of platelet collection are executed except that the buffy coat collection process is not executed and that a line cleansing process is executed for cleansing the platelet collection branch line with plasma.

[0213] [30] to [32] The same processes as the processes [20] to [22] are executed.

[0214] [33] The same process as the process [23] is executed.

[0215] Nearly concurrently with the process [33] (second plasma collection process), the control unit 13 feeds platelet concentrate, which is collected (reserved) temporarily in the temporary reservoir bag 26', to the leukoreduction filter 261. Thus, the platelet concentrate is filtered, that is, leukocyte contained in the platelet concentrate are separated or reduced.

[0216] Specifically, the seventh channel open/close means 87 is unblocked under the control of the control unit 13. Consequently, the platelet concentrate in the temporary reservoir bag 26' passes through the tube 262a, leukoreduction filter 261, and tube 263a owing to a fall (own weight). The platelet concentrate is thus carried to the platelet collection bag 26. At this time, the platelet concentrate almost entirely passes through the filtration member of the leukoreduction filter 261. However, the filtration member catches leukocyte. Consequently, the leukocyte contained in a platelet product are highly efficiently reduced.

[0217] In order to carry platelet concentrate from the temporary reservoir bag 26' to the platelet collection bag 26, a pump may be employed.

[0218] Moreover, instead of the means to be activated under the control of the control unit 13, the seventh channel open/close means 87 may be a clamp capable of manually opening or closing the middle of a channel of the tube 262a.

[0219] [34] and [35] The same processes as the processes [24] and [25] are executed.

[0220] [36] The same process as the process [26] is executed.

[0221] In the present process [36], the platelet concentrate collected into the temporary reservoir bag 26' is fed to the leukoreduction filter 261 and filtered.

[0222] [3A] Thereafter, the blood component collection system 1 executes a line cleansing process. In the line cleansing process, plasma is fed from the plasma collection bag 25 to the platelet collection branch line, and the platelet collection branch line is cleansed.

[0223] The line cleansing process that is a constituent feature of the present invention will be described with reference to the flowchart of Fig. 8. First, under the control of the control unit 13, the blood component collection system 1 feeds platelet concentrate, which is temporarily collected (reserved) in the temporary reservoir bag 26', to the leukoreduction filter 261, and then executes filtration for separating or reducing leukocyte from the platelet concentrate (S401). The filtration is started substantially concurrently with the start of the second plasma collection process in the final cycle of platelet collection. Thus, the binding time during which a donor is bound is shortened.

[0224] The filtration is carried out according to a procedure described below. Specifically, the seventh channel open/close means 87 is unblocked under the control of the control unit 13. This causes the platelet concentrate in the temporary reservoir bag 26' to pass through the tube 262a, leukoreduction filter 261, and tube 263a due to a fall (own weight). The platelet concentrate is thus carried to the platelet collection bag 26. At this time, the platelet concentrate almost entirely passes through the filtration member of the leukoreduction filter 261. However, the filtration member catches leukocyte. Thus, the leukocyte contained in the platelet concentrate are separated or reduced. Eventually, the leukocyte mixed in the platelet product are minimized.

[0225] Nearly concurrently with the filtration, the second plasma collection process included in the final cycle of platelet collection is started (S402). At this time, the seventh channel open/close means 87 located downstream the temporary reservoir bag 26' is unblocked. Consequently, platelet concentrate collected in the second plasma collection process in the final cycle is fed to the leukoreduction filter 261 and filtered.

[0226] Thereafter, the control unit 13 calculates a fed amount of plasma (PPP) according to an expression below (S403).

$$\text{Fed amount of plasma} = \text{Full amount of a target platelet product} - \text{Collected amount of platelet concentrate (PC)}$$

[0227] Herein, the full amount of a target platelet product is normally determined prior to blood collection and depends on the specification and unit adopted for a platelet product. Moreover, the collected amount of platelet concentrate (PC) depends on the total number of rotations by which the first fluid feeder pump 11 is rotated with the fourth channel open/close means 84 unblocked.

[0228] After the control unit 13 calculates the fed amount of plasma, the control unit 13 feeds plasma to the platelet

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collection branch line (executes plasma feed) (S404, step S327 in Fig. 7). Specifically, while the second channel open/close means 82 and fourth channel open/close means 84 are left unblocked, the rotating speed of the first fluid feeder pump 11 and the rotational frequency of the rotor 142 are changed under the control of the control unit 13.

[0229] The rotating speed of the second fluid feeder pump 11 is, preferably, about 250 mL/min or less, or more preferably, ranges from about 40 mL/min to about 250 mL/min.

[0230] Moreover, the rotational frequency of the rotor 142 is set to be larger than the rotational frequency of the rotor 142 adopted in the processes [30] to [36] by, for example, a value ranging from about 300 rpm to about 800 rpm. Preferably, the rotational frequency ranges from about 5000 rpm to about 5500 rpm.

[0231] Consequently, the plasma in the plasma collection bag 25 is routed (fed) to the platelet collection bag 26 by way of the first tube 25a, first line 21, rotor 142 (centrifugal separator 20), second line 22, and tube 261a. That is, the plasma is routed (fed) from the upstream of the temporary reservoir bag (first container) 26' through the temporary reservoir bag 26', tube 262a, leukoreduction filter 261, and tube 263a to the platelet collection bag 26.

[0232] At this time, the platelets (platelet concentrate having leukocyte separated or reduced) remaining in the leukoreduction filter 261 and the channel defined by the tube 263a are collected together with the plasma into the platelet collection bag 26. This results in a high yield of platelets in a platelet product.

[0233] Moreover, since plasma is fed from the upstream of the temporary reservoir bag 26', the plasma is routed together with the platelet concentrate (first blood component), which remains in the temporary reservoir bag 26' and the channel of the tube 262a, to the leukoreduction filter 261. The yield of platelets in a platelet product can be improved.

[0234] As mentioned above, in the cleansing process, the full amount of a platelet product (a blood component in the platelet collection bag 26) is adjusted based on a fed amount of plasma. Consequently, another process for adjusting the full amount of a platelet product can be omitted. Moreover, since the adjustment can be performed in the blood component collection circuit 2 (closed state), a sterile state can be maintained.

[0235] The fed amount of plasma ranges, preferably, from about 5 mL to about 200 mL, or more preferably, from about 12 mL to about 150 mL.

[0236] The fed amount of plasma is detected as a change (decrease) in the weight of the plasma collection bag 25 by the weight sensor 16.

[0237] The control unit 13 then judges from the detection signal sent from the weight sensor 16 whether plasma has been fed to the temporary reservoir bag 26' by the fed (set) amount calculated at step S403 (S405). At this time, if the amount of plasma has not reached the set amount (S405: No), plasma is kept fed (S404). If the amount of plasma has reached the set amount (S405: Yes), the control unit 13 extends control to block the channel open/close means 81 to 84 and 86 and to inactivate the first fluid feeder pump 11. Thereafter, a platelet product is collected (S406). The present process [3A] (line cleansing process) is then terminated.

[0238] Prior to the present process [3A], the control unit 13 may extend control to suspend the first fluid feeder pump 11 with the rotor 142 kept rotated. Consequently, in the process [36] (platelet collection process), the buffy coat layer 132 and the layer of red blood cells 133 which are diffused in the blood reservoir space 146 of the rotor 142 (whose thicknesses are increased) can be compressed (the thicknesses can be decreased). Therefore, in the process [3A] (line cleansing process), the buffy coat or red blood cells can be reliably prevented from being mixed in plasma flowing out of the outlet 144 of the rotor 142.

[0239] Moreover, the process [3A] may be started after the completion of release of platelet concentrate from the temporary reservoir bag 26'. This can be realized by disposing a bubble sensor or the like, which can detect the presence of bubbles in a channel, in the tube 262a near the temporary reservoir bag 26'.

[0240] [38] and [39] The same processes as the processes [28] and [29] are executed. Incidentally, the same process as the process [27] is omitted.

[0241] Consequently, the third cycle of platelet collection is completed.

[0242] The number of times by which platelet collection is performed is not limited to three. If necessary, the platelet collection may be performed twice or four or more times.

[0243] In the foregoing blood component collection system 1, the leukoreduction filter 261 is used to separate or reduce leukocyte from platelet concentrate separated or collected from blood. Therefore, a platelet product having the least number of leukocyte mixed therein can be prepared.

[0244] Moreover, platelets remaining in the leukoreduction filter 261 and tube 263a are washed away with plasma and collected into the platelet collection bag 26. Consequently, a platelet product containing platelets at a very high yield can be prepared.

[0245] Moreover, platelets are collected (washed away) using plasma (blood component). Therefore, compared with when physiological saline or an anticoagulant is employed, a higher-quality platelet product can be prepared.

[0246] Moreover, the configuration of the blood component collection circuit 2 included in the blood component collection system 1 can be determined appropriately but not limited to the illustrated one.

[0247] For example, a tube (line) linking the plasma collection bag 25 and platelet collection branch line may be included. In this case, a method for feeding (carrying) plasma from the plasma collection bag 25 to the platelet collection

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branch line may be a method utilizing a fall or a method employing a pump. Even in this case, the plasma collection bag 25 is, preferably, disposed upstream the temporary reservoir bag 26'.

[0248] Moreover, for example, a second plasma collection bag different from the plasma collection bag 25 may be included. Plasma to be fed to the platelet collection branch line during the line cleansing process may be reserved in the second plasma collection bag.

[0249] Furthermore, in the blood component collection system 1, conditions can be set for each of processes constituting platelet collection (blood component collection). Moreover, if necessary, any process can be added or omitted.

[0250] The blood component collection system according to the present invention has been described in conjunction with the illustrated embodiment. The present invention is not limited to the embodiment. The components of the blood component collection system may be replaced with others that can exhibit the same abilities.

[0251] For example, the present invention is not limited to the illustrated optical sensor. Alternatively, for example, a line sensor will do.

[0252] The blood component collection system of the present invention is not limited to a case where a platelet product is prepared. Alternatively, for example, the blood component collection system may be adapted to a case where a plasma product, an albumin product, a red blood cell product, or the like is prepared. Moreover, a kind of cells to be separated or reduced using the cell separating filter is not limited to leukocyte.

[0253] Next, a concrete example of the present invention will be described.

(Example)

[0254] A blood component collection circuit (Terumo Leukoreductive Apheresis set (with a leukoreduction filter) manufactured by Terumo Corp.), and a blood component collection system (Terumo Apheresis machine AC-550 manufactured by Terumo Corp.) were remodeled in order to construct the blood component collection system shown in Fig. 1. The system was used to perform platelet collection (four times) by executing the aforesaid processes.

[0255] Moreover, the conditions for each of the processes to be executed in order to achieve platelet collection will be listed below. The interface between blood components to be detected was the interface between a layer of plasma and a buffy coat layer.

[First plasma collection process]	
Rotor: rotational frequency	4800 rpm
First fluid feeder pump	rotating speed: 60 mL/min
Condition for terminating the process	A collected amount should reach 30 g.

[Constant-speed plasma circulation process]	
Rotor: rotational frequency	4800 rpm
First fluid feeder pump: rotating speed	200 mL/min
Condition for terminating the process	30 sec should elapse.

[Second plasma collection process]	
Rotor: rotational frequency	4800 rpm
First fluid feeder pump	rotating speed: 60 mL/min
Condition for terminating the process	The output voltage of the first optical sensor should become 1.8 V.

[Accelerated plasma circulation process]	
Rotor: rotational frequency	4800 rpm
First fluid feeder pump: rotating speed	60 mL/min (initial speed), 5.0 mL/min/sec (acceleration)
Condition for terminating the process	The rotating speed of the first fluid feeder pump should be 170 mL/min.

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[Third plasma collection process]	
Rotor: rotational frequency	4800 rpm
First fluid feeder pump	rotating speed: 60 mL/min
Condition for terminating the process	A collected amount should reach 10 g.

[Platelet collection process]	
Rotor: rotational frequency	4800 rpm
First fluid feeder pump: rotating speed	60 mL/min (initial speed), 2 mL/min/sec (first acceleration) When the rotating speed becomes 150 mL/min, the acceleration is changed. 10 mL/min/sec (second acceleration) 200 mL/min (maximum speed)
Condition for terminating the process	A collected amount of platelet concentrate should reach 50 mL.

[Buffy coat collection process]	
Rotor: rotational frequency	4600 rpm
First fluid feeder pump	rotating speed: 205 mL/min
Condition for terminating the process	A calculated amount of a buffy coat should have been collected

[Blood return process]	
First fluid feeder pump	rotating speed: 90 mL/min
Condition for terminating the process	A calculated amount of blood to be returned should have been returned.

[Buffy coat restoration process]	
Rotor: rotational frequency	4800 rpm
First fluid feeder pump	rotating speed: 100 mL/min
Condition for terminating the process	A calculated amount of a buffy coat should have been restored.

[Line cleansing process]	
Rotor: rotational frequency:	5200 rpm
First fluid feeder pump:	rotating speed: 60 mL/min
Condition for terminating the process:	15 mL of plasma should have been fed.

(Comparative example)

[0256] A blood component collection circuit (Terumo Leukoreductive Apheresis set (with a leukoreduction filter) manufactured by Terumo Corp.) and a blood component collection system (Terumo Apheresis machine AC-550 manufactured by Terumo Corp.) were remodeled in order to construct the blood component collection system shown in Fig. 1. Using the system, platelet collection was performed (four times) in the same manner as in the above example except that the line cleansing process was omitted.

[0257] Incidentally, the platelet collection in the comparative example was performed on the same donor as the one in the example and was executed two weeks after the platelet collection.

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(Evaluation)

[0258] In both the example and comparative example, the collected amount of platelet concentrate in the temporary reservoir bag and the collected amount of a platelet product in the platelet collection bag were measured.

[0259] Moreover, the platelet concentrate in the temporary reservoir bag and the platelet product in the platelet collection bag were sampled in order to measure the number of contained platelets and the number of contained leukocyte. For the measurement, a cytometer (Sysmex® SE-9000 manufactured by Sysmex Corp.) was employed. The lower limit of the number of leukocyte measurable by the Sysmex SE-9000 is calculated as 0.1×10^2 cells/μL. The number of leukocyte contained in a sample and falling below the lower limit is measured according to a Nageotte [1:9] method.

[0260] The results of the measurement are listed in Table 1.

[Table 1]

		In temporary reservoir bag (platelet concentrate)	In platelet collection bag (platelet product)	Yield (%)
Example	collected amount [ml]	200	200	96.35
	the number of platelets [cells/bag]	2.19×10^{11}	2.11×10^{11}	
	the number of leukocyte [cells/bag]	3.0×10^7	1.0×10^4	
Compar ative Ex.	collected amount [ml]	200	200	92.37
	the number of platelets [cells/bag]	2.36×10^{11}	2.18×10^{11}	
	the number of leukocyte [cells/bag]	5.6×10^7	1.0×10^4	

[0261] As seen from Table 1, since the line cleansing process is included in the example, a loss of platelets occurring over the platelet collection branch line can be reduced more successfully than it can in the comparative example. Consequentially, the yield of platelets in a platelet product can be improved more successfully.

[0262] Specifically, the yield of platelets in the example was 96.35 %, while the yield of platelets in the comparative example was 92.37 %. Thus, the yield of platelets in a platelet product could be improved approximately 4 %. Herein, the yield is calculated as follows: the number of platelets in the platelet collection bag /. the number of platelets in the temporary reservoir bag × 100 (%).

[0263] Incidentally, in both the example and comparative example, leukocyte were successfully reduced from a platelet product.

Industrial Applicability

[0264] As described so far, in a blood component collection system according to the present invention, a cell separating filter is used to separate or reduce a predetermined kind of cells. In order to prepare a blood product, for example, a platelet product, leukocyte (especially, lymphocytes) can be reduced from the platelet product (blood product) at a high removable rate. The risk of an attack of fever, isoantigen sensitization, virus infection, or the like can be lowered. High safety can be guaranteed.

[0265] Moreover, in a blood component collection system according to the present invention, when a blood product, for example, a platelet product is prepared, platelets remaining in a cell separating filer are collected using, for example, plasma (blood component) as a medium. This results in a high yield of platelets in a platelet product. Moreover, since platelets are collected using the blood component, a high-quality platelet product (blood product) can be prepared.

Claims

1. A blood component collection system comprising: a centrifugal separator including a rotor having a blood reservoir space therein and an inlet and an outlet which communicate with the blood reservoir space, and centrifuging blood

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introduced through the inlet with the rotation of the rotor, into a plurality of components in the blood reservoir space; a first container for temporarily reserving therein a first blood component; a cell separating filter for separating or reducing a predetermined kind of cells from the first blood component; and a second container for reserving the first blood component having passed through the cell separating filter,

wherein the blood component collection system further comprises:

channel open/close means for opening or closing a channel linking the first container and the cell separating filter; and
control means for controlling action of the channel open/close means,

the channel open/close means is used to carry the first blood component in the first container to the second container through the cell separating filter, then supply a second blood component, and collect the first blood component, from which the predetermined kind of cells remaining in the cell separating filter have been separated or reduced, together with the second blood component into the second container.

2. A blood component collection system comprising: a centrifugal separator including a rotor having a blood reservoir space therein and an inlet and an outlet which communicate with the blood reservoir space, and centrifuging blood introduced through the inlet by rotation of the rotor, into a plurality of components in the blood reservoir space; a first container for temporarily reserving therein a first blood component; a cell separating filter connected to the first container through a feed tube, and used to separate or reduce a predetermined kind of cells from the first blood component fed through the feed tube; and a second container which is connected to the cell separating filter through a release tube and used for reserving therein the first blood component having passed through the cell separating filter,

wherein the blood component collection system further comprises:

channel open/close means for opening or closing a channel of the feed tube; and
control means for controlling action of the channel open/close means,

the channel open/close means is used to carry the first blood component in the first container to the second container through the feed tube, cell separating filter, and release tube in response to a command sent from the control means,

thereafter, a second blood component is fed, and the first blood component that remains in the cell separating filter and the channel of the release tube and that has the predetermined cells separated or reduced therefrom is collected together with the second blood component into the second container.

3. The blood component collection system according to claim 1 or 2, wherein a full amount of a blood component to be collected into the second container is adjusted according to a 'fed amount of the second blood component.

4. The blood component collection system according to any one of claims 1 through 3, wherein the fed amount of the second blood component is determined based on a difference between a target full amount of the blood component to be collected into the second container and an amount of the first blood component to be carried to the second container.

5. The blood component collection system according to any one of claims 1 through 4, further including a third container for reserving the second blood component, wherein the second blood component is fed from the third container.

6. The blood component collection system according to any one of claims 1 through 5, wherein the second blood component is fed together with the first blood component which remains in the first container, to the cell separating filter.

7. The blood component collection system according to any one of claims 1 through 6, wherein the first blood component is plasma containing platelets.

8. The blood component collection system according to any one of claims 1 through 7, wherein the second blood component is plasma.

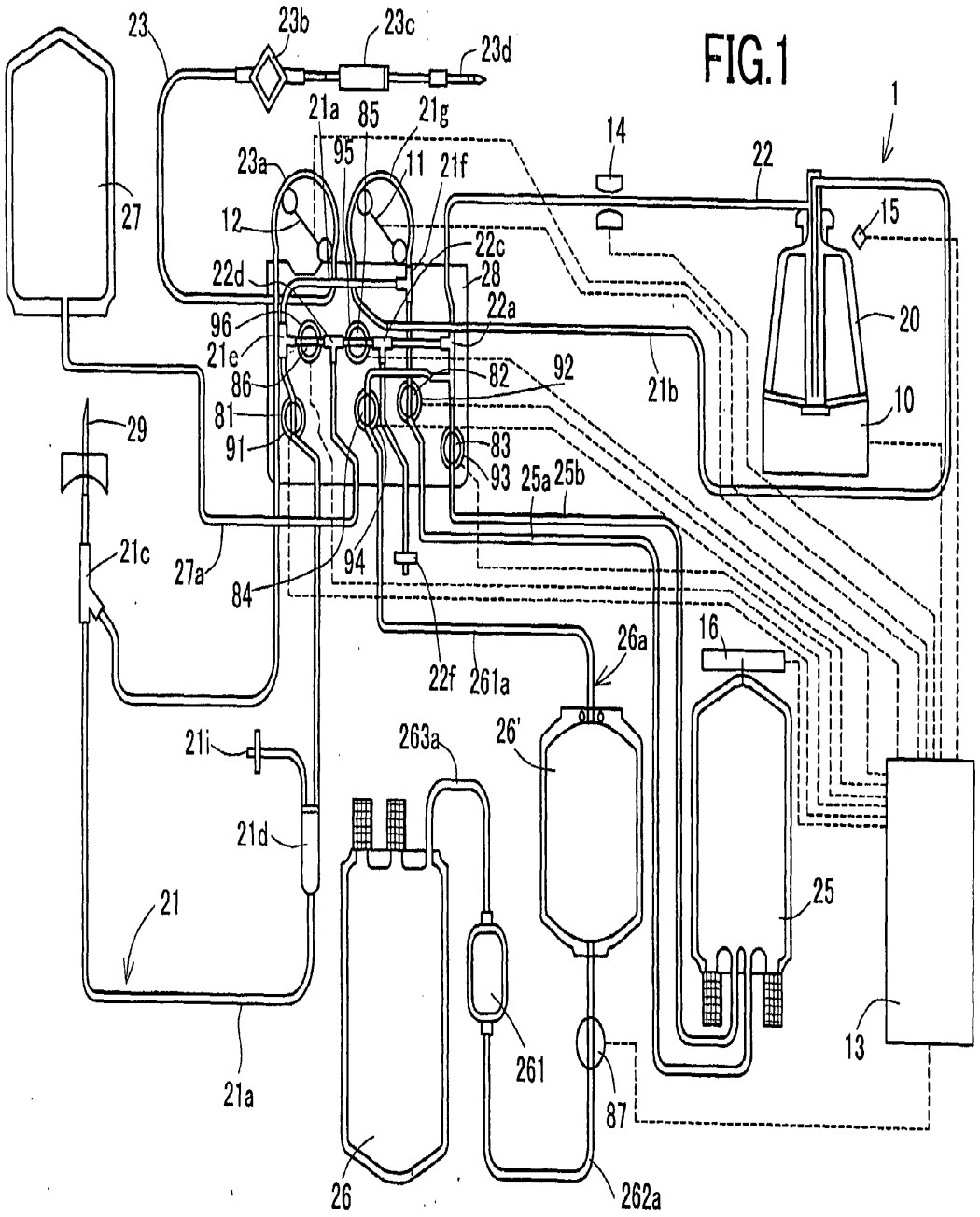
9. The blood component collection system according to any one of claims 1 through 8, wherein the cell separating

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filter is a leukoreduction filter.

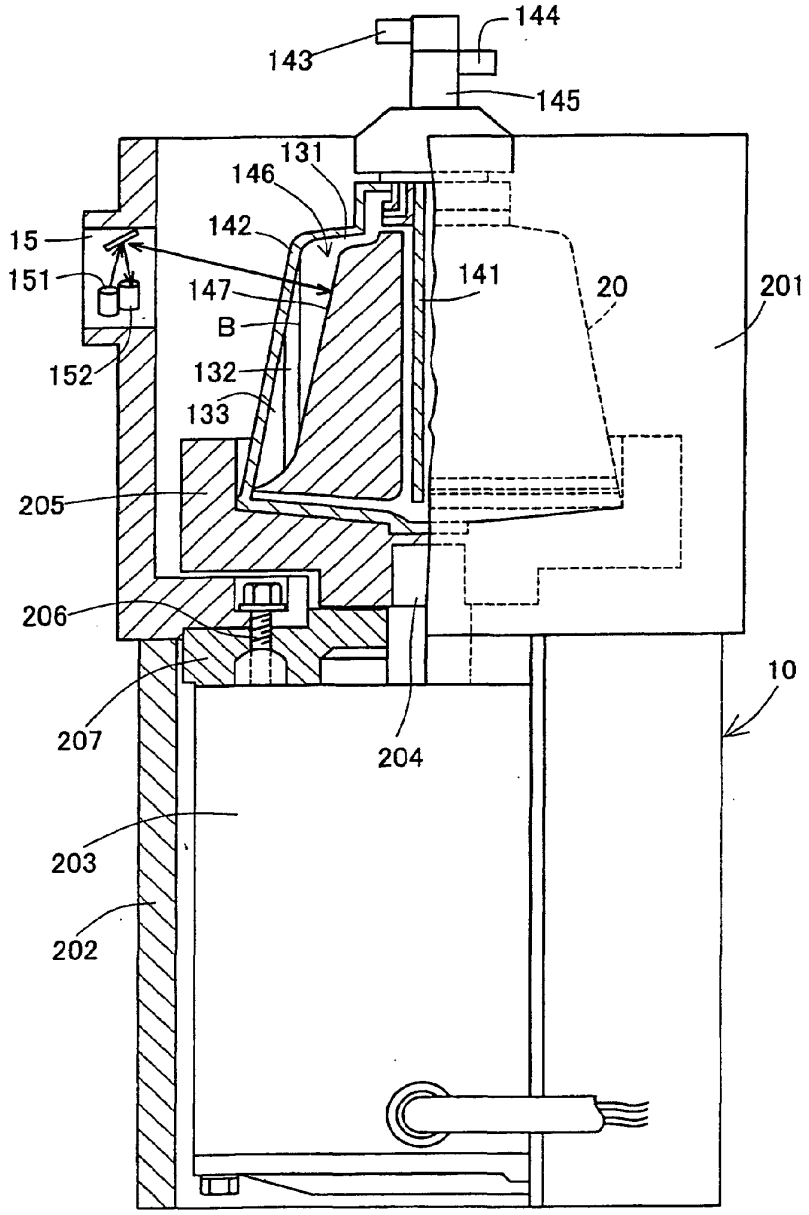
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FIG.1

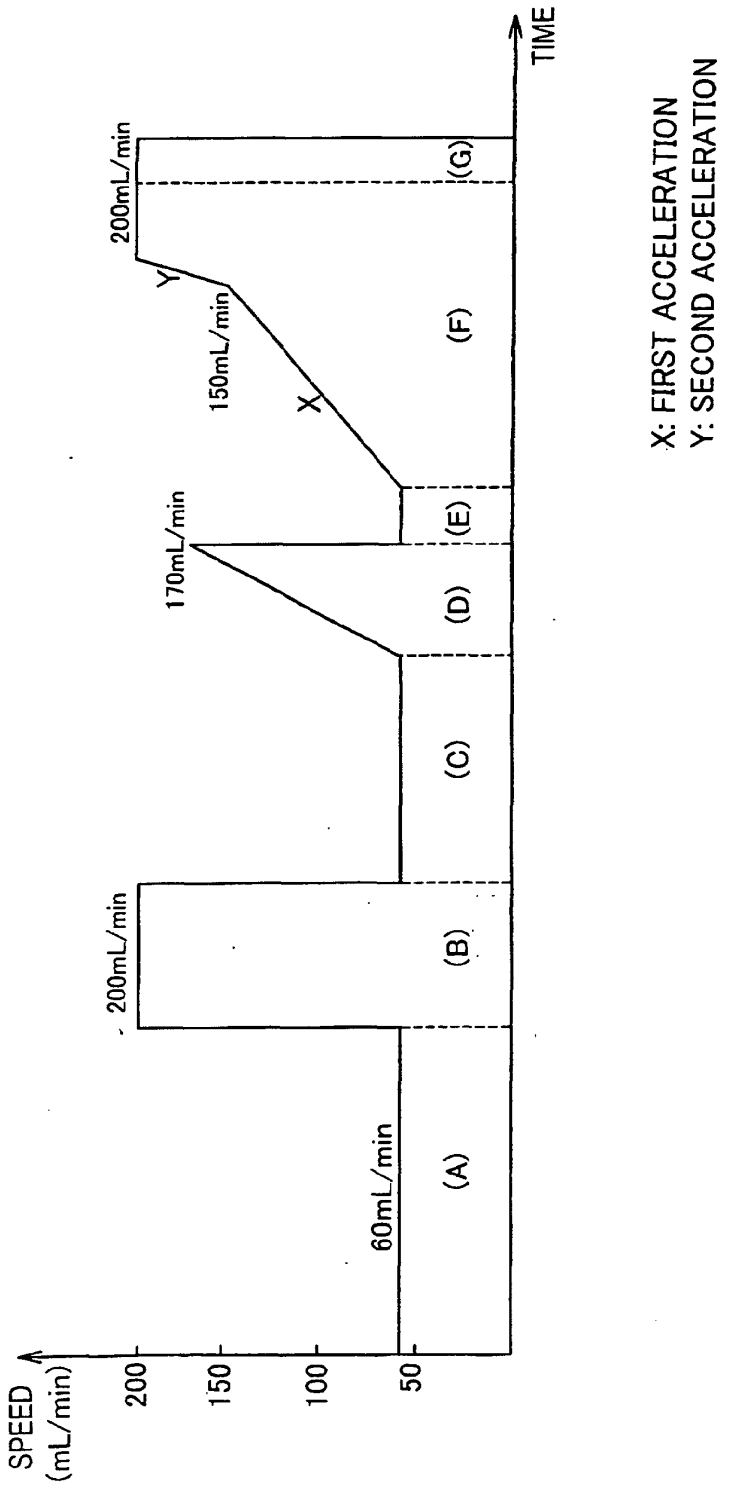


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FIG.2

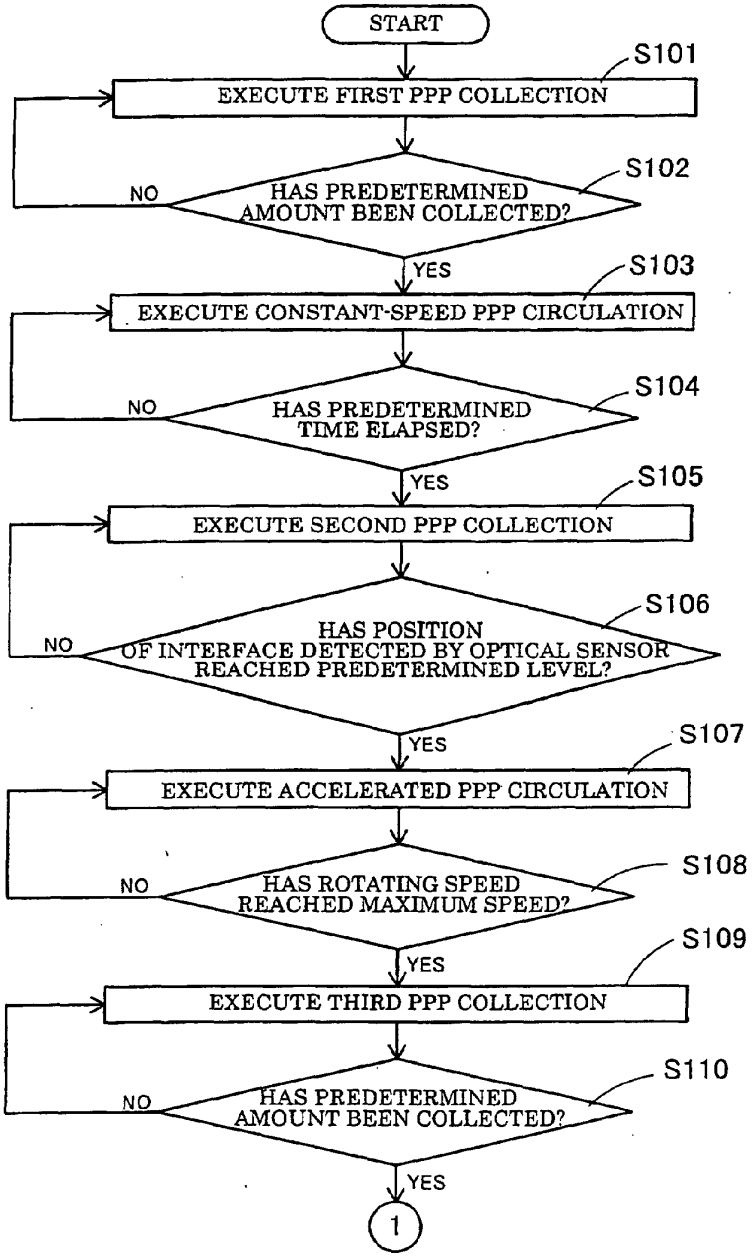


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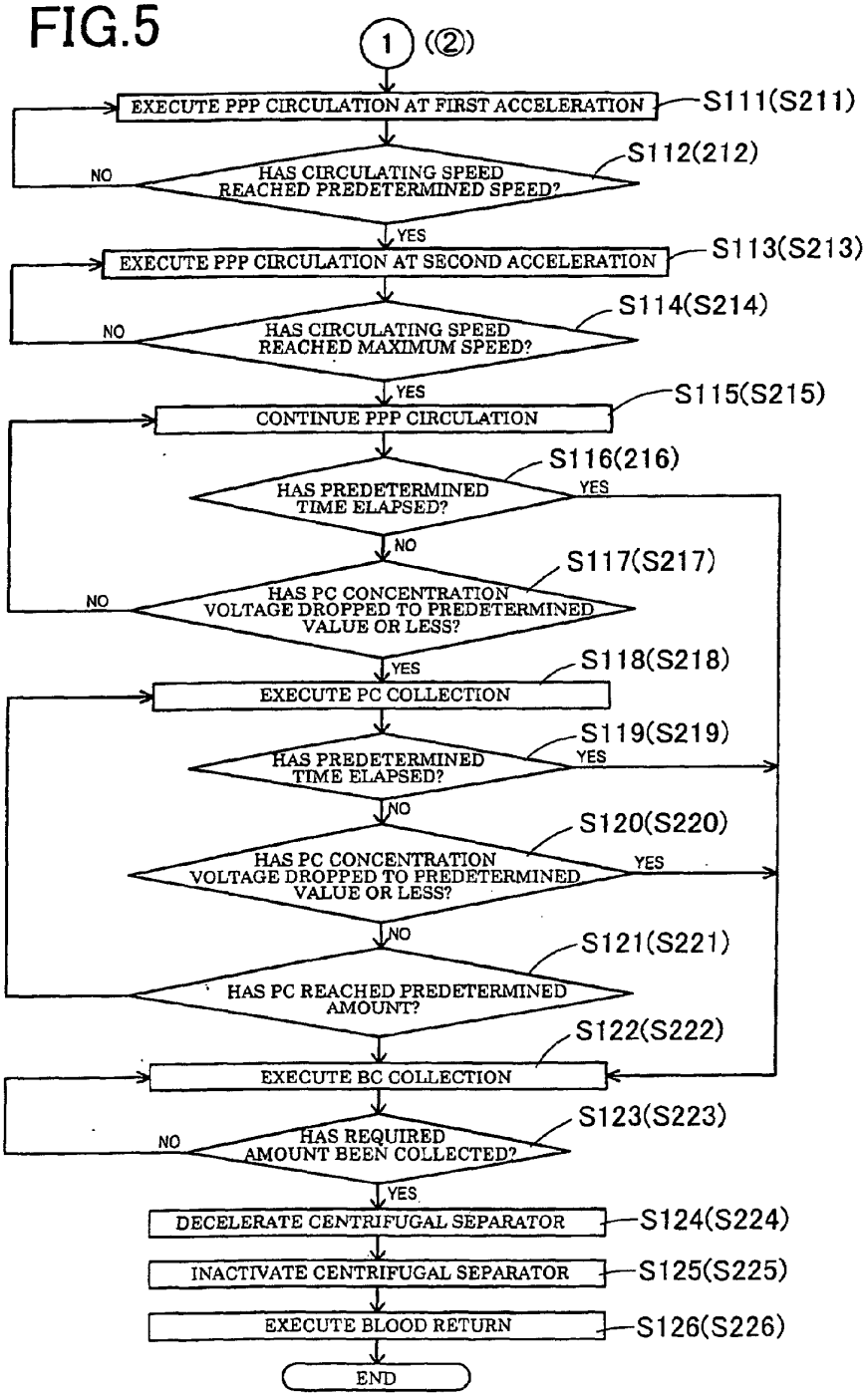
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FIG.4



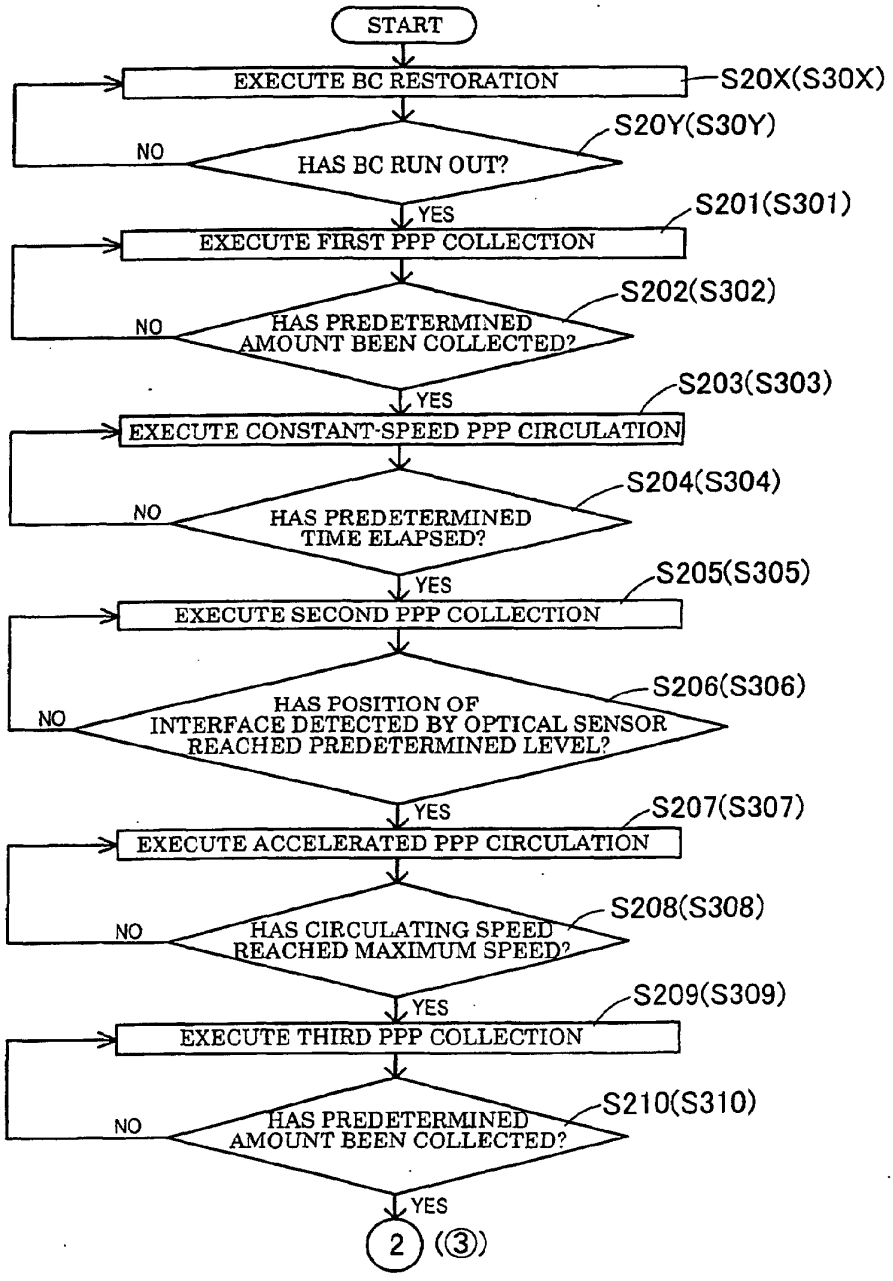
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FIG.5



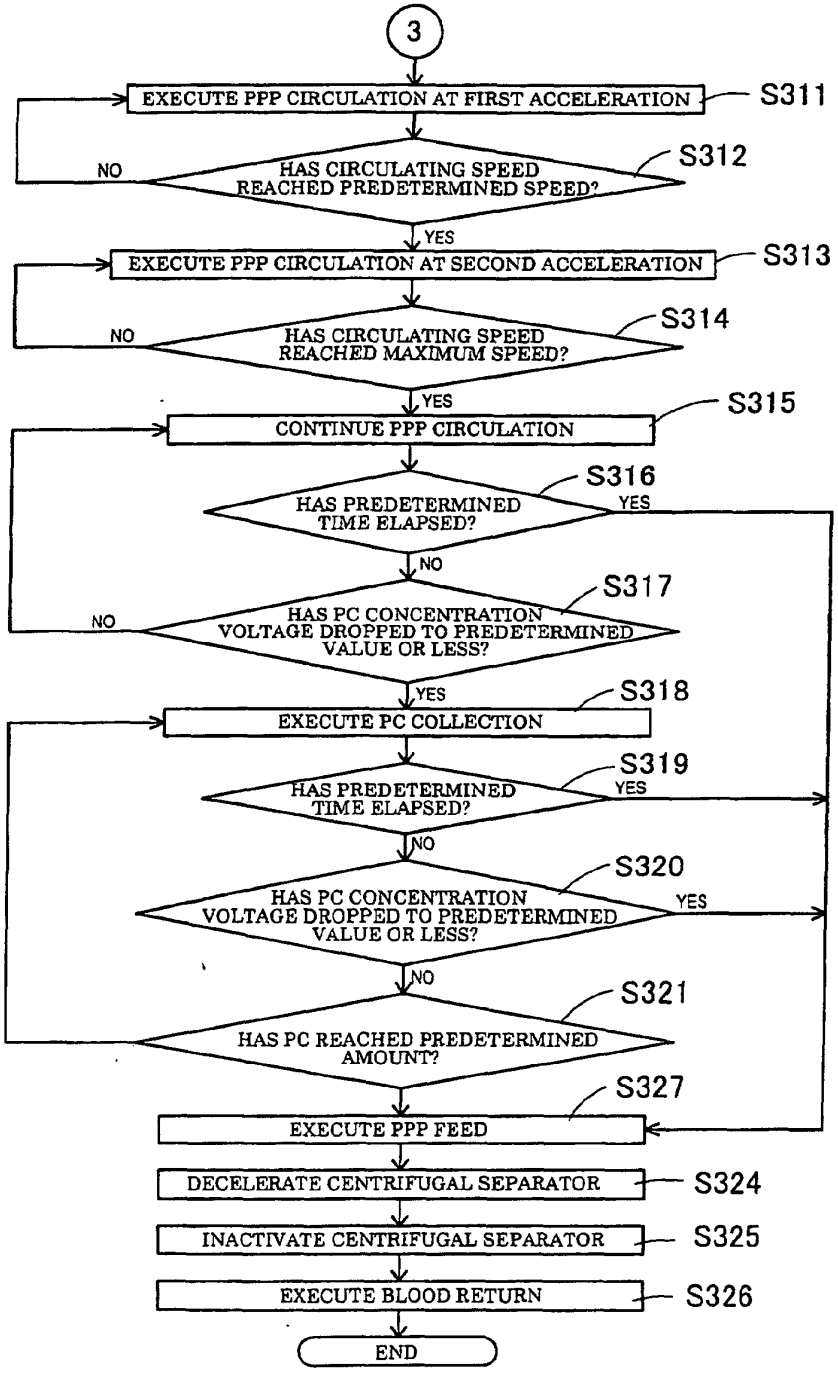
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FIG.6



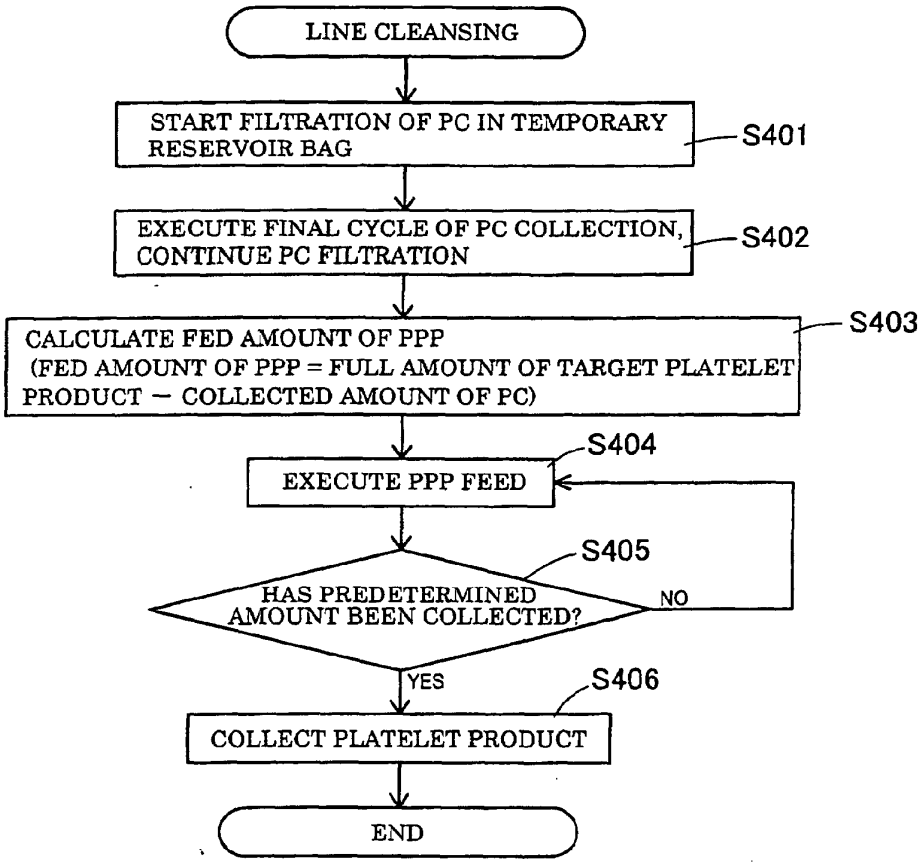
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FIG.7



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FIG.8



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/02625

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61M1/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61M1/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Jitsuyo Shinan Koho	1922-1996	Toroku Jitsuyo Shinan Koho	1994-2002
Kokai Jitsuyo Shinan Koho	1971-2002	Jitsuyo Shinan Toroku Koho	1996-2002

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 7-265407 A (Terumo Corp.), 17 October, 1995 (17.10.95), Full text; Figs. 1 to 5 (Family: none)	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"E" earlier document but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 June, 2002 (06.06.02)	25 June, 2002 (25.06.02)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1998)

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Application Number:	15608183
International Application Number:	
Confirmation Number:	7286
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Customer Number:	86738
Filer:	Jonathan Lovely
Filer Authorized By:	
Attorney Docket Number:	130670-08002
Receipt Date:	10-JAN-2019
Filing Date:	30-MAY-2017
Time Stamp:	11:10:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	130670-08002_-_CN2735985Y.pdf	340053 363881fe4191b9e89c6f1da01d7a50d7d18e2943	no	8

Warnings:

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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Espacenet

Bibliographic data: CN2735985 (Y) — 2005-10-26

Disposable blood cell separating device

Inventor(s): CHEN HUA [CN] ± (HUA CHEN)

Applicant(s): SHANGHAI DAHUA MEDICAL APPARAT [CN] ± (SHANGHAI DAHUA MEDICAL APPARATUS CO., LTD)

Classification: **- international:** ***A61M1/38;*** (IPC1-7): A61M1/38
- cooperative:

Application number: CN2004282755U 20040910

Priority number (s): CN2004282755U 20040910

Abstract of CN2735985 (Y)

The utility model relates to a blood cell separator with centrifugal separation principle, comprising a blood needle joint, a blood return needle joint, an anticoagulant bag and a salt water bag, which are connected to a centrifugation separator via a multi-cavity pipe; the centrifugation separator is composed of a centrifugation bin, a separation bag positioned in the centrifugation bin, and a collecting bag. A rich constituent blood plasma transporting pipe controlled and connected via a blood plasma pump is provided between the separation bag and the collecting bag. Adopting the structure chiefly solves the technical problem that the existing blood cell centrifugal separator adopts the single centrifugal separation structure to separate the blood cells, which leads to that the blood cells in the blood can not be fully utilized; disposable using and completing the complete-set the single blood sampling cell separation and recirculation processes of the blood sampling process, the centrifugation process, the separation process and the recirculation process can reduce the cross infections in high limit, protects the health of the blood donor and saves the blood resource.

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[12] 实用新型专利说明书

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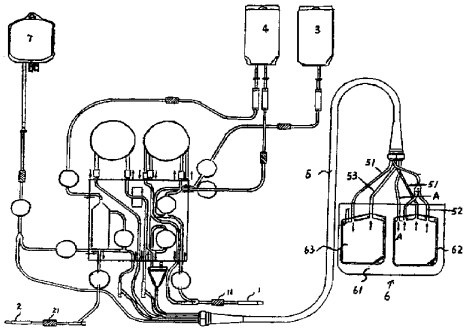
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代理人 王敏杰

权利要求书 1 页 说明书 4 页 附图 1 页

[54] 实用新型名称 一次性使用血细胞分离器

[57] 摘要

一种离心分离原理的血细胞分离器，包括进血针接头、返血针接头、抗凝剂袋和盐水袋，它们通过多腔管路连接到一离心分离机构；该离心分离机构由一离心仓和位于离心仓内的分离袋、收集袋组成，分离袋和收集袋之间有一通过血浆泵控制连通的富成分血浆输送管。藉由上述结构主要解决现有的血细胞离心分离机采用单次离心分离结构分离血细胞，以致血液中的血细胞不能被充分利用的技术问题，一次性使用完成采血、离心、分离、回输全套单采血细胞分离、回输过程，能最大限度减少交叉传染，保护献血员健康，节约血资源。



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1、一种一次性使用血细胞分离器，包括进血针接头、返血针接头、抗凝剂袋和盐水袋，它们通过多腔管路连接到一离心分离机构，其特征在于：该离心分离机构由一离心仓和位于离心仓内的分离袋、收集袋组成，分离袋和收集袋之间有一通过血浆泵控制连通的富成分血浆输送管。

2、根据权利要求 1 所述的一次性使用血细胞分离器，其特征在于：连接进血针接头和返血针接头的管路上具有压力传感器。

3、根据权利要求 1 所述的一次性使用血细胞分离器，其特征在于：该离心仓内有温度探测器、湿度探测器及转子平衡探测器。

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一次性使用血细胞分离器

技术领域：

本实用新型涉及一种一次性使用医用消耗器具，特别是一种离心分离原理的一次性使用血细胞分离器。

背景技术：

人体血液成分依其比重排列，分别是红细胞、粒细胞、淋巴细胞、血小板和血浆。医疗上根据需要只会给病人输入其所需要的成分，这样，对血液药源是一种节约。

目前，国内除了一些大城市的血液中心配备了血液分离机外，大部分地区血细胞分离均系手工采集。健康献血员的血液被采集后，经体外离心，再还输给献血员，这一过程不是密闭循环，极易出现还输失误和交叉传染。因此，中国实用新型专利说明书（授权公告号：CN2404534Y）公开了一种断续流动式血细胞分离机配套使用的一次性使用医用消耗器材，主要由抗凝剂袋、采样袋、血浆袋、产品收集袋、分离杯、采血针、药液过滤器、穿刺器及连接管、各种接头等构成，自成封闭式循环体系，能一次性使用完成采血、离心、分离、回输全套单采血细胞分离、回输过程，能最大限度减少交叉传染，保护献血员健康，节约血资源。

但是，这种血细胞分离机仍然存在一定缺陷，主要是分离杯采用单

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次离心分离采集血细胞，使得血液中的血细胞不能被充分利用。

实用新型内容：

本实用新型的目的是提供一种一次性使用血细胞分离器，解决现有的血细胞离心分离机采用单次离心分离结构分离血细胞，以致血液中的血细胞不能被充分利用的技术问题。

为解决上述技术问题，本实用新型是这样实现的：

一种一次性使用血细胞分离器，包括进血针接头、返血针接头、抗凝剂袋和盐水袋，它们通过多腔管路连接到一离心分离机构，其特征在于：该离心分离机构由一离心仓和位于离心仓内的分离袋、收集袋组成，分离袋和收集袋之间有一通过血浆泵控制连通的富成分血浆输送管。

连接进血针接头和返血针接头的管路上具有压力传感器。

该离心仓内有温度探测器、湿度探测器及转子平衡探测器。

藉上述结构，本实用新型具有如下优点：

1、本实用新型的离心仓内具有分离袋和收集袋，当分离袋对血液进行第一次离心分离后，由血浆泵将富成分血浆输送到收集袋再进行二次离心分离，确保了对血液中的血细胞进行充分地利用。

2、本实用新型能一次性使用完成采血、离心、分离、回输全套单采血细胞分离、回输过程，能最大限度减少交叉传染，保护献血员健康，节约血资源。

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附图说明：

图 1 是本实用新型的结构示意图。

具体实施方式：

请参阅图 1，它是本实用新型一次性使用血细胞分离器的结构示意图。如图所示：它包括进血针接头 1、返血针接头 2、抗凝剂袋 3 和盐水袋 4，它们通过多腔管路 5 连接到一离心分离机构 6。

该离心分离机构 6 由一离心仓 61 和位于离心仓 61 内的分离袋 62、收集袋 63 组成，分离袋 62 和收集袋 63 之间有一通过血浆泵控制连通的富成分血浆输送管 51。

连接进血针接头 1 和返血针接头 2 的管路上具有压力传感器 11、21。

该离心仓 61 内有温度探测器、湿度探测器及转子平衡探测器。

在运行过程中，抗凝的全血在全血泵的作用下，被泵入正在旋转的分离袋 62 中，血液成分分离的第一步发生在分离袋 62，可以看作是血液成分收集过程的第一次离心。当全血 A 进入分离袋后，较大密度的血液成分（主要是红细胞），在离心力的作用下，向分离袋 62 的外侧压积，然后通过 PRBC（压积红细胞）管路 52 退出分离袋；而那些密度较小的成分，如：血浆、血小板和/或百细胞可被血浆泵通过 CRP（富成分血浆）管路 51 运动到收集袋 63 内，血液成分分离的第二阶段在这里进行。可以看作是血液成分收集过程的第二次离心，当 CRP 进入收集袋 63 的底部，密度较大的成分入血小板和/或血细胞在离心力的作用下，向收集

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袋 63 的外侧积压。所要收集的成分留在收集袋 63 内，而密度较小的 CPP（穷血浆）通过 CPP 管路 53 退出收集袋。CPP 和 PRBC 混合后返还给献血员/病人，（或收集 CPP 至转输袋 7 内）。

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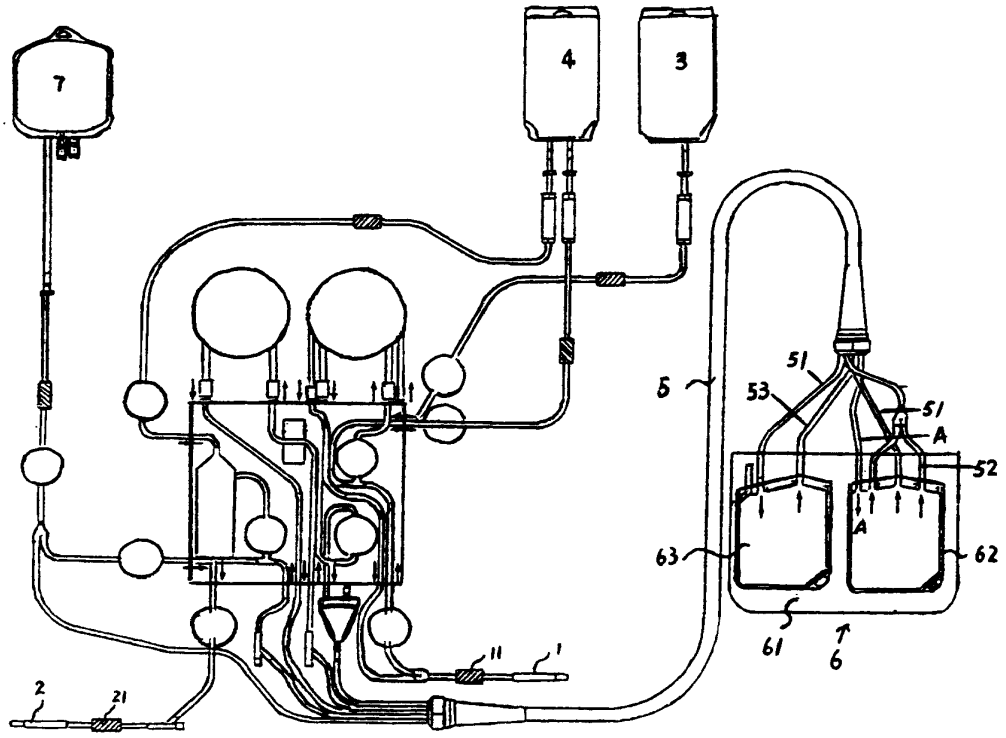


图 1

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(54) Single needle blood fractionation system having adjustable recirculation through filter.

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Description

Background of the invention

The present invention relates generally to systems and apparatus for processing whole blood, and more specifically to blood fractionation systems and apparatus having a filter component for separating and collecting a desired blood component, such as plasma, from whole blood through a single-lumen phlebotomy needle.

Various methods and apparatus have been developed for the in vivo processing of whole blood, wherein whole blood is taken from a donor, a desired blood component is separated and collected, and the processed blood is returned to the donor. Blood components typically collected using such processing include plasma (plasmapheresis), while blood cells (leukopheresis) and platelets (plateletpheresis).

In vivo blood processing apparatus may be of the centrifugal type, wherein the differing density of the collected blood component causes the component to congregate for collection at a particular radial distance in a centrifuge, or may be of the filter type, wherein the particle size of the collected component allows only that component to pass through a filter membrane into a collection chamber. Filter type apparatus is generally preferable for in vivo plasmapheresis applications, since such apparatus does not require complex rotating machinery and is more compact and less costly to manufacture.

One form of filter which is particularly attractive for use in plasmapheresis apparatus utilizes a plurality of parallel microporous hollow fibers arranged side-by-side in the form of a bundle within a hollow cylinder. As whole blood is caused to flow through the fibers the plasma component passes through the walls of the fibers to the surrounding container, which forms a collection chmber from which the component is transported to a collection container.

The efficiency of a flow-through filter in separating plasma from whole blood depends on the hematocrit of the donor, and the flow rate and pressure of the whole blood as it is pumped through the filter. Insufficient flow rates or whole blood pressures result in less than optimum yields. Excessive flow rates or whole blood pressures result in hemolysis, or damage to the red blood cells, within the filter, and possible failure of the filter to exclude red blood cells from the collected plasma. Thus, a practical limit exists for the percentage of plasma that can be recovered by a flow-through membrane filter in a single pass of whole blood.

To improve the efficiency of blood fractionation systems it has been proposed that once-filtered plasma-deficient whole blood be recirculated through the filter. This enables the filter to refilter the previously-filtered whole blood, recovering an additional percentage of the remaining plasma component.

However, in certain procedures, as where a high hematocrit is encountered in the whole blood drawn from a donor, the hematocrit of the once-filtered plasma-deficient whole blood may be so high as to require a reduction in the filter flow rate and pressure with an attendant reduction in filter efficiency, to avoid hemolysis in the second pass through the filter. This has the effect of increasing the time required to separate a given quantity of plasma, thereby increasing the inconvenience of the procedure to the donor. Accordingly, the need has developed for a blood fractionation system wherein recirculation through the filter is obtained while maintaining hematocrit, flow rate and pressure parameters which provide optimum system efficiency.

Furthermore, for user comfort it is desirable that in vivo blood fractionation systems withdraw and return whole blood to the donor through a single phlebotomy needle at a single injection site. This necessitates either the use of a single dual-lumen phlebotomy needle, in conjunction with a continuous flow non-batch system, or of a single-lumen phlebotomy needle in conjunction with a bidirectional batch system, whereby batches of whole blood are alternately drawn through the needle, passed through a plasma separation filter, and returned through the same needle. Sueh bidirectional single-lumen batch systems have the advantage of utilizing a smaller and potentially less traumatic single lumen needle. However, since such systems have heretofore not provided plasma separation from the batch in process during both the draw and return cycles, they have undesirably prolonged the time required to collect a desired volume of plasma.

The present invention is directed to a bidirectional single-needle batch type blood fractionation system which provides for user-controlled partial recirculation of plasma-deficient whole blood through the system filter during the blood return cycle, thereby enabling optimum plasma separation efficiency to be maintained in the system notwithstanding variations in whole blood hematocrit.

The present invention, by increasing the plasma separation efficiency of the system, makes a reduction in the volume of the system filter possible. This is advantageous in that it reduces the quantity of extracorporeal blood in process, and the cost of the system filter and the microporous filter material utilized therein.

DE—A—2745041 discloses a blood fractionation system for separating a blood fraction from whole blood comprising means including a donor interface conduit adapted for connection to a phlebotomy needle for alternately drawing whole blood from a donor and returning a component-deficient blood fraction to the donor. Whole blood is pumped through a main conduit to a separation means for separating the blood fraction and the blood fraction is stored in a reservoir. The pump is reversible, to return the component-deficient fraction through the main conduit back to the donor interface conduit and the donor,

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in response to a predetermined quantity of the blood fraction having been collected. The pre-characterising clause of Claim 1 is based on this disclosure.

The present invention is characterised by second fluid conveyance means including a return pump responsive to the volume in said reservoir reaching a predetermined maximum level for conveying the component deficient blood fraction from said reservoir to said donor interface conduit to reduce the volume in said reservoir to a predetermined minimum level; and said second pump rate being set relative to said first pump rate whereby upon said operation of said second fluid conveyance means a selected portion of the flow from said reservoir is caused to recirculate through said separation means, while the remaining portion is caused to be returned through the phlebotomy needle to the donor.

The invention, together with the further objects and advantages thereof, may best be understood by reference to the following description taken in conjunction with the accompanying drawings, in the several figures of which like reference numerals identify like elements, and in which:

Figure 1 is a perspective view of a single-needle partial-recirculation plasmapheresis blood fractionation system constructed in accordance with the invention.

Figure 2 is a functional block diagram showing the principal components of the blood fractionation system of Figure 1.

Figure 3 is an enlarged front elevational view of the control panel of the blood fractionation apparatus of Figure 1.

Figure 4 is an enlarged front elevational view partially in section showing the electrical weight transducer of the system in conjunction with the in-process fluid reservoir of the system.

Figure 5 is a simplified schematic diagram of the mode control circuit of the blood fractionation system.

Figure 6a is a simplified schematic diagram of the inlet pump motor control circuit of the blood fractionation system.

Figure 6b is a simplified schematic diagram of a portion of the return pump motor control circuit of the blood fractionation system.

Figure 7 is a simplified schematic diagram of the ACD pump drive circuit of the blood fractionation system.

Figure 8a is a simplified flow diagram of the blood fractionation system showing the system in the draw portion of its operating cycle.

Figure 8b is a flow diagram similar to Figure 8a showing the blood fractionation system adapted for recirculation in the return portion of its operating cycle.

Figure 8c is a flow diagram similar to Figure 8a showing the blood fractionation system adapted for non-recirculation in the return portion of its operating cycle.

Figure 8d is a flow diagram similar to Figure 8a showing the plasmapheresis system in its prime mode.

Figure 9 is a simplified depiction of plasma collection versus time useful in comparing the operation of various types of blood fractionation systems.

Figure 10 is a simplified depiction of collected plasma volume versus time for various types of blood fractionation systems useful in comparing the systems.

Figure 11 is a top plan view of a disposable fluid circuit for use in conjunction with the blood fractionation system of the invention.

Description of the preferred embodiment

Referring to the Figures, and particularly to Figure 1, a blood fractionation apparatus 20 for use in conjunction with a single-needle filter-type blood fractionation system having filter recirculation in accordance with the invention is seen incorporated within a table-mounted housing 21. The housing preferably includes a pair of vertical support poles 22 and 23 from which a horizontal bar 24 is mounted to allow a plurality of collection and dispensing containers of conventional construction to be hung by means of appropriate hangers.

The fractionation apparatus 20 operates in conjunction with a disposable fluid circuit, generally identified by the reference numeral 25 in Figure 1 and shown schematically in Figure 2. The fluid circuit 25 includes a plurality of flexible plastic tubing segments which form fluid conduits between various components of the fluid circuit. As shown in Figure 2, whole blood derived from or returned to a donor is conveyed through the lumen of a single single-lumen phlebotomy needle 26 and a bidirectional donor interface conduit segment 27 to which the needle is connected. Conduit 27 communicates with a T-connector 28, which communicates with a tubing segment 30. Whole blood is conveyed through tubing segment 30 and an inline mixing chamber 31 by a peristaltic-type inlet pump 32 to a hollow fiber-type flow-through filter 33. The operation of the inlet pump is monitored by a positive pressure (+P) monitor circuit 34 connected to tubing segment 30 by a short tubing segment. Negative pressure, such as might occur upon the collapse of a vein, is monitored by means of a negative pressure (−P) monitor circuit 35 connected to tubing segment 30 upline of inlet pump 32 by another short tubing segment.

To prevent blood from clotting while in process anticoagulant (ACD) solution from a supply container 36 is introduced into conduit segment 30 through a tubing segment 37 and a T-connector 38. A drip chamber 39 may be provided inline in segment 37 to monitor ACD flow. A peristaltic-type pump 40 is

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provided along tubing segment 37 to provide a controlled rate of addition of the anticoagulant fluid to the whole blood.

Plasma separated from whole blood within filter 33 is conveyed by a tubing segment 41 to a plasma collection container 42. The pressure provided by inlet pump 32 provides flow through filter 33 to the collection container. A weight scale of conventional construction may be provided to provide an indication to the user of the volume of plasma collected.

Plasma-deficient blood from filter 33 is conveyed through a tubing segment 43 to an in-process fluid storage reservoir 44. In accordance with the invention, this plasma-deficient blood is periodically withdrawn from reservoir 44 through a tubing segment 45 by a peristaltic-type return pump 46 for return to conduit 27 at T-connector 28. The whole blood conveyed through tubing segment 45 passes through a combined bubble trap and fluid absence detector 47, which may be similar in structure and operation to that described in U.S. Patent No. 4,341,116 to Arnold C. Bilstad et al.

Reservoir 44 and plasma container 42 are preferably hung at the same height to avoid the need for an equalizer valve at the whole blood and collected plasma outlets of filter 33. However, under other circumstances an equalizer valve may be provided to restrict the plasma outlet port until the pressure of the plasma in the filter reaches that of plasma-deficient blood flowing from the filter, and thereafter to modulate plasma flow through line 41 to maintain the pressure equivalence. A transmembrane pressure (TMP) monitoring system 48 may be provided in apparatus 20 to assist the user in making adjustments for maximum operating efficiency of filter 33.

For system priming purposes, a saline fluid may be added to segment 30 through a tubing segment 51, which is connected at one end to a saline container 52 and at its other end to a T-connector in conduit segment 30. A second saline line 53 is provided between container 52 and bubble trap 47 for use in the purging procedure to enable trapped air to escape. Drip chambers and clamps of conventional construction may be provided in lines 51 and 53 to assist the procedure. A safety clamp 54 positioned along tubing segment 45 downline of bubble trap 47 actuates in the event of detection of a bubble or in the event of a malfunction in the apparatus to preclude uncontrolled infusion of fluid into the donor.

Referring to Figure 1, the blood fractionation apparatus 20 includes a sloped control panel 55 containing operator-actuated controls for operating the apparatus. As shown in Figure 3, control panel 55 includes a pair of selector switches 60a and 60b by which the draw and return mode operating speeds of anticoagulant pump 40 are set, a pair of potentiometer controls 61a and 61b and a digital readout 62 by which the draw and return mode operating speeds of the inlet pump 32 are controlled, and a pair of potentiometer controls 63a and 63b and a digital readout 64 by which the draw and return mode operating speeds of the return pump 46 are controlled. A plurality of push button switches 65 are provided to establish the operating mode of the apparatus. A plurality of status indicating lights 66a—66f provide status and alarm indications, and three pairs of indicator lights 66g and 66h associated with respective ones of the system pumps indicate the draw and return operating cycles of the pumps. An emergency stop switch 67 provides for an immediate operator-initiated shutdown in the event of a malfunction.

A display 68 displays the total volume of whole blood processed by the apparatus since the beginning of a particular procedure. A display 69 displays fluid pressure readings, as called for by a trio of pushbutton switches 69a—69c. Actuation of switch 69a causes the inlet pressure of filter 33 to be displayed. Actuation of switch 69b causes the collected plasma pressure of the filter to be displayed. Actuation of switch 69c causes the inlet transmembrane pressure (TMP) of the filter to be displayed as derived by TMP monitoring circuit 48.

Referring to Figure 2, the inlet pump 32 is driven by a motor 70. Power for operating motor 70 is provided by a motor control circuit 72 which responds to potentiometer controls 61a and 61b and a tachometer feedback signal from a tachometer (not shown in Figure 2) associated with the motor to maintain a desired motor operating speed. The inlet pump flow rate is displayed by readout 62 as part of a display circuit which responds to the tachometer output signal.

Similarly, the return pump 46 is driven by a motor 76. Power for motor 76 is provided by a motor control circuit 78 which responds to a tachometer feedback signal from a tachometer (not shown in Figure 2) associated with the motor and panel-mounted potentiometers 63a and 63b to maintain a desired constant motor speed. The return pump flow rate is displayed by readout 64 as part of the display circuit.

The anticoagulant pump 40 is driven by a stepper motor 79. Drive signals for motor 79 are developed by a motor control circuit 80 which responds to rate selection switches 60a and 60b to maintain a desired anticoagulant flow rate.

The operation of the various pump motors is controlled by a control circuit 81 which includes the mode select pushbutton switches 65 on control panel 55. Certain system conditions, such as negative pressure at pressure monitor 35, or excessive positive pressure at pressure monitor 34, or the occurrence of a bubble or other fluid absence as signalled at the output of the combined bubble trap and fluid absence detector 47, result in the application of an alarm signal to control circuit 81. This circuit in turn produces a control signal which is applied to motor control circuits 72, 78 and 80 by way of a motor control line 82 to interrupt operation of the motors. In addition, an alarm 83 associated with the control circuit may be sounded and an appropriate one of indicator lamps 66a—66f may be lit to alert the operator. Each of motor control circuits 72, 78 and 80 also includes internal stall protection whereby an alarm signal is developed and applied to

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control circuit 81 by way of a control line 84 to terminate operation of blood fractionation apparatus 20 in the event of a pump malfunction.

Basically, the hollow fiber membrane-type filter device 33 employed in blood fractionation apparatus 20 includes a generally cylindrical housing within which a bundle of microporous hollow fibers are mounted. The housing includes end caps which close the ends of the housing to form a plasma collection chamber within the housing. A whole blood inlet port is formed on one end cap, and a whole blood outlet port is formed on the other end cap. Blood introduced through the inlet port enters the adjoining open ends of the hollow fiber membrane elements and proceeds to flow lengthwise through the fibers. Plasma in the whole blood flows through the micropores in the hollow fibers and out into the collection chamber formed within the housing circumferentially surrounding the bundle. The housing includes two side plasma outlet ports which communicate with the collection chamber. One outlet port communicates with the plasma collection container 42 to collect plasma separated by the filter. The other outlet port is used to sense plasma outlet pressure in conjunction with a tubing segment 85, a pressure transducer 86, and the transmembrane pressure (TMP) monitoring system 48. Plasma-deficient blood (containing red cells, leukocytes and platelets), having passed through the hollow fiber membrane elements, exists through the outlet port for temporary storage in the intermediate in-process fluid reservoir 44.

Plasma-deficient whole blood in reservoir 44 is periodically pumped by return pump 46 back to donor conduit segment 27. Inlet pump 32 continues to operate at this time at a rate set by the operator, so that a portion of the returned plasma-deficient blood dependent on the ratio of the return pump rate to the whole pump rate is recirculated through filter 33, thereby continuing plasma collection during the return cycle. For example, with inlet pump 32 continuously operating at 60 ml/min, and return pump 46 operating at 100 ml/min, 60 ml/min, or 60% of the processed plasma-deficient blood, is recirculated through the filter, and 40 ml/min, or 40%, is returned to the donor.

In performing a normal batch-mode procedure blood fractionation apparatus 20 operates in alternate draw and return cycles. During each draw cycle inlet pump 32 operates to draw whole blood through the phlebotomy needle into conduit 27 and to advance the whole blood through tubing 30 and mixing chamber 31 to filter 33. After a predetermined volume of plasma-deficient whole blood has been pumped through filter 33 into reservoir 44, the draw cycle is terminated and the return cycle is initiated. Return pump 46 then operates to pump plasma-deficient blood from reservoir 44 into conduit 30 at T-fitting 28. Depending on the relative operating speed of return pump 46 and inlet pump 32, a user-selectable portion of the plasma-deficient whole blood is pumped into mixing chamber 31 for subsequent recirculation through filter 33, and the remaining portion is returned to the donor through donor tubing segment 27 and needle 26. Upon the volume of the plasma-deficient blood in reservoir 44 reaching a predetermined minimum level, the return cycle is terminated and the draw cycle is again initiated. The cycles continue in alternation until a desired quantity of blood has been processed or a desired quantity of plasma has been collected.

The blood fractionation apparatus 20 is, in further accord with the invention, conditioned between the draw cycle and the return cycle by a circuit responsive to the weight of the intermediate in-process fluid reservoir 44. To this end, the blood fractionation apparatus 20 includes a weight transducer unit 100 from which the reservoir container 44 is suspended. As shown in Figure 4, the weight transducer unit 100 may include a housing 101 mounted by clamps 102 or other appropriate means to the horizontal support bar 24 of the apparatus. Within housing 101 reservoir 44 is suspended from the sense pin 103 of an electrical weight transducer 104, which may be conventional in construction and operation, provides an electrical output signal which is conveyed to the apparatus housing 21 through a connecting cable 106.

Within housing 21, blood fractionation apparatus 20 includes a mode control circuit 107 (Figure 2) which provides, in accordance with the magnitude of the signal from weight transducer 100, a pair of mode control signals for application to motor control circuits 72, 78 and 80 by way of a control line 108a and 108b. A mode select switch 109, located on control panel 55 (Figure 3), is provided to enable the user to selectively disable mode control circuit 107 when it is desired to operate the plasmapheresis apparatus as a continuously running system, as in conjunction with a continuous-flow two needle in vivo blood fractionation procedure.

Referring to Figure 5, within the weight transducer unit 100 the weight transducer 104 is seen to comprise a strain gauge bridge circuit 112. One input terminal of network 112 is connected to a source of positive current through a series-connected transistor 113, and the other input terminal is connected to ground. The conduction level of transistor 113, and hence the voltage applied to network 112, is controlled by a differential amplifier 115 having its non-inverting input connected to a source of regulated voltage, and its inverting input connected to a voltage divider comprising resistors 114a and 114b. The output of differential amplifier 115 is connected to the base of transistor 113 through a resistor 116, with the result that the voltage applied to network 112 is held constant at all times.

The output of bridge circuit 112, which depends on the force exerted on sense pin 103, is applied to a differential amplifier 120 included in mode control circuit 107. A necessary offset is introduced to this signal by an adjustable voltage divider network comprising resistors 121, 122, 123 and 124 connected between the regulated input terminal of network 112 and ground and the non-inverting input of differential amplifier 120.

To establish predetermined minimum and maximum volume thresholds for the plasma-deficient whole blood in reservoir 44 the output of differential amplifier 120 is applied to the non-inverting input of a

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comparator amplifier 125 and to the inverting input of a comparator 126. The inverting input of amplifier 125 is connected to a voltage divider comprising a resistor 127 and a potentiometer 128 connected between a source of regulated voltage and ground, and the inverting input. Depending on the setting of potentiometer 128, comparator amplifier 125 produces a logic high output signal as the volume of whole blood reaches a predetermined maximum level within reservoir 44. This output signal is applied to the set input of an RS-type flip-flop 130 which provides at its Q output the draw and return cycle mode control signal.

The non-inverting input of comparator amplifier 126 receives a reference voltage developed by a voltage divider comprising a resistor 131 and a potentiometer 132. Depending on the setting of potentiometer 132, the threshold of comparator amplifier 126 is varied to establih the minimum threshold level. Comparator 126 produces a logic low output which is applied to the reset input of flip-flop 130. Resistors 133 and 134 supply necessary operating current to the outputs of comparator amplifiers 125 and 126.

To enable blood fractionation apparatus 20 to be used for a continuous flow procedure wherein the ACD, inlet and return pumps are continuously controlled by controls 60a, 61a and 63a, respectively, an AND gate 136 is connected between the Q output of flip-flop 130 and control line 108a, and an OR gate 137 is connected between the Q output and control line 108b. One input of gate 136 is connected to a positive current source by a resistor 138, and to ground by mode switch 109. Gate 137 is similarly connected through an inverter 139. When switch 109 is open, corresponding to operator selection of a continuous-flow procedure, AND gate 136 is inhibited, rendering control line 108a logic low and control line 108b logic high, causing the pumps to operate continuously under the controls of 60a, 61a and 63b. However, when switch 109 is closed, AND gate 136 is enabled and the logic state of control line 108 is dependent on the operating state of RS flip-flop 130, and hence the volume of plasma-deficient blood accumulated in reservoir 44.

Referring to Figure 6a, the motor control circuit 72 provided for supplying operating power to the inlet pump motor 70 comprises a series-connected power transistor 140 and a reactance control network comprising an inductance 141 and a capacitor 142. These components supply power from a unidirectional motor current source (not shown) to the motor. The return line from the motor includes a series-connected current metering resistor 143.

Pump motor 70 is a direct current type motor and receives excitation over a variable duty cycle through power transistor 140. Conduction of this transistor is controlled by a pulse width modulator 144 which provides an apparatus control signal to the base electrode of the transistor. A tachometer formed by a light emitting diode 145 and a photodetector 146 operates in a conventional manner to provide output pulses indicative of incremental rotation of the pump motor. These pulses are applied to a tachometer output line through an amplifier 147 for use by other systems within the apparatus, and through an amplifier 148 to a frequency-to-voltage converter circuit 149. This circuit develops an analog output voltage in proportion to the frequency of the tachometer pulses. This signal is applied to the inverting input of a comparator amplifier 150, wherein it is compared with a speed control signal applied to the non-inverting input from potentiometer 61a or 61b through a trio of analog devices 151—153.

The control gate of switch device 151 is connected to the pump control line 82 so that in the absence of an appropriate motor enabling signal from the apparatus control circuit 81 no reference signal is applied to comparator 150. The control gate of switch device 152 is connected to mode control line 108a through an inverter 154 so that in the absence of a logic high signal on this control line an analog control signal may be applied to comparator 150 by the draw mode whole blood rate control potentiometer 61a. The control gate of switch device 153 is connected directly to mode control line 108a, so that in the presence of a logic high signal on this line the output of the return rate potentiometer 61b is applied to comparator 150.

Comparator amplifier 150 operates in a conventional manner to produce an output signal indicative of the difference between its inputs. This output signal is applied through an isolation circuit 155 to pulse width modulator 144, wherein it controls the duty cycle of power transistor 140, and hence the speed of pump motor 70.

Referring to Figure 6b, the return pump motor control circuit 78 may be identical to motor control circuit 72, except for the input circuit provided for potentiometer rate controls 63a and 63b and control line 108b.

To provide protection against overspeed operation, the excitation level applied to pump motor 70 is continuously monitored by an overspeed detection circuit 156. In the event of an overspeed condition, this circuit provides an output which is coupled through an OR gate 157 to the alarm output line 84, and to the inhibit input of pulse width modulator 144, wherein it prevents the application of current to the base of transistor 140, thereby stopping the motor. Additional protection against malfunction is provided by a stall detection circuit 158 which provides an input to OR gate 157 upon motor 70 becoming stalled, as detected by the voltage level across series-connected resistor 143.

Referring to Figure 7, a multi-phase drive signal is applied to the anticoagulant pump stepper motor 79 by a stepper motor drive circuit 160 of conventional design. Control pulses for initiating the multi-phase drive signal from drive circuit 160, and consequently each incremental rotation of the motor, are provided by a clock circuit 161. In the draw mode, output pulses from the clock are applied through a pair of analog switch devices 162 and 163 to a rate multiplier 164. Rate multiplier 164, which may be conventional in

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construction and operation, responds to an operator-selected rate set by switch 60a to provide a preselected rate multiplication to the applied clock pulses. This results in stepper motor drive circuit 160 being impulsed at a user-selected rate, and consequently the stepper motor 79 being driven at the desired rate.

Alternatively, clock pulses from clock 161 are supplied to a second rate multiplier 165 through switch device 162 and a third analog switch device 166. When devices 162 and 166 are conductive, rate multiplier 165 is active to control motor speed according to the setting of return mode rate selector switch 60b.

Control over operation of stepper motor 79 is obtained by apparatus control circuit 81 by applying the pump enable control signal developed on control line 82 to analog switch device 162. During batch mode operation of the blood fractionation apparatus, analog switch device 162 is enabled continuously. Switch device 163, which is connected to mode control line 108a through an inverter 167, is enabled during each draw cycle to render switch 60a operative. Switch device 166, which is connected directly to control line 108a, is conductive only during each return cycle. Consequently, switch 60b controls return rate. In a non-recirculation procedure, control line 108a provides a continuous logic low signal and only rate multiplier 164 and switch 60a are utilized. The outputs of rate multipliers 164 and 165 are applied to stepper motor drive circuit 160 and a stall detection circuit 168 through an OR gate 169.

The anticoagulant pump drive circuit 80 also includes a tachometer comprising a light emitting diode 170, a slotted disk 171 and a photodetector 172. As disk 171 turns with motor 79, output pulses produced by photodetector 172 are supplied through a first inverter amplifier 173 to a tach output line. Pulses are also supplied through a second inverter amplifier 174 to stall detector 168, which provides an output on alarm line 84 upon stepper motor 79 stalling.

The operation of blood fractionation system 20 is illustrated in Figures 8a—8d and 9. In the batch mode, the system operates as illustrated in Figures 8a and 8b. Where no recirculation through the filter is desired in the batch mode, the system operates as illustrated in Figures 8a and 8c. Where the system is to be primed, the system operates as illustrated in Figure 8d.

During the draw cycle, as shown in Figure 8a, whole blood is drawn from a donor through a single-lumen phlebotomy needle 26 and the bidirectional donor interface conduit 27 by inlet pump 32, which pumps the whole blood along conduit segment 30 to mixing chamber 31. Within the mixing chamber, the freshly drawn whole blood is, in accordance with one aspect of the invention, mixed with whole blood previously advanced along segment 30 by pump 32, and the resulting mixture is advanced through filter 33 to reservoir 44.

As the mixed whole blood from chamber 31 passes through filter 33, a portion of the plasma component contained therein is separated from the whole blood by the membrane element of the filter and is caused to flow through tubing segment 41 to plasma collection container 42. The volume of plasma thus collected can be readily determined by reference to a conventional weight scale 180 from which the plasma collection container is suspended. Alternatively, a collected volume monitoring system such as that described in the copending application of Arnold C. Bilstad et al, entitled "Blood Fractionation Apparatus Having Collected Volume Monitoring System", Serial No. 330,899, filed December 15, 1981, may be utilized to provide a direct readout of collected plasma volume.

During the draw cycle the operating rate of the inlet pump 32 is set by potentiometer 61a. The operating rate of the return pump 46, which is normally not operative during the draw cycle, may be set to zero by setting potentiometer 63a to zero. As an alternative, to preclude operation of the return pump 46 during the draw cycle, potentiometer 63a may be eliminated in the replacement pump motor control circuit 78 and the input to analog switch device 152 in that circuit may be connected to ground, as shown in Figure 6b. The operating rate of ACD pump 40 is set by selector switch 60a to operate a rate appropriate to the operating rate of inlet pump 32 to maintain a desired ratio of ACD to whole blood.

The plasma-deficient whole blood from the filter continues to collect in reservoir 44 during the draw cycle. As the weight of the whole blood in the reservoir increases, transducer 100 produces a progressively increasing output signal. When this signal reaches a level corresponding to fluid level l_1, in reservoir 44, the signal applied to comparator 125 (Figure 5) by differential amplifier 120 causes comparator 125 to produce an output signal which conditions RS flip-flop 130 to its set state. As a consequence, the Q output of flip-flop 130 becomes logic high, and, assuming AND gate 136 is enabled by mode switch 109 being open for batch operation, mode control line 108a conveys a logic high control signal. This causes termination of the draw cycle and initiation of the return cycle.

During the return cycle, as illustrated in Figure 8b, return pump 46 is operated to pump plasma-deficient whole blood from reservoir 44 back through conduit segment 45 to donor conduit 27 and conduit segment 30 at T-connector 28. The flow rate of the plasma-deficient whole blood, as established by return pump 46, under the control of potentiometer 63b, is set higher than the flow rate of the whole blood in conduit segment 30, as established by inlet pump 32 under the control of potentiometer 61b. As a result, the plasma-deficient whole blood flowing from reservoir 44 is caused to divide between donor conduit 27, wherein it causes a flow reversal and flow into the donor through the lumen of the single-lumen phlebotomy needle, and conduit segment 30, wherein it is advanced toward mixing chamber 31 and filter 33.

Within mixing chamber 31 the recirculating portion of the plasma-deficient whole blood divided into conduit segment 30 is caused to mix with whole blood previously pumped into the chamber, as during the

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previous draw cycle of the system. The resulting mixture, which has a hematocrit determined by the hematocrits of the recirculating plasma-deficient whole blood and the previously pumped resident whole blood, is advanced through filter 33 into reservoir 44 by inlet pump 32. This causes an additional quantity of plasma to be separated from the whole blood mixture by filter 33 and stored in plasma container 42.

The ratio of plasma-deficient whole blood returned to the donor to plasma-deficient whole blood recirculated through filter 33 is dependent on the relative operating rates of the inlet pump 32 and the return pump 46. For a relatively higher return pump rate, a higher percentage of plasma-deficient whole blood is returned to the donor. The actual operating rates of the inlet and return pumps during the return cycle are set by the operator by means of potentiometers 61b and 63b on panel 55. In practice, these rates are limited by practical considerations, such as the flow rate and pressure requirements of filter 33, the maximum permissible draw and return rates of the donor, and the capacity of the conduit segments and associated system components. The ACD pump 40 may be operated during the return cycle at a rate selected by selector switch 60b to maintain a desired percentage of ACD solution in the in-process whole blood.

Operation in the return cycle continues until the volume of plasma-deficient whole blood in fluid reservoir 44 reaches a predetermined minimum level, corresponding to level l_2 in Figure 8b. At this time the output signal produced by weight transducer 100 causes comparator 126 (Figure 5) to toggle RS flip-flop 130 to its reset state, causing a logic low on mode control lines 108a and 108b. This causes analog switch devices 152 (Figures 6a and 6b) and 163 (Figure 7) to close and analog switch devices 153 and 166 to open, thereby enabling the inlet pump draw cycle potentiometer 61a (and replacement pump draw cycle potentiometer 63a in a similar manner) and the ACD draw cycle rate selector switch 60a. Consequently, the return cycle is terminated and a new draw cycle is initiated.

Referring to Figure 9, during alternate draw and return cycles of blood fractionation system 20 the volume 181 of plasma-deficient blood in reservoir 44 is seen to vary between a predetermined maximum level, corresponding to level l_1, and a predetermined minimum level, corresponding to level l_2. At the same time, the volume 183 of plasma collected in container 42 is seen to increase with each cycle, at a faster rate during draw cycles as freshly drawn blood is filtered, and at a slower rate during return cycles, as recirculated blood is filtered with previously drawn blood. Normally, the fractionation procedure is continued until a desired volume of plasma (or other-desired blood fraction) has been collected, as determined by the weight of the collected plasma as read on scale 180.

As a result of the partial recirculation of plasma-deficient whole blood from reservoir 44 during each return cycle, the system filter operates during both draw and return cycles and the time required for separating a given volume of plasma is significantly reduced.

For example, the effect of recirculation through the filter for a system yield of 600 ml plasma, a donor of 5000 ml whole blood, a 200 ml/min return pump rate, a mixing chamber volume of 30 ml, and an in-process fluid reservoir having a predetermined maximum volume of 50 ml and a predetermined minimum volume of 30 ml, can be summarized for varying whole blood hematocrits and flow rates as follows:

		No recirculation			With recirculation		
Whole blood flow rate (ml/min)	Donor hemato-crit (%)	Procedure time (min)	Blood processed (ml)	Max filter hematocrit (%)	Procedure time (min)	Blood processed (ml)	Max filter hematocrit (%)
50	40	44.5	1690	41	39.7	1520	48
50	45	48.5	1831	46	42.9	1631	53
50	50	53.2	1990	51	46.7	1765	58
50	55	58.5	2178	56	51.3	1923	62
60	40	39.6	1667	41	34.0	1454	48
60	45	42.9	1802	46	36.6	1555	54
60	50	46.8	1958	51	39.9	1686	58
60	55	51.5	2138	56	43.6	1835	63
70	40	36.5	1694	41	30.5	1451	51
70	45	39.5	1826	46	33.1	1556	56
70	50	43.2	1985	51	35.9	1669	62
70	55	47.8	2183	56	39.3	1820	66

Thus, for hematocrits within the normally encountered range of 40—55% the single-lumen single needle partial-recirculation blood fractionation system of the present invention requires less processing time and less whole blood than a non-recirculation single-lumen single needle batch system wherein whole blood is drawn, filtered and returned in discrete batches and no recirculation through the filter takes place. Only the more complex and less convenient two needle continuous flow systems, which requires two phlebotomy needles, has a greater system efficiency. This is illustrated in Figure 10, wherein collected

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plasma volumes 183, 184 and 185 are depicted for two needle continuous, single needle recirculation and single needle batch systems, respectively.

Where it is desired to operate the blood fractionation system without recirculation, as where a donor is encountered having an unusually high hematocrit which raises the probability of hemolysis in a second pass through the filter, the operating speed of the inlet pump during the return cycle can be set to zero by means of potentiometer 61b. Then, as shown in Figure 8c, all of the plasma deficient whole blood pumped from reservoir 44 during the return cycle is caused to flow back to the donor through the donor interface conduit 27 and the single lumen phlebotomy needle 26. Inlet pump 32, being motionless, functions as a valve to prevent flow through tubing segment 30, thereby obviating the need for separate fluid flow control valves and their attendant control systems.

Where exceptionally low hematocrits are encountered, substantially all of the plasma deficient whole blood from reservoir 44 can be recirculated through filter 33 by setting the inlet pump 32 and the replacement pump 46 to operate at the same rate. It is contemplated that this procedure would be used only for short time periods, such as required to complete a second pass through the filter, to avoid subjecting the filter to excessively high hematocrits and attendant hemolysis.

During the draw and return cycles the ACD pump 40 introduces ACD solution into conduit segment 30 at respective rates selected by the operator. The operation of the ACD pump and the rate selected are options available to the physician and may vary according to the particulars of the procedure.

Prior to initial operation of the blood fractionation system a prime mode may be provided wherein air is removed from the conduit segments and fluid path elements of the system. As shown in Figure 8d, the saline lines 51 and 53, heretofore clamped closed during the drawn and return cycles, are opened. The donor conduit segment 27 is clamped shut and pumps 32, 40 and 46 are operated to pump saline solution from container 52 and ACD solution from container 36 throughout the system. Trapped air and bubbles are forced into the combined bubble trap and fluid absence detector 47, wherein they are collected and discharged through line 53 to saline container 52. Fluid absence detector 47 is disabled and the procedure continues until all trapped air has been exhausted. The procedure is then terminated by the operator, and after the system has been connected to the donor, an appropriate input is applied to control circuit 81 to initiate a draw cycle.

Thus, the blood fractionation system of the invention can be conveniently set up, and once in use can operate automatically without continuous operator intervention. By reason of its increased plasma separation efficiency, the system of the invention can utilize a smaller volume filter component and hence a smaller volume flow system, to accomplish a given blood fractionation procedure. Since the smaller filter requires a smaller microporous filter element, the cost of the filter component, and hence the cost of the system, is reduced.

The fluid flow system 25 utilized in conjunction with the system may be formed of vinyl and other plastic non-pyrogenic materials as a single use disposable flow set, as shown in Figure 11. The set is preferably individually packaged in a sterile condition for convenient long term storage prior to use.

The mixing chamber 31 is provided up-line of filter 33 to mix the plasma-deficient whole blood diverted for recirculation with previously drawn whole blood, thereby averaging the hematocrit of whole blood circulating through the filter over successive draw and return cycles and enabling the flow rate and pressure at the filter to be more nearly optimized. To this end, the mixing chamber preferably has a volume substantially equal to or greater than the volume of plasma-deficient whole blood pumped from reservoir 44 during the return cycle. This assures that the recirculated plasma-deficient blood will mix with at least an equal volume of previously pumped blood. In practice the mixing chamber may have a volume which is a multiple of the volume pumped from the in-process chamber. For example, in one successful application of the invention, which utilized an intermediate fluid reservoir having a volume of 100 ml, a high limit of 50 ml, and a low limit of 30 ml, a mixing chamber having a volume of 50 ml was provided in conjunction with a filter having a 5 ml volume. In this application, a return pump speed of 200 ml/min was utilized in conjunction with inlet pump speeds of 50—70 ml/min. This provided a ratio of 3:1 between the pump speeds, which has been found to provide good efficiency with the 40—55% hematocrit levels typically encountered, as shown in the previous tabulation.

While the use of a weight-responsive transducer has been shown for controlling the return cycle, it is possible to use other control means, such as electrical switches actuated by a mechanical weight scale linkage on which reservoir 44 is supported, or a pair of ultrasonic level detectors arranged to sense blood level in the reservoir. Also, the system may be used in conjunction with a pressure cuff.

The blood processing system of the invention has the further advantage of being dependent only on the volume of separated cellular component, or plasma-deficient whole blood, which is directly related to the volume of whole blood processed; and not on the volume of the collected non-cellular component, or plasma, which is dependent on the hematocrit of the whole blood and therefore not directly related to processed volume. This enables the system to draw and return without readjustment batches of uniform volume from different donors, notwithstanding differences in hematocrits between the donors.

While the invention has been shown in conjunction with a hollow fiber type filter, it will be appreciated that it can be utilized in conjunction with other types of filters, such as a flat membrane type filter, or a centrifugal separator. Also, in conjunction with the hollow fiber membrane filter shown, a pressure regulator valve and TMP monitoring system may be employed for more accurate TMP control.

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Claims

1. A blood fractionation system for separating a blood fraction from whole blood, comprising means including a donor interface conduit (27) adapted for connection to a phlebotomy needle (26) for alternately drawing whole blood from a donor and returning a component-deficient blood fraction to the donor; a fluid reservoir (44); separating means (33) for separating the blood fraction from whole blood; first fluid conveyance means (25) including an inlet pump (32) for conveying fluid from said donor conduit through said separation means to said reservoir (44); the system being adapted to return the component-deficient blood fraction to the donor interface conduit (27) from the reservoir (44), characterised by second fluid conveyance means (45) including a return pump (46) responsive to the volume in said reservoir (44) reaching a predetermined maximum level for conveying the component deficient blood fraction from said reservoir to said donor interface conduit (27) to reduce the volume in said reservoir to a predetermined minimum level; and said second pump rate being set relative to said first pump rate whereby upon said operation of said second fluid conveyance means (45) a selected portion of the flow from said reservoir is caused to recirculate through said separation means (33), while the remaining portion is caused to be returned through the phlebotomy needle to the donor.

2. A blood fractionation system according to Claim 1, wherein the second fluid conveyance means (45) is responsive to the weight of the contents of the reservoir (44).

3. A blood fractionation system according to Claim 1 or 2, wherein the rates of said inlet and return pumps (32, 46) are operator-adjustable.

4. A blood fractionation system according to Claim 1, 2 or 3, wherein the volume of said first fluid conveyance means (32) is substantially equal to or greater than the volume of component-deficient blood fraction returned from said reservoir upon operation of said second fluid conveyance means (45).

5. A blood fractionation system according to Claim 4, wherein said first fluid conveyance means (32) includes a fluid mixing chamber (31) upline of the separation means (33) having a volume substantially equal to or greater than the volume of component-deficient blood fraction returned from said reservoir (44) upon a single operation of said second fluid conveyance means (45).

6. A blood fractionation system according to any preceding claim, wherein said separation means (33) is a membrane type filter such as a hollow fiber type filter.

7. A blood fractionation system according to Claim 1 including means for monitoring the volume of the component-deficient blood fraction, and control means for commencing return thereof to the donor when the volume of the collected component-deficient blood fraction reaches a predetermined maximum level, and for terminating the return of the cellular component when the volume thereof reaches a predetermined minimum level.

8. A blood fractionation system according to Claim 7, wherein said control means include an electrical weight transducer providing an output signal indicative of the weight of the component-deficient blood fraction.

9. A blood fractionation system according to Claim 7 or 8, wherein the control means operates said inlet pump (32) at a preselected rate for continuously pumping blood through the first conveyance means (25) and operates said return pump (46) intermittently at a preselected rate for intermittently pumping a predetermined aliquot of the component-deficient blood fraction through the second conveyance means (45).

Patentansprüche

1. Blut-Fraktionierungsystem zum Abtrennen eines Blutbestandteils vom Gesamtblut, umfassend Mittel einschließlich einer Spender-Verbindungsleitung (27) zur Verbindung mit einer Phlebotomienadel (26) zum abwechselnden Abziehen von Gesamtblut von einem Spender und Zurückführen einer Blutfraktion, der eine Komponente fehlt, zum Spender; ein Flüssigkeitsreservoir (44); Abtrennungsmittel (33) zum Abtrennen des Blutbestandteils vom Gesamtblut; erste Flüssigkeitsförderungsmittel (25), einschließlich einer Einlaßpumpe (32) zum Fördern von Flüssigkeit von der Spender-Leitung durch die Abtrennungsmittel zum Reservoir (44); wobei das System so ausgebildet ist, daß der Blutbestandteil mit fehlender Komponente zur Spender-Verbindungsleitung (27) vom Reservoir (44) zurückführbar ist, gekennzeichnet durch zweite Flüssigkeitsförderungsmittel (45) einschließlich einer Rückführpumpe (46), um in Antwort darauf, daß das Volumen im Reservoir (44) einen vorbestimmten Maximalpegel erreicht, den Blutbestandteil mit fehlender Blutkomponente vom Reservoir zur Spender-Verbindungsleitung (27) zur Verminderung des Volumens im Reservoir auf einen vorbestimmen Minimalpegel zu fördern; und wobei die zweite Pumprate in Relation zur ersten Pumprate eingestellt wird, wodurch bei Arbeiten der zweiten Flüssigkeitsfördermittel (45) ein ausgewählter Teil des Flusses vom Reservoir zur Rückströmung durch die Abtrennungsmittel (33) veranlaß wird, während der übrige Teil durch die Phlebotomienadel zum Spender zurückgeführt wird.

2. Blutfraktionierungssystem nach Anspruch 1, wobei die zweiten Flüssigkeitsförderungsmittel (45) auf das Gewicht des Inhaltes des Reservoirs (44) ansprechen.

3. Blutfraktionierungssystem nach Anspruch 1 oder 2, wobei die Raten der Einlaß- und Rückführpumpen (32, 46) von einer Bedienungsperson einstellbar sind.

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4. Blutfraktionierungssystem nach den Ansprüchen 1, 2 oder 3, wobei das Volumen der ersten Flüssigkeitsförderungsmittel (32) im wesentlichen gleich oder größer als das Volumen des Blutbestandteils mit fehlender Komponente ist, welcher vom Reservoir beim Arbeiten der zweiten Flüssigkeitsförderungsmittel (45) zurückgeführt werden.

5. Blutfraktionierungssystem nach Anspruch 4, wobei die ersten Flüssigkeitsförderungsmittel (32) eine Flüssigkeitsmischkammer (31) umfassen, die stromauf der Abtrennungsmittel (33) liegen und ein Volumen aufweisen, das im wesentlichen gleich oder größer dem Volumen des Blutbestandteils mit fehlender Komponente ist, der vom Reservoir (44) auf eine einzige Inbetreibnahme der zweiten Flüssigkeitsförderungsmittel (45) zurückgeführt wird.

6. Blutfraktionierungssystem nach einem der vorhergehenden Ansprüche, wobei die Abtrennungsmittel (33) ein Membranfilter wie z.B. einen Hohlfaser-Filter umfassen.

7. Blutfraktionierungssystem nach Anspruch 1, umfassend Mittel zum Überwachen des Volumens des Blutbestandteils mit abgetrennter Komponente und Steuermittel zum Beginnen dessen Rückführung zum Spender, wenn das Volumen des Blutbestandteils mit fehlender Komponente einen vorbestimmten Maximalpegel erreicht und zum Beenden der Rückführung der zellulären Komponente, wenn deren Volumen einen vorbestimmten Minimalpegel erreicht.

8. Blutfraktionierungssystem nach Anspruch 7, wobei die Steuermittel einen elektrischen Gewichtswandler umfassen, der ein Ausgangssignal abgibt, welches des Gewicht des Blutbestandteils mit fehlender Komponente wiedergibt.

9. Blutfraktionierungssystem nach Anspruch 7 oder 8, wobei die Steuermittel die Einlaßpumpe (32) mit einer vorbestimmten Rate ansteuern, um kontinuierlich Blut durch die ersten Förderungsmittel (25) zu pumpen, und die Rückführungspumpe (46) intermittierend mit vorbestimmter Rate ansteuern, um einen vorbestimmten anderen Teil des Blutbestandteils mit fehlender Komponente durch die zweiten Förderungsmittel (45) zum pumpen.

Revendications

1. Système de fractionnement du sang pour séparer une fraction de sang du sang entier, comprenant des moyens comportant un conduit (27) d'interface de donneur prévu pour le raccordement à une aiguille de phlébotomie (26) pour alternativement extraire du sang entier d'un donneur et renvoyer une fraction de sang apprauvrie en un composant au donneur; un réservoir de fluide (44); des moyens de séparation (33) pour séparer la fraction de sang du sang entier; des premiers moyens de transport de fluide (25) comportant une pompe d'entrée (32) pour faire circuler le fluide venant dudit conduit de donneur vers ledit réservoir (44), à travers lesdits moyens de séparation; le système étant prévu pour renvoyer la fraction de sang appauvrie en composant au conduit d'interface de donneur (27) à partir du réservoir (44), caractérisé en ce qu'il comprend des deuxièmes moyens de transport de fluide (45) comportant une pompe de retour (46) qui répond à l'arrivée du volume dans ledit réservoir (44) à un niveau maximal prédéterminé, pour faire circuler la fraction de sang appauvrie en composant dudit réservoir audit conduit d'interface de donneur (27) afin d'abaisser le volume dans ledit réservoir à un niveau minimal prédéterminé, le débit de ladite deuxième pompe étant fixé par rapport au débit de ladite première pompe de sorte que, lors dudit fonctionnement desdits deuxièmes moyens de transport de fluide (45), une partie déterminée du débit venant dudit réservoir est amenée à récirculer à travers lesdits moyens de séparation (33), tandis que la partie restante est renvoyée vers le donneur par l'intermédiaire de l'aiguille de phlébotomie.

2. Système de fractionnement du sang suivant la revendication 1, dans lequel les deuxièmes moyens de transport de fluide (45) sont sensibles au poids du contenu du réservoir (44).

3. Système de fractionnement du sang suivant la revendication 1 ou 2, dans lequel les débits desdites pompes d'entrée et de retour (32, 46) sont réglables par l'opérateur.

4. Système de fractionnement du sang suivant la revendication 1, 2 ou 3, dans lequel le volume desdits premiers moyens de transport (32) est sensiblement égal ou supérieur au volume de la fraction de sang appauvrie en composant renvoyée à partir dudit réservoir, lors du fonctionnement desdits deuxièmes moyens de transport de fluide (45).

5. Système de fractionnement du sang suivant la revendication 4, dans lequel lesdits premiers moyens de transport de fluide (32) comprennent une chambre de mélange de fluide (31) qui est située en amont des moyens de séparation (33) et qui a un volume sensiblement égal ou supérieur au volume de la fraction de sang appauvrie en composant renvoyée à partir dudit réservoir (44) lors d'un fonctionnement unique desdits deuxièmes moyens de transport de fluide.

6. Système de fractionnement du sang suivant l'une quelconque des revendications précédentes, dans lequel lesdits moyens de séparation (33) sont constitués par un filtre du type à membrane, tel qu'un filtre du type à fibres creuses.

7. Système de fractionnement du sang suivant la revendication 1, comprenant des moyens de contrôle du volume de la fraction de sang appauvrie en composant, et des moyens de commande pour commencer son renvoi au donneur lorsque le volume de la fraction de sang appauvrie en composant collectée atteint un niveau maximal prédéterminé, et pour terminer le renvoi du composant cellulaire lorsque son volume atteint un niveau minimal prédéterminé.

8. Système de fractionnement du sang suivant la revendication 7, dans lequel lesdits moyens de

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commande comprennent un transducteur de poids électrique fournissant un signal de sortie indicatif du poids de la fraction de sang appauvrie en composant.

9. Système de fractionnement du sang suivant la revendication 7 ou 8, dans lequel les moyens de commande actionnent ladite pompe d'entrée (32) à un débit prédéterminée, pour pomper continuellement le sang à travers les premiers moyens de transport (25), et actionnent ladite pompe de retour (46) de façon intermittente à un débit prédéterminé, pour pomper par intermittance une partie aliquote prédéterminée, de la fraction de sang appauvrie en composant à travers les deuxièmes moyens de transport (45).

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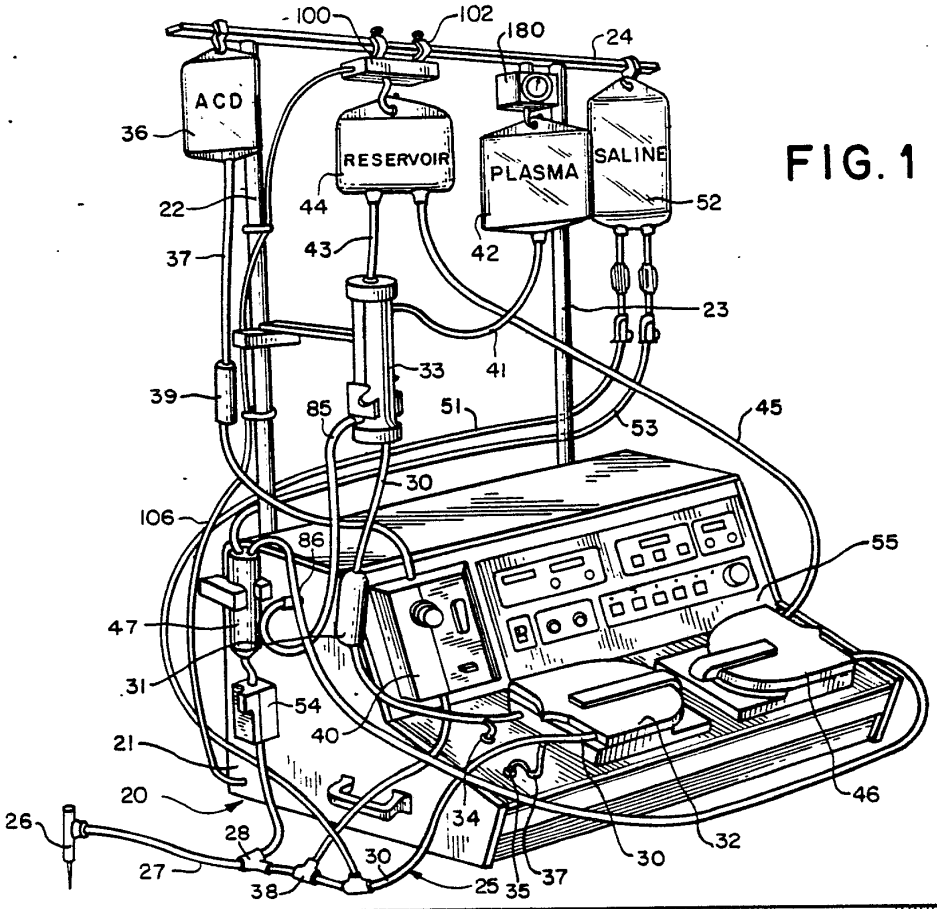


FIG. 1

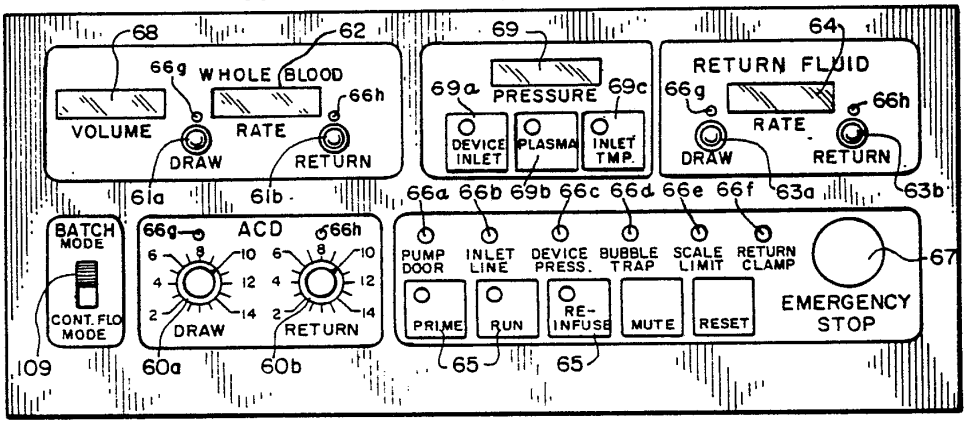
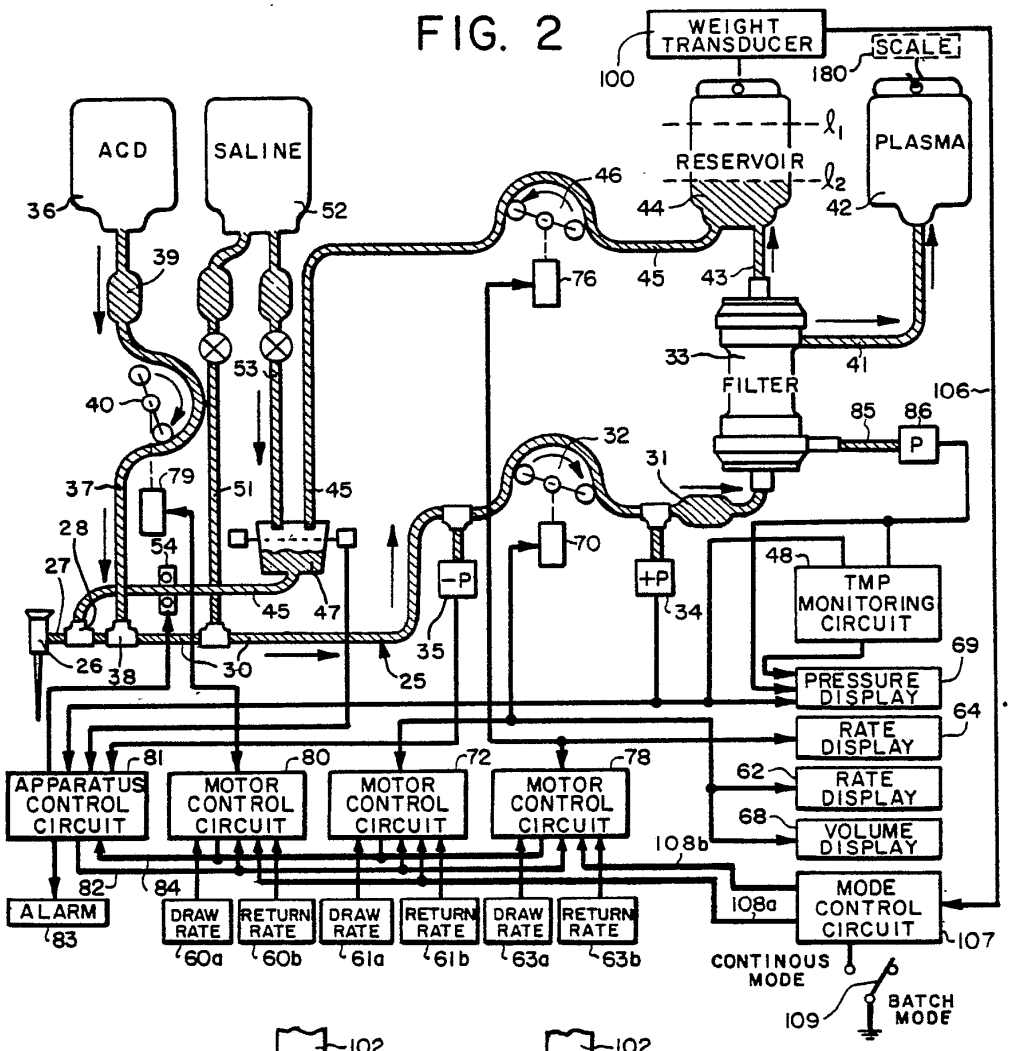


FIG. 3

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FIG. 2



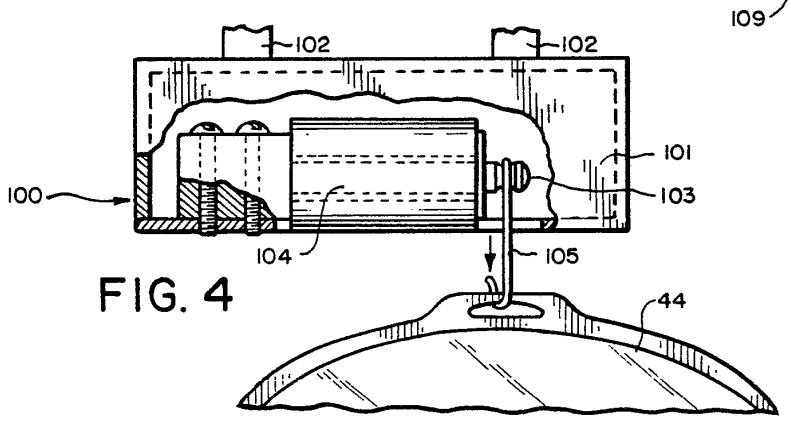


FIG. 4

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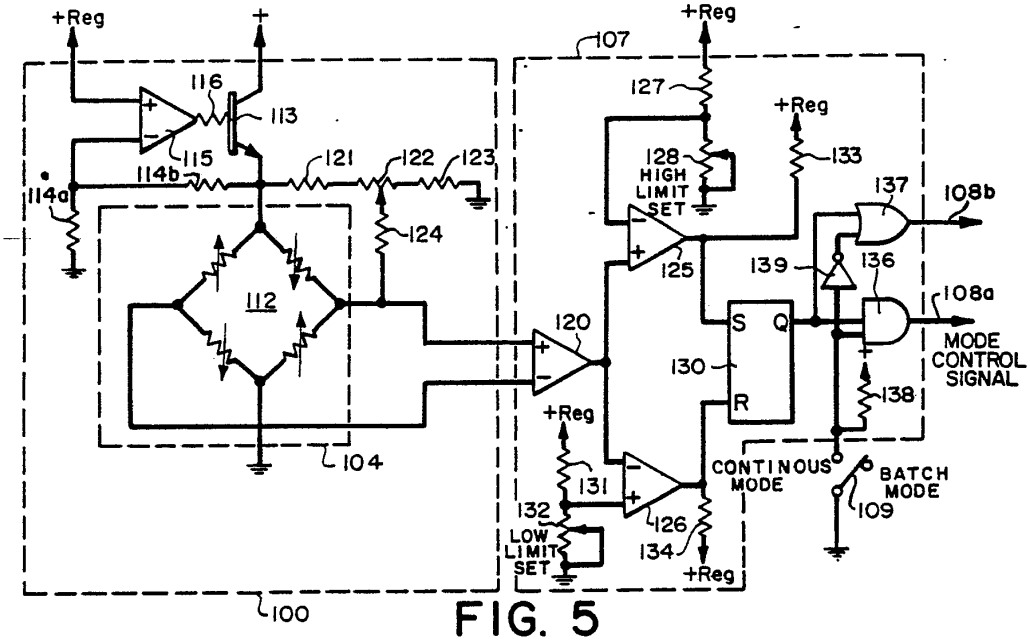


FIG. 5

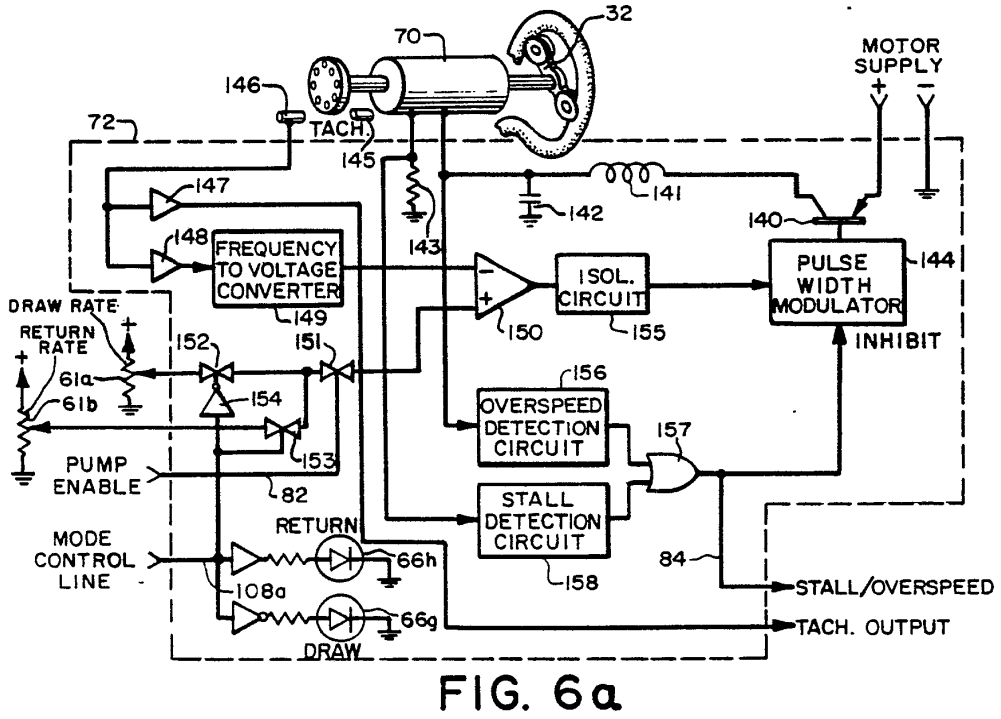


FIG. 6a

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FIG. 7

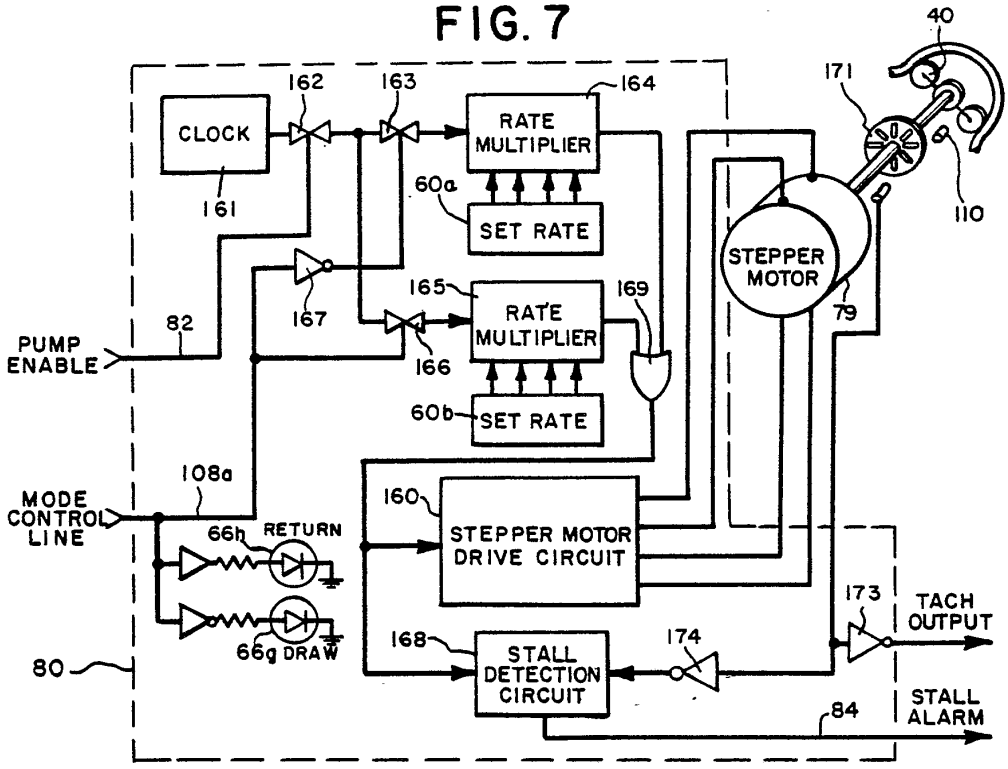
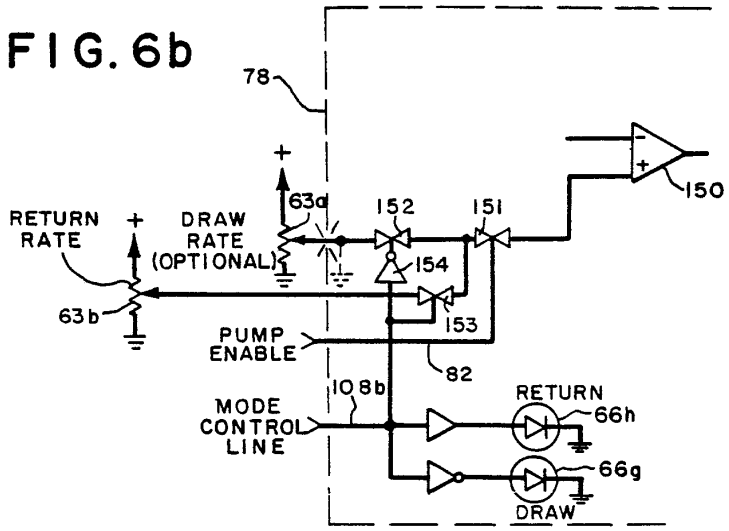


FIG. 6b



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FIG. 8a
(DRAW)

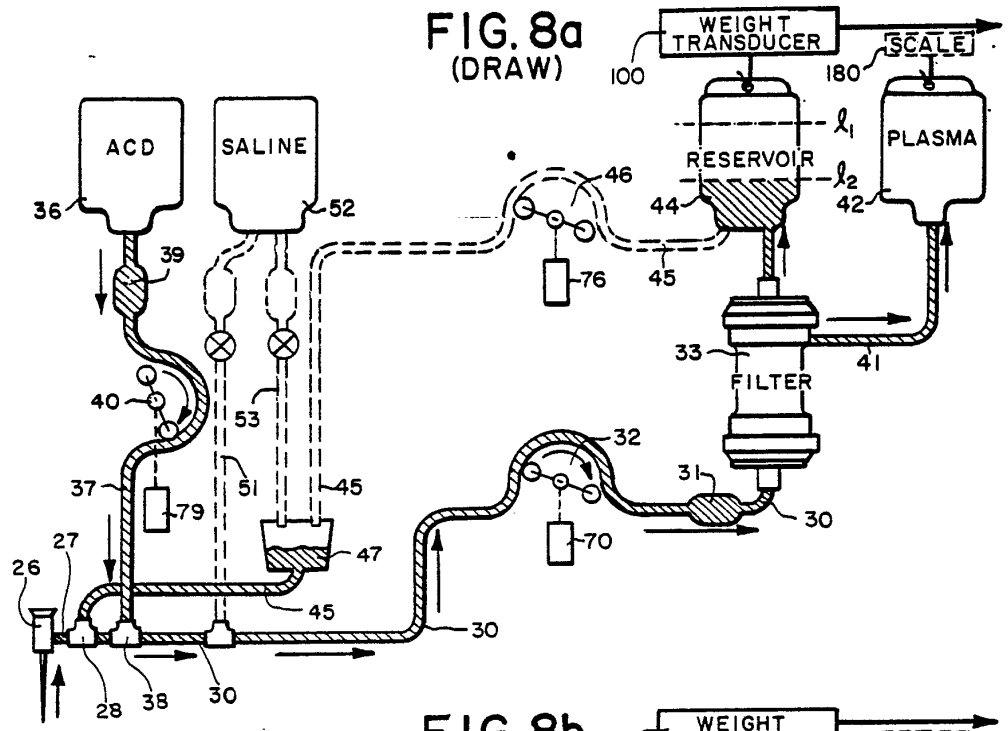
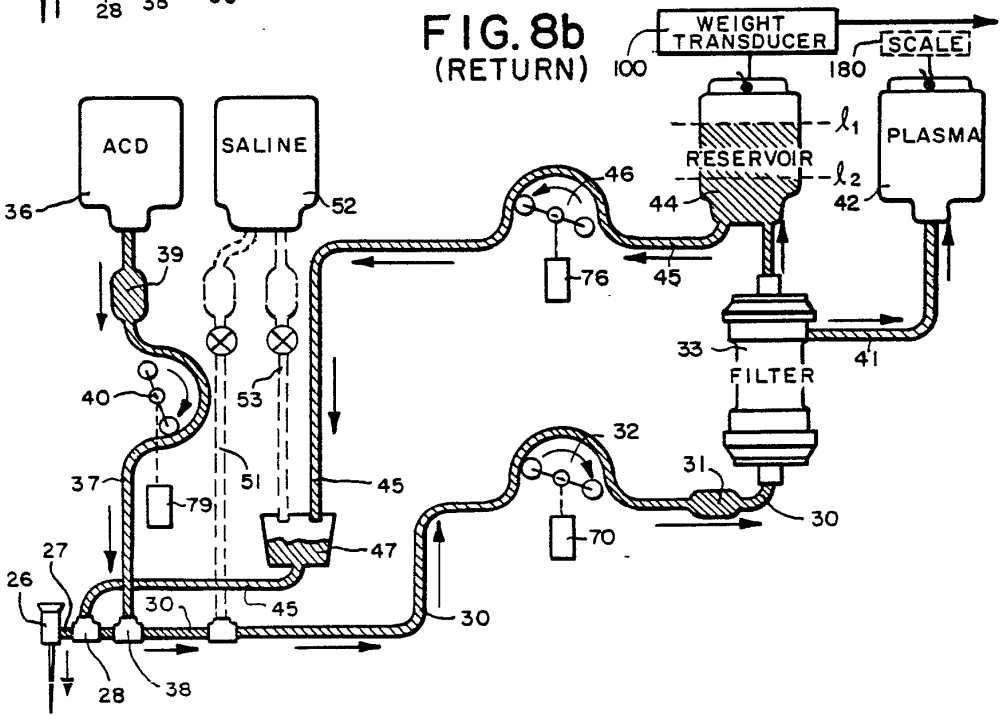


FIG. 8b
(RETURN)



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FIG. 8c
(RETURN- NO RECIRCULATION)

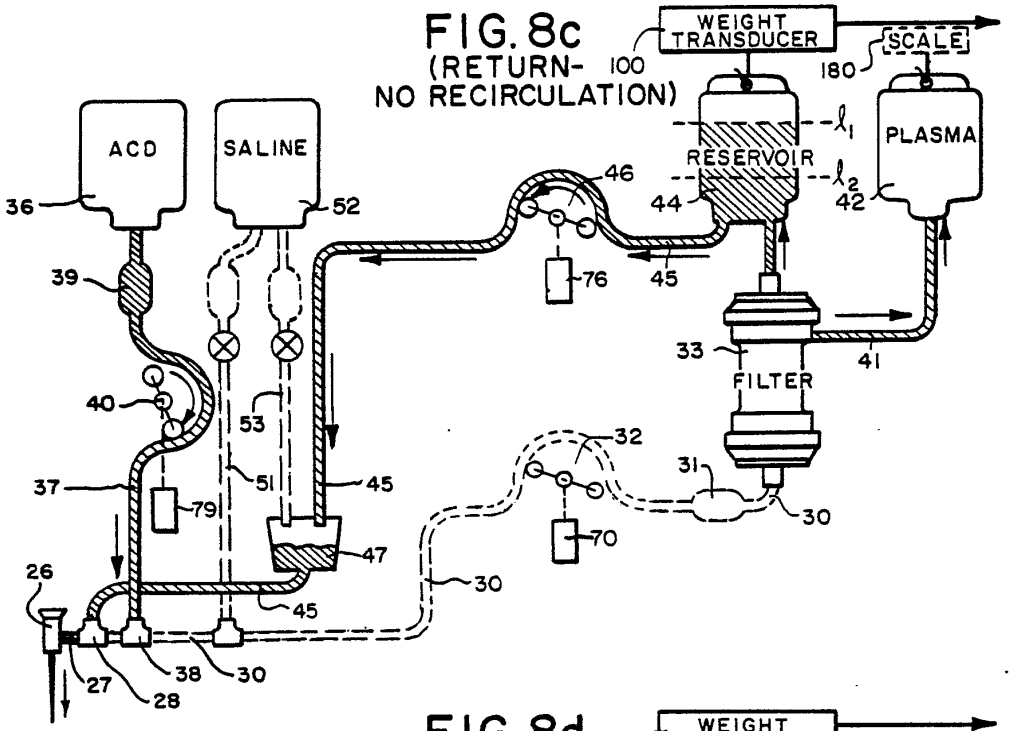
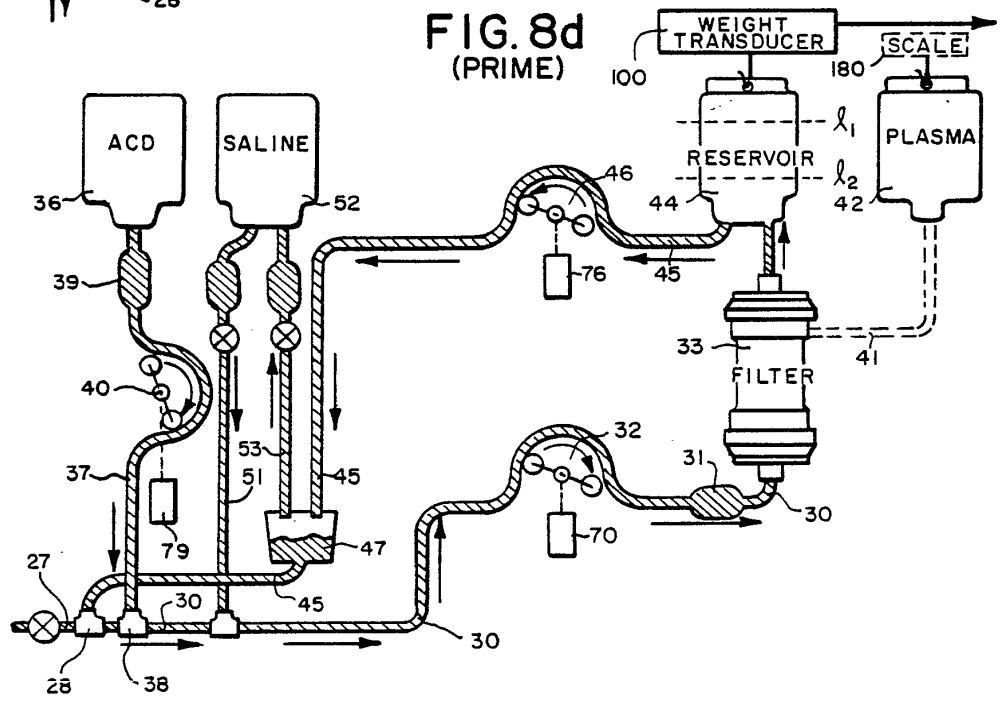
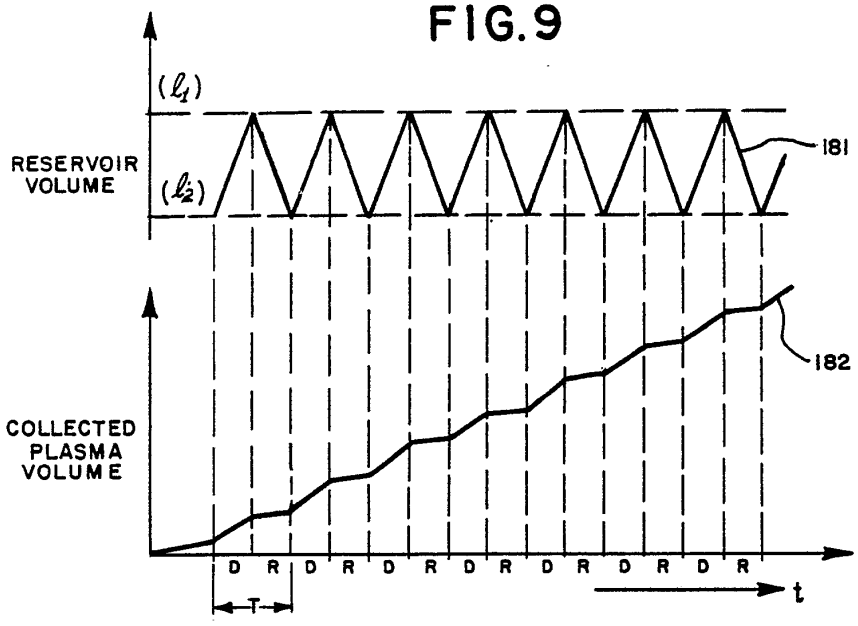


FIG. 8d
(PRIME)



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FIG.9



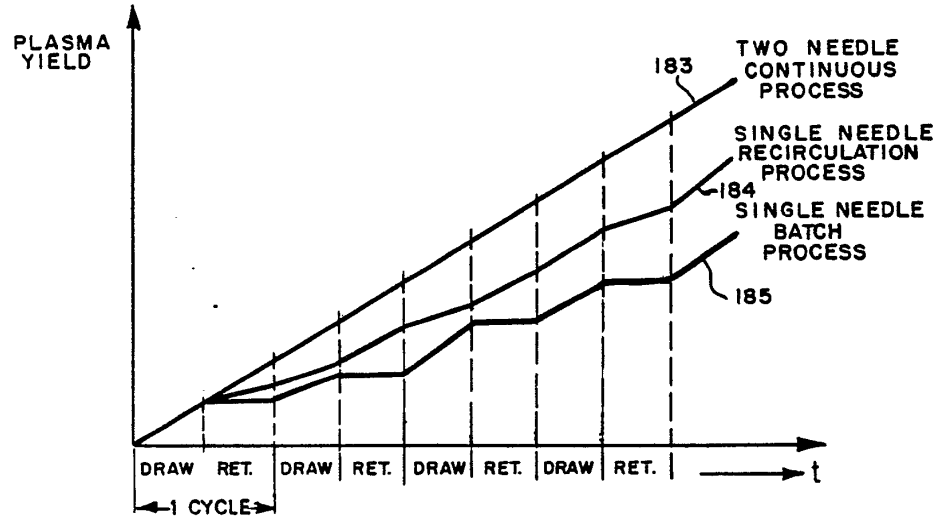


FIG.10

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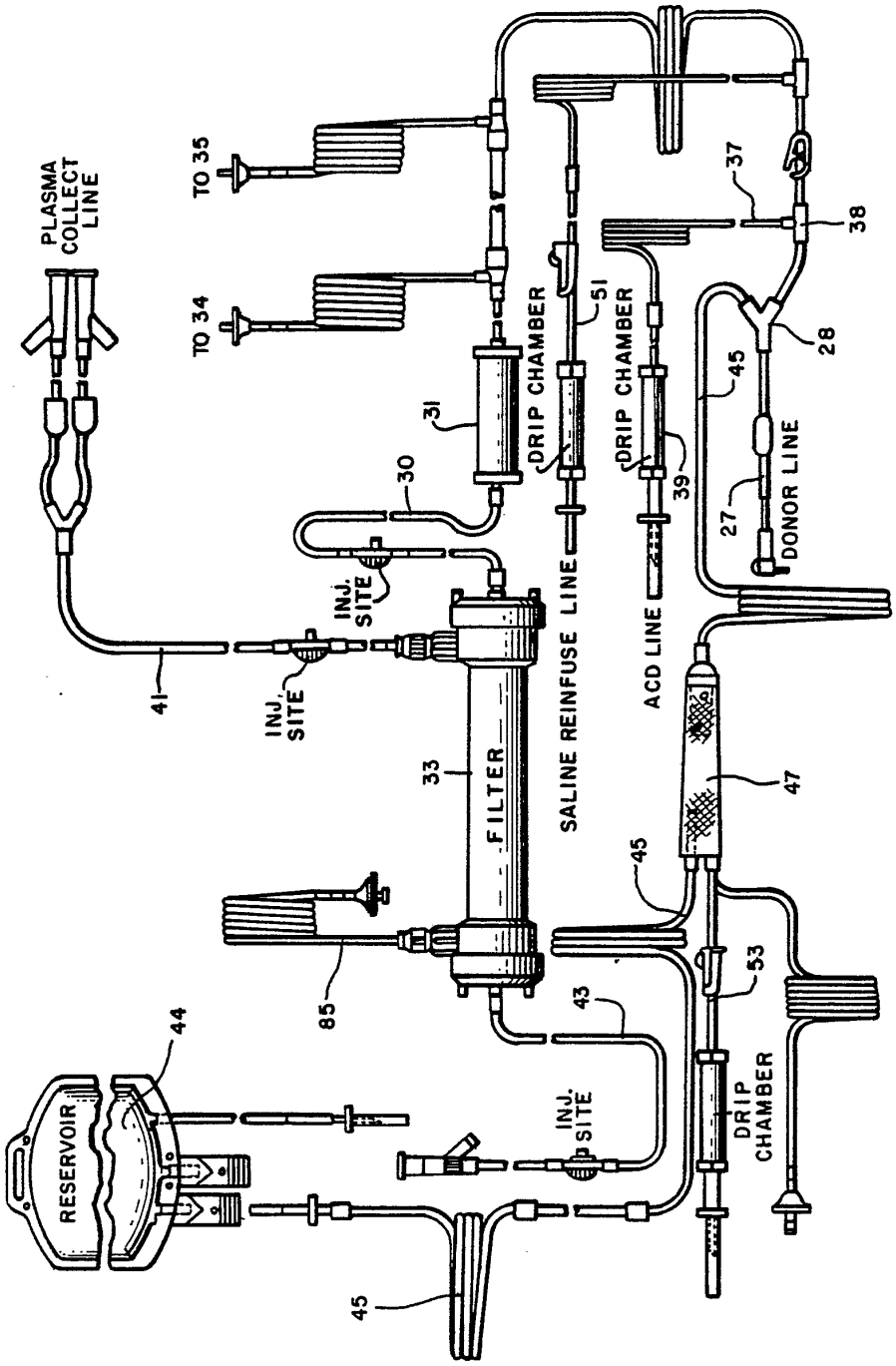


FIG.11

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EP-A-0 112 152
EP-A-0 131 529
WO-A-81/02979
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EP 0 171 749 B1

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Courier Press, Leamington Spa, England.

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Description

Background of the invention

1. Field of the invention:

This invention relates to an apparatus wherein a membrane-type blood plasma separator is used to separate blood plasma without continuously circulating blood externally of a donor, yet at an efficiency approximately equivalent to that of a continuous external circulation system by adopting a semicontinuous system in which blood is collected and returned in repeated fashion.

2. Description of the prior art

A well-known method of gathering blood plasma is to centrifugally separate whole blood taken from a healthy donor and collected in a blood bag. An apparatus has recently been developed for obtaining a large quantity of blood plasma from a single donor by means of semicontinuous or continuous centrifugation. Membrane-type blood plasma separators have also appeared and make it possible to separate large quantities of blood plasma anywhere with facility, and much research has been done in the area of so-called plasma exchange therapy, in which a large amount of blood plasma is separated from a patient suffering from a serious immunological or metabolic illness and the patient is supplemented with blood plasma collected from a healthy donor. Blood plasma obtained from healthy donors is also used for such purposes as nutritional supply of gravity patients, supply of coagulation factor and invigoration of the immunity function, and demand for such plasma is ever increasing. For this reason, a variety of research is being conducted into methods of obtaining large quantities of blood plasma from healthy donors safely, inexpensively and with facility. The membrane-type plasma separator is particularly promising as it features a higher separating speed than a continuous centrifuge and can be handled without costly specialized equipment.

However, with the conventional continuous separation of blood plasma using a membrane, it is necessary for a vein to be punctured at two locations, namely, on the side at which blood is collected from e.g., a donor, and on the side at which blood is returned to the donor, and it is also required that continuous extracorporeal circulation of blood be performed. Accordingly, the risk of injury to the donor is high. Moreover, since a plasma pump is provided to prevent hemolysis due to a rise in TMP caused by resistance on the blood-return side, the separator operates at less than maximum performance. This results in a low separation efficiency.

With the conventional semicontinuous separation of blood plasma using a membrane, separator resistance at return of the blood from a blood reservoir rises owing to the concentrated blood obtained from the separation process. The result is damage to the blood cells and an extended period of time for return of the blood. Though a bypass can be provided to alleviate the problem, this would result in loss time equivalent to the time needed for the bypass. Furthermore, since the TMP internally of the separator in a one-pump system becomes a negative pressure at return of the blood so that the collected plasma flows backward, it is necessary to interrupt the separation process at return of the blood or to provide a blood return pump and a switching valve.

An apparatus according to the preamble part of Claims 1 and 6 is known from EP—A—0 085 016. This apparatus is adapted to sample blood from and to return blood to a donor via a single needle. Further, this apparatus includes a plasma separator for concentrating the blood and a reservoir for temporarily pooling concentrated blood. So, with the known apparatus the blood passes twice to separator, the first time when blood is collected in the reservoir and a second time when the blood is returned to the donor via the plasma separator. However, in this known apparatus, all the blood concentrated by the plasma separator is collected in the reservoir, and it is only returned to the plasma separator when the blood from the reservoir is returned to the donor. So, the known apparatus cannot achieve a plasma separation with a good efficiency.

In EP—A—0 131 529, which is based on a prior application, but has not been published before the priority date of this application, a similar apparatus is described comprising additionally an internal circulating circuit. In this apparatus according to the prior art, the efficiency of the plasma separation is improved. However, there is another disadvantage. When the blood circulating in the plasma separator is concentrated, a rise in viscosity results whenever plasma is separated from the blood. As a result, it becomes progressively more difficult for the blood to flow internally of the separator, and so, there is an increasing danger of hemolysis occurring.

The present invention has been devised to solve the aforementioned problems of the prior art, and an object of the invention is to provide an apparatus for separating blood plasma, wherein the vein of a donor need be punctured at only one location, the risk of extracorporeal blood circulation can be avoided, and plasma can be separated continuously from blood collection to blood return, thereby enabling plasma to be collected at an efficiency higher than that heretofore obtainable with a continuous system regardless of adoption of a semicontinuous plasma separation method in which blood collection and return are performed intermittently.

According to the present invention, the foregoing object is attained in a first embodiment with the features of Claim 1 and in a second embodiment with the features of Claim 6.

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According to the invention, the membrane-type blood plasma separating means is provided with means for varying the cross-sectional area of blood passages internally of the separating means.

Additionally, the blood reservoir means may comprise a sealed bag made of a flexible synthetic resin. Further, the blood feed means for introducing and discharging blood may comprise a roller pump capable of forward and reverse rotation. Preferably, the apparatus of the invention further includes at least two pumps, one for driving the blood feed means and the other for driving the circulating means.

Other features and advantages of the present invention will be apparent from the following description taken in conjunction with the accompanying drawings, in which like reference characters designate the same or similar parts throughout the figures thereof.

Brief description of the drawings

Figure 1(a) is a perspective view showing a blood plasma separating apparatus according to ths present invention;

Figure 1(b) is a circuit diagram of a blood plasma separating apparatus according to the present invention;

Figure 1(C) is an enlarged sectional view showing an embodiment of a blood plasma separator;

Figure 1(d) is an enlarged sectional view showing a pressing device operatively associated with the separator of Figure 1(C);

Figures 2(A) and 2(B) are block diagrams illustrating the operating principle of the blood plasma separating apparatus at collection and return of blood.

Figure 3 is a graph illustrating the relation between the amount of blood plasma separated and the operating time of the apparatus;

Figure 4 is a circuit diagram of an experiment using the plasma separating apparatus for practicing the plasma separating method of the illustrated embodiment;

Figure 5 is a circuit diagram of an experiment indicative of the conventional continuous-type blood plasma separating method;

Figures 6(A) and 6(B) are block diagrams illustrating the operating principle of a modification of the blood plasma separating apparatus for practicing the blood plasma separating method of the illustrated embodiment:

Figure 7 is a circuit diagram of a second embodiment of a blood plasma separating apparatus according to the present invention;

Figures 8(A) and 8(B) are block diagrams illustrating the operating principle of the blood plasma separating apparatus at collection and return of blood;

Figure 9 is a circuit diagram of an experiment indicating the second embodiment of the plasma separating apparatus according to the present invention;

Figure 10 is a circuit diagram of an experiment indicating the conventional continuous-type separation method; and

Figures 11(A), 11(B), 12(A) and 12(B) are block diagrams illustrating modifications of the second embodiment of the blood plasma separating apparatus according to the present invention.

Description of the preferred embodiments

Figure 1(A) is a perspective view showing a blood plasma separating apparatus for practicing an embodiment of a blood plasma separating method, Figure 1(B) is a circuit diagram of the blood plasma separating apparatus shown in Figure 1(A), and Figures 2(A) and 2(B) are block diagrams illustrating the operating principle of the blood plasma separating apparatus at collection and return of blood.

With reference to Figure 1(A), the plasma separating apparatus of the present invention includes a membrane-type plasma separator 1, a recirculating pump 3 connected to the separator 1, a pressure monitoring air chamber 5 connected to the recirculating pump 3, a pressure gauge 6 connected to the air chamber 5, a blood feed pump 7 connected to the line between separator 1 and air chamber 5, a blood reservoir 8 connected to the line between the separator 1 and recirculating pump 3, a replacement liquid pump 9 connected to the blood feed pump 7, a vessel of anticoagulant 10 connected to the pump 9, a vessel of a replacement liquid 11 connected to the pump 9, and a plasma collecting vessel 12 connected to the separator 1. Also included are an air bubble detector 13, a negative pressure detector 14, a switching valve 15 for selecting either the anticoagulant 10 or the replacement liquid 11, a display and control section 17, a venipuncture needle 18, and a pressing device 19 serving as adjusting means for varying the cross-sectional area of blood flow passages in the separator 1.

As shown in the circuit diagram of Figure 1(B), the plasma separating apparatus separates plasma from blood by way of the membrane-type separator 1, includes a blood circulation circuit for recirculating the resulting concentrated blood from a blood outlet 2 of the plasma separator 1 to a blood inlet 4 thereof 1 by the recirculating pump 3, and causes blood collected from an individual, such as a donor or patient, to flow into the line of the circulation circuit between the recirculating pump 3 and the blood inlet 4 of plasma separator 1 by means of the blood feed pump 7, which is reversibly rotatable. Some of the concentrated blood from the blood outlet 2 of the plasma separator 1 branches from the circuit leading to the recirculating pump 3 and collects in the blood reservoir 8, with the amount of the blood fed to the plasma separator 1 being fixed. The arrangement is such that blood in the reservoir 8 and circulation circuit is

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returned to the individual by reversing the rotation of the blood feed pump 7. The pressure of the blood flowing into the plasma separator 1 of the recirculating circuit is monitored by the pressure gauge 6 connected to the pressure monitoring air chamber 5.

Let us now describe the operation of the plasma separating apparatus of the illustrated embodiment.

The interior of the circuitry is primed with a physiologic saline solution or the like introduced from the terminus of the circuitry by driving the pump 7. Following priming, the recirculating pump 3 is set into operation to form the blood circulating circuit, after which blood is introduced from the needle 18 at the terminus of the circuitry by rotating the pump 7 in the forward direction. At this time the anticoagualant 10, such as heparin, ACD solution or sodium citrate solution, should be mixed with the blood by operating the replacement liquid pump 9. The blood which has entered the recirculating circuit passes through the plasma separator 1, where plasma is separated from the blood and then collected in the plasma collecting vessel 12. Meanwhile, the concentrated blood resulting from the separation process in the plasma separator 1 is circulated through the circuit by the recirculating pump 3 to be diluted with blood obtained afresh from the donor and is reintroduced to the plasma separator 1 where further concentration is performed. Some of the concentrated blood which flows out of the separator 1 is pooled in the blood reservoir 8. It is preferred that the blood reservoir 8 comprise a sealed bag made of a flexible synthetic resin, for a reservoir of such construction will automatically follow up changes in pressure.

As soon as a predetermined amount of blood has been collected from the donor, the blood feed pump 7 is rotated in the reverse direction to cause the concentrated blood in reservoir 8 to flow back into the recirculating circuit. The concentrated blood thus enters the recirculating circuit, flows through the recirculating circuit and some of the concentrated blood is returned to the donor by the blood feed pump 7 while the remainder re-enters the plasma separator 1 from the blood inlet 4, whereby the blood is concentrated again. Some of this reconcentrated blood is returned to, e.g., the donor, by the blood feed pump 7. Plasma is continuously separated from the donor's blood by repeating this process. During this process the amount of the blood in the recirculating circuit must be larger than that of the blood to be returned to the donor. In other words, the amount of blood which is recirculated is the amount of blood flow produced by pump 3 minus the amount of blood flow produced by pump 7. At this time the diluting liquid 11, such a physiologic saline or glucose solution, may be administered to the donor, rather than the anticoagulant 10, by the pump 9. Note that a prescribed amount of blood will circulate through the membrane-type plasma separator 1 due to the inflow of blood to the reservoir 8 at blood collection and the outflow of blood from the reservoir 8 at blood return.

It is preferred that a separator of the kind shown in the enlarged sectional view of Figure 1(C) be used as the plasma separator 1. The structure of this separator will now be described.

The separator 1 comprises a case composed of a cylindrical case body 100 and a plunger 104, which serves also as the separator cap. The case body 100 has a bottom centrally provided with a body fluid (blood) inflow port 101, and a side wall provided with a filtration residue (concentrated blood) outflow port 102. The plunger 104 has filtrate (blood plasma) outflow ports 103, 103, and has an O-ring 105 attached to its outer circumferential portion. Disposed within the case are a plurality of filtration membrane units 112. Each unit 112 includes two circularly shaped filtering membranas 107a, 107b which embrace, from above and below, a filtrate flow passage forming plate 106 of circular shape comprising a screen mesh having a central opening 111 and filtrate passageways 108 located near the periphery of the plate. Each filtration membrane unit 112 has its outer circumferential portion as well as its inner circumferential portion about the central opening sealed as by thermal fusion or adhesive, and a sealing member 109 is bonded to the outer periphery of each filtrate passageway 108. It should be noted that the filtrate flow passage forming plate 106 is not limited to the above mentioned mesh; what is essential is that flow passages for the filtrate be assured.

Arranged between neighboring ones of the filtration membrane units 112 is a body fluid flow passage regulating plate 110 of circular shape having a central opening 111′ and filtrate passageways 108′ corresponding to those in the units 112, as well as a multiplicity of projections on the upper and lower surfaces thereof. Note that the outer peripheral portion of each filtrate passageway 108′ has a flat configuration. Also provided in the case body 100 of the separator 1 are two body fluid flow passage regulating plates 113 each of circular shape having a multiplicity of projections on one side surface thereof. One of the plates 113 is arranged with its projections in abutting contact with the upper surface of the uppermost filtration membrane unit 112, and the other of the plates 113 is arranged with its projections in abutting contact with the lower surface of the lowermost filtration membrane unit 112. Each of the body fluid flow passage regulating plates 113 is provided with a central opening 111″ and filtrate passageways 108″ corresponding to those in the units 112. Note that the outer peripheral portion of each filtrate passageway 108″ has a flat configuration. The filtration membrane units 112 and the body fluid flow passage regulating plates 110, 113 are stacked in the manner described and inserted in the case body 100, the entirety is capped under pressure by the plunger 104 to fit the assembly snugly into the case body 100, and the O-ring 150 provides a liquid-tight seal between the plunger 104 and the case 100. The assembly that results is the plasma separator 1. Owing to the pressure applied by the plunger 104, the filtration membrane units 112 and the body fluid flow passage regulating plates 110, 113 are integrally joined at the outer peripheral portions of the filtrate passageways 108, 108′, 108″ by means of the sealing members 109, so that these passageways are brought into communication with one another. It should be noted that

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Figure 1(C) depicts membrane thickness, the size of the projections and the spacing between the layers in exaggerated form.

Figure 1(D) is an enlarged sectional view showing the details of the pressing device 19 [Figure 1(A)]. A base 211 of suitable shape is provided with a pressing rod 212 capable of moving freely in the axial direction. The distal end of the pressing rod 212 is provided with a pressing plate 213 capable of being rotated freely about the axis of the pressing rod. Attached to the base 211 so as to rotate coaxially with respect to the pressing plate 213 is a frame-shaped holder 214 capable of accommodating the separator 1 in such a manner that the plunger 104 of the separator 1 may be abutted against the pressing plate 213. The holder 214 is provided with holder locking mechanisms 215 so that the holder can be fixed to the base 211 at a predetermined rotational position with respect thereto.

The arrangement for supporting the plasma separator 1 is thus characterized in that the pressing plate 213 is not only movable in unison with the pressing rod 212 in the axial direction thereof but is also freely rotatable about the axis of the pressing rod, the holder 214 is not only movable axially of the pressing rod 212 but is also rotatable coaxially with respect to the pressing plate 213, and the holder locking mechanisms 215 enable the holder 214 to be fixed to the base 211 at a predetermined rotational position.

The base 211 may consist of any suitable material and have any appropriate shape. As an example, the base 211 may have a columnar configuration and consist of cast iron. The pressing rod 212 is mounted on the base 211 so as to project therefrom and is freely movable axially of the plunger 104 held by the holder 214. In the illustrated embodiment, the pressing rod 212 is supported by the base 211 and by a bearing block 216 attached to the base 211 and, by turning a knob 217, may be moved freely in the axial direction so as to deliver a large axial thrust. A mechanism for rectilinear motion is interposed between the knob 217 and the pressing rod 212 and serves to convert horizontal motion of the knob 217 into axial motion of the rod 212. The mechanism may be of any suitable construction but in the illustrated embodiment includes a worm screw 218 coupled to the knob 217, and a worm 219 meshing with the worm screw 218. The pressing rod 212 is threadedly engaged with female screws provided on the worm 219 and is supported by the bearing block 216 (essentially the base 211) via a sliding key or spline 220, which prevents the pressing rod 212 from rotating. Turning the knob 217 rotates the worm 219 and the worm screw 218 meshing therewith, with the worm 219 rotating while in threaded engagement with the pressing rod 212. Since the pressing rod 212 is non-rotatable, it is free to move in the axial direction.

It should be noted that the bearing block 216 is essentially a part of the base 211. The amount by which the knob 217 is rotated is indicated by an indicator 221.

The pressing plate 213 is provided at the projecting end of the pressing rod 212 and is rotatable about the axis of the rod and movable axially in unison with the rod so as to apply pressure to the plunger 104 of the plasma separator 1.

In the illustrated embodiment, the pressing plate 213 comprises a disk portion 231 and a skirt portion 232 contiguous with the disk portion and covering the outer circumference of the flange portion 261 of the bearing block 216. The pressing plate 213 is fitted securely on the pressing rod 212 in such a manner that the skirt portion 232 covers a bearing flange 222 screwed securely onto the pressing rod 212.

The holder 214 surrounding the pressing plate 213 is mounted on the base 211 so as to be capable of rotating coaxially with respect to the pressing rod 212. The holder 214 has a frame-like construction and comprises a frame portion 241 having a cavity at a position facing the pressing plate 213 for receiving the plasma separator 1, and a hatch portion 242 for closing the cavity of the frame portion 241. The holder 214 is adapted to rigidly hold the case body 100 of the separator 1 in such a manner that the opening to the separator vessel confronts the pressing plate 213.

In the illustrated embodiment, the frame portion 241 of the holder 214 comprises a front part 241a and a pair of side parts 241b, 241b. The hatch portion 242 comprises a pressing part 242a and an arm part 242b. The hatch portion 242 may be swung open and closed relative to the frame portion 241 and, when closed, may be locked in place by fixing means 223. The front part 241a is fitted rotatably over the outer circumferential surface of the bearing block 216 and is embraced by the base 211 and the flange 261 of the bearing block 216. The two side parts 241b, 241b extend in parallel with the axis of the pressing rod 212 from respective ends of the front part 241a so as to surround the pressing plate 213, and each has a receiving projections 243, 243 on which the separator 1 is placed from below. The arm part 242b of the hatch portion 242 is formed integrally with the pressing part 242a and extends across the two side parts 241b, 241b of the frame portion 241. One end of the arm part 242b is pivotally connected by a pin shaft 244 to one end of one side part 241b, so that the other end of the arm part 242b may be swung about the pivot point. A slit (not shown) is provided in the arm part 242b so as to extend from said other end thereof to a point part of the way along the pressing part 242a and arm part 242b. Fitting the fixing means 223 into the slit locks the hatch portion 242 to the front part 241a in the closed condition.

The fixing means 223 has one end 331 thereof pivotally connected by a pin 224 to the side part 241b, and is formed to include a locking portion 332 at its other end. With the fixing means 223 fitted into the slit formed in the hatch portion 242, the locking portion 332 comes into abutting contact with the side face on the openable end of the arm part 242b from the outside thereof to lock the hatch portion 242 in place. Preferably, and by way of example, the fixing means 223 has a hatch locking mechanism for maintaining the locking engagement between the openable end of the arm part 242b and the corresponding side part 241b.

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The holder locking mechanism 215 has a locking recess 251, a locking projection 251a provided at one end of a pin body 252, a resilient member 253, and a locking release lever 254. The locking recess 251 is provided in the outer circumferential surface of the bearing block 216 (essentially in the base 211 at a position opposing the holder 214). The pin body 252 having the locking projection 251a, the resilient member 253 and the locking release lever 254 are provided in the holder 214. The pin body 252 is linked with the locking release lever 254, and the locking projection 251a at the one end of the pin body 252 is urged by the resilient means 253 into engagement with the locking recess 251 at a prescribed rotational position of the holder 214. The resilient member 253 may be any suitable resilient means, such as a spring.

The locking release lever 254 should be provided at a desired position and operable in the radial direction, namely in a direction perpendicular to the rotational axis of the holder 214. In the illustrated embodiment, the locking release lever 254 is provided on the outer surface of the side part 241b at a position in the proximity of the base 211 and is pivotally supported at an intermediate point by a pin shaft 255 in such a manner that both ends thereof are capable of being swung outwardly at right angles to the axis of the pressing rod.

The pin body 252, resilient member 253 and locking release lever 254 are provided at two diametrically opposed locations, namely at two locations 180° apart circumferentially of the holder 214. Accordingly, when the holder 214 is rotated through 180° to position the two side parts 241b thereof in a horizontal plane which contains the pressing rod 212, the holder 214 will be locked automatically to the base 211.

In order to assure rotation of the pressing plate 213 and holder 214, a thrust bearing 226 is provided between the bearing block 216 and the holder 214, and a thrust bearing 227 is mounted between the bearing flange 222 and the pressing plate 213.

In operation, either of the locking projections 251a of the holder locking mechanism 215 is mated with the locking recess 251 to lock the holder 214 to the base 211. Under these conditions, the hatch portion 242 of the holder 214 is swung open horizontally, the body fluid inlet port 101 of the separator 1 is pointed upward, and the separator 1 is placed in the holder 214 through the opening thereof with the plunger 104 being faced toward the pressing plate 213. This is followed by closing the hatch portion 242, fitting the fixing means 223 into the slit formed in the hatch portion 242, and locking the hatch portion 242 in the closed state by the hatch locking mechanism.

The plunger 104 is moved up and down by turning the knob 217 back and forth. Moving the plunger 104 up and down causes a change in the cross-sectional area of the blood flow passages in the plasma separator 1. The blood circulating in the plasma separator 1 is concentrated and, hence, experiences a rise in viscosity whenever plasma is separated from it. As a result, it becomes progressively more difficult for the blood to flow internally of the separator 1, the pressure loss rises and TMP increases. If unchecked, this can lead to hemolysis, namely damage to the red blood cells. Accordingly, if the plunger 104 is lowered by turning the knob 217, the cross-sectional area of the blood flow passages increases, thereby diminishing pressure loss internally of the separator 1 and regulating TMP to within a prescribed range, thus preventing hemolysis. The plasma separator 1 is thus capable of completely separating plasma from entrant blood.

With the plasma separating apparatus for practicing the plasma separating method of the illustrated embodiment, blood concentrated once and pooled in the blood reservoir 8 is recirculated through the recirculating circuit and concentrated again by the separator 1 at return of the blood to the individual, so that plasma is collected even when blood is returned. This enables separation to be performed continuously without interruption when blood is returned.

Let us describe this process in slightly more detail with reference to Figures 2(A) and 2(B). Figure 2(A) illustrates the blood collection cycle. Blood feed pump (P1) 7 is rotated in the forward direction to draw blood from the donor and feed the blood into the circulating circuit. Recirculating pump (P2) 3, which always rotates in the forward direction circulates the blood through the plasma separator (PS) 1, where plasma is separated and stored in the plasma collecting vessel, not shown in Figure 2(A). The concentrated blood resulting from this separation process exits from the plasma separator 1 and flows into the circulating circuit owing to the action of the pump 3. Some of the concentrated blood enters the blood reservoir (R) 8 and the remainder reenters the inlet side of the plasma separator 1 before mixing with fresh blood introduced from the donor by the feed pump 7 upstream of the separator. The mixture of concentrated blood and fresh blood is subjected to plasma separation by the plasma separator 1. The foregoing steps are then repeated.

Figure 2(b) shows the blood return cycle performed when a predetermined amount of blood has been introduced into the system. Here the blood feed pump 7 is operated in the reverse direction to return the blood cell fraction to the donor from the point between the recirculating pump 3 and the inlet side of the plasma separator 1. As mentioned above, however, the recirculating pump 3 continues rotating in the forward direction. Accordingly, the concentrated blood pooled in the blood reservoir 8 during the collection cycle is now withdrawn from the reservoir and introduced into the circulating circuit by the pump 3. Some of this concentrated blood is returned to the donor upstream of the plasma separator 1 by the action of the blood feed pump 7, as mentioned above, and the remainder enters the plasma separator 1 where it is again subjected to plasma separation and, hence, reconcentration. It will thus be understood that plasma separation takes place even while blood is being returned to the donor.

Figure 3 is a graph showing the relation between the amount of plasma separated and the operating time of the apparatus. Curve 510 represents the results achieved with a conventional semicontinuous

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membrane-type plasma separating apparatus, and curve 500 shows the results achieved with the apparatus of the illustrated embodiment. Curve 50 indicates that plasma separation takes place even during return of the blood and, hence, is carried out in a highly efficient manner. Curve 51 shows that since separation is suspended during return of the blood, a longer period of time is required to separate an equivalent amount of plasma with respect to curve 50.

Figure 4 illustrates an example of an experimental set-up indicative of an embodiment of the plasma separating apparatus of the present invention. In the experiment, use was made of a membrane-type plasma separator 1' in which were stacked eight porous membranes each consisting of cellulose acetate with a pore size of 0.45 μm and having a donut-shaped configuration with an inner diameter of 3.6 cm and an outer diameter of 10 cm. The membranes presented an effective membrane surface area of 546.6 cm^2. The circuitry, inclusive of the separator 1', was arranged as shown. It should be noted that the membrane-type plasma separator is not limited to a flat membrane-type configuration, for a hollow fiber-type plasma separator can also be employed. Three liters of fresh bovine blood (hematocrit: 42%) with ACD serving as the anticoagulant was prepared in an Erlenmeyer flask 20 and the blood was stirred by a stirrer 22 in a water bath 21 at 37°C. The flask 20 containing the cow blood served as an imitation donor. After the interior of the circuitry was filled with a physiologic saline solution, the blood feed pump 7 was rotated to provide a blood flow rate (Q_B) of 60 ml/min. At the same time, the recirculating pump 3 was rotated to provide a blood flow rate (Q_R) of 110 ml/min. Plasma separation began immediately, with the separated plasma being received by a measuring cylinder 23 to measure the total amount (V) of plasma accumulated. Concurrently, blood inflow pressure (P) was measured for a requisite period of time by the pressure gauge 6 connected to the air chamber 5, with 0 min being taken as the start of blood extraction. When the total amount of blood extracted attained a value of 500 ml, the blood feed pump 7 was reversed to provide a return flow rate of 60 ml/min, and the recirculating pump 3 was rotated at a higher speed to increase the blood flow rate to 160 ml/min, thereby returning the blood to the flask 20. At the end of blood return, the Erlenmeyer flask 20 was replenished with an amount of physiologic saline 24 equivalent to the amount of plasma collected in the measuring cylinder 23. The foregoing process was repeated to provide the experimental results shown in the following Table 1:

TABLE 1

Time (min)	Pressure (mmHg) P	Collection/ return flow rate (ml/min) Q_B	Recirc. flow rate (ml/min) Q_R	Amt. of separated plasma (ml) V
0	75	+60	110	0
2	100	+60	110	60
4	135	+60	110	120
6	140	+60	110	175
8	145	−60	200	230
10	140	−60	200	250
12	145	+60	110	270
14	140	+60	110	325
16	145	+60	110	375
18	150	+60	110	425
20	135	−60	200	445
22	140	−60	200	460
24	120	+60	110	485
26	135	+60	110	515
28	140	−60	200	525
30	—	—	—	—

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In Table 1, the plus signs in the collection/return flow rate column indicate blood collection and the minus signs indicate blood return.

For the purpose of comparison, the inventor performed a plasma separation experiment using 3 l of fresh cow blood mixed with ACD, as in the experiment of Figure 4, employing a continuous separation method considered to be the most efficient at the present time. The experimental set-up, shown in Figure 5, utilizes the plasma separator 1', which has the same specifications at the separator 1' employed in the experiment of Figure 4. The results obtained are as shown in Table 2.

TABLE 2

Time (min)	Pressure (mmHg)	Collection/ return flow rate (ml/min)	Amount of separated plasma (ml)
0	60	60	0
2	135	60	40
4	140	60	75
6	145	60	110
8	145	60	145
10	145	60	180
12	145	60	215
14	145	60	250
16	145	60	280
18	145	60	310
20	145	60	340
22	150	60	370
24	145	60	405
26	145	60	435
28	145	60	470
30	145	—	500

In the experiments of Figures 4 and 5, the cross-sectional area of blood flow passages in the separator 1 was so controlled by the pressing device as to keep the pressure from exceeding 150 mmHg.

A comparison of Tables 1 and 2 shows that 500 ml of plasma can be collected in less than 26 min with the separating method of the illustrated embodiment, while it takes 30 min to collect 500 ml of plasma with the continuous separation method of Figure 5. It will be appreciated that plasma can be separated from blood in a highly efficient manner according to the illustrated embodiment.

Figures 6(A) and 6(b) are block diagrams of a modification of the invention. In the illustrated arrangement, the reservoir 8 is incorporated into the recirculating circuit. Figure 6(A) illustrates operation at blood collection, and Figure 6(B) shows operation at blood return. The results obtained are the same as those with the arrangement of Figures 2(A) and 2(B). However, with the set-up shown in Figures 2(A), 2(B), the concentrated blood finds refuge in the blood reservoir 8 so that the concentration of the blood inside the reservoir 8 is substantially constant. With the set of shown in Figures 6(A), 6(B), on the other hand, blood in the reservoir 8 is being continuously circulated and concentrated at all times so that the blood concentration internally of the reservoir changes.

A second embodiment of the present invention will now be described. Figure 7 is a circuit diagram of a blood plasma separating apparatus of the second embodiment according to the present invention and Figures 8(A) and 8(B) are block diagrams illustrating the operating principle of the blood plasma separating apparatus at collection and return of blood for practicing the second embodiment of the plasma separation

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method. Portions similar to those shown in Figures 1(A) and 1(B) are designated by like reference characters. The second embodiment of the apparatus includes a three-way valve 31 in the line between the recirculating pump 3 and the blood reservoir 8, a vessel of physiologic saline solution 32, and a transfusion solution set 33 connected between the three-way valve 31 and the physiological saline solution vessel 32. Numeral 34 denotes the forearm of a donor. Unlike the first embodiment, blood from the donor is introduced directly to the blood reservoir 8, rather than being fed directly into the blood circulating circuit.

In the operation of the second embodiment of the present invention, the three-way valve 31 is opened and the pump 3 is set into operation to fill the circuitry with the physiologic saline solution 32 introduced from the transfusion solution set 33. Next, the blood feed pump 7 is driven into rotation to collect blood from the needle 18 inserted into a vein in the donor's forearm 34. The negative pressure monitor 14 for monitoring the state of blood collection from the donor and a brancher 35 can be provided in the tubing between the needle 18 and the blood feed pump 7, and the anticoagulant 10 or physiological saline 11 can be mixed with the blood by changing over the valve 15 and driving the pump 9 at a rate fixed in proportion to the operating rate of the blood feed pump 7. Whole blood collected by operation of the feed pump 7 begins to pool in the blood reservoir 8, which is made of a flexible synthetic resin. At the same time, the recirculating pump 3 is operated so that the blood pooled in the reservoir 8 flows into the plasma separator 1 from the blood inlet 4 thereof via the air chamber 5. Plasma separated inside the separator 1 flows from a filtrate outflow port 50 thereof into the tubing of the recirculating circuit for collection in the plasma collecting vessel (collecting bag) 12 by opening a valve 42.

The concentrated blood in the separator 1 resulting from separation of the plasma flows out from the blood outlet 2, returns to the reservoir 8 where mixing with newly collected blood takes place, and is then fed again, together with the fresh blood, from the reservoir 8 into the separator 1 by the pump 3. Repeating this process enables plasma to be separated from blood in continuous fashion. The concentration of the blood in the blood reservoir 8 is monitored by the pressure gauge 6.

When collection of a predetermined amount of blood from the donor by operation of the blood fed pump 7 ends, the valve 15 is switched so that the donor may be administered replacement physiological saline or glucose 11 in an amount equivalent to the amount of separated plasma by operation of the pump 9. At the same time, the blood feed pump 7 is reversed to return the blood in reservoir 8 to the donor. The recirculating pump 3 continues operating even during return of the blood, so that the plasma separator 1 goes on concentrating the blood up to the final target concentration. As soon as the concentrated blood have been returned to the donor, the blood feed pump 7 is again rotated in the forward direction to start collecting fresh blood from the donor so that the foregoing process may be repeated.

Thus, as in the first embodiment of the present invention, the above-described second embodiment also causes concentrated blood in the reservoir 8 to be subjected to concentration again by the separator 1 when blood is returned, so that plasma is separated from the concentrated blood even during the return stage of the process. Accordingly, the relation between the amount of plasma separation and the apparatus operating time is similar to that shown in the graph of Figure 3, so that approximately the same effect is obtained and a highly efficient blood collecting operation made possible.

Described next will be an experiment indicative of the plasma separating method of the second embodiment. The set-up is as shown in Figure 9.

Three liters of fresh bovine blood (hematocrit: 42%) with ACD serving as the anticoagulant was prepared in an Erlenmeyer flask 20 and the blood was maintained at a temperature of 37°C by a constant temperature bath 21. At the same time, the blood in the flask 20 was stirred by a stirrer 22 so that the blood would separate by standing. Next, the pump 3 was set into operation to fill the circuitry with the minimum amount of the necessary physiologic saline solution 51. The blood feed pump 7 was rotated to provide a blood flow rate of 60 ml/min and to introduce the blood into the blood reservoir 8.

At the same time, the recirculating pump 3 was rotated to provide a blood flow rate of 150 ml/min, introduce the blood through the air chamber 5 into the membrane-type separator 1', and then return the blood from the separator 1' to the reservoir 8, thereby setting up a circulating flow. At the same time that this closed circuit became filled with blood, the filtrate outflow port 50 was opened to collect the separated plasma in the measuring cylinder 23. The pressure of the blood fed into the separator 1' by the pump 3 was monitored by the pressure gauge 6 connected to the air chamber 5. The membrane-type plasma separator 1' was composed of eight stacked flat-type porous membranes each consisting of cellulose acetate with a pore size of 0.45 μm and having a donut-shaped configuration with an inner diameter of 3.6 cm and an outer diameter of 10 cm. The membranes presented an effective membrane surface area of 546.6 cm^2. The plasma separator 1' was filled with 12 ml of blood. In order to hold the filtration pressure constant, the structure of the separator 1' was such that the cross-sectional area of the blood flow passages could be varied in accordance with the concentration of the blood in the reservoir 8 as monitored by the pressure gauge 6. Though not employed, a hollow fiber-type membrane configuration can be adapted to the separator 1'. The results of the experiment are as shown in Table 3.

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TABLE 3

Operating time (min)	Flow rate QB1 (ml/min)	Flow rate QB2 (ml/min)	P (mmHg)	V (ml)
0	+60	0	0	0
2	+60	150	78	—
3	+60	160	100	50
6	+60	160	140	140
8	+60	160	150	200
9	−60	160	150	230
12	+60	160	165	255
14	+60	160	150	290
18	+60	160	155	350
21	−60	160	157	400
27	+60	160	160	440
28	−60	160	160	475
30	+60	160	154	485
31	−60	160	160	500
33	−60	160	0	—

The operating time column represents elapsed time immediately after start of blood collection. For example, the table shows that 500 ml of plasma were separated in 31 min. QB1 denotes the blood feed rate of the blood feed pump 7, where the plus sign indicates blood collection and the minus sign blood return. QB2 designates blood flow rate performed by the recirculating pump 3. P indicates that the blood flow passage pressure is controlled and held at a substantially constant value by monitoring the pressure at the inlet to the plasma separator 1' by the pressure gauge 6. V represents the total amount of plasma separated and shows that separation is carried out even when blood is returned to the donor. At return of the blood, physiologic saline 24 in an amount equivalent to the separated amount of plasma was returned to the flask 20. The maximum amount of blood collected in the reservoir 8 from the flask 20 was 500 ml.

For the purpose of comparison, the inventor performed a plasma separation experiment using 3 l of fresh bovine blood (hematocrit: 40%) mixed with ACD and employing the membrane-type plasma separator 1' of Figure 9. As shown in Figure 10, the plasma was separated by the conventional continuous process. The bovine blood, prepared in the flask 20, was held at 37°C in the constant temperature bath 21 and was stirred to uniformity in the flask 20 by the stirrer 22. At a collecting flow rate of 60 ml/min, blood was fed into the separator 1' through the air chamber 5 by the blood feed pump 7, and the separated plasma was collected in the measuring cylinder 23 from the filtrate outflow port 50 of the separator 1'. The physiologic saline 51 in an amount equivalent to that of the separated plasma was delivered by a pump 52 to a second air chamber 5', where the saline solution was mixed with the concentrated blood. The mixture of physiologic saline and concentrated blood was returned to the flask 20. The pressures on the inflow and outflow sides of the separator 1' were monitored by pressure gauges 6, 6' connected to the respective chambers 5, 5', and the flow passage pressure internally of the separator 1' was regulated to give a pressure loss similar to that obtained in the above experiment. The experimental results are shown in Table 4.

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TABLE 4

Operating time (min)	Flow rate (ml/min)	Inflow pressure (mmHg)	Outflow pressure (mmHg)	Amount of separated plasma (ml)
0	60	145	0	—
5	60	150	0	75
10	60	150	0	150
15	60	150	0	230
20	60	150	0	295
25	60	150	0	360
30	60	150	0	420
35	60	154	2	480
37	60	148	0	500
38	60	150	3	—

The operating time column represents elapsed time from the start of separation to the conclusion or blood return. Specifically, the table shows that 500 ml of plasma were obtained in 37 min and that 38 min was needed for the conclusion of the entire operation inclusive of blood return.

The blood flow rate is the flow rate established by the pump 7, the inflow and outflow pressures are those measured by the respective pressure gauges 6, 6', and the amount of separated blood plasma is the total accumulated amount measured by the measuring cylinder 23.

A comparison of Tables 3 and 4 clearly shows that the plasma separating apparatus for practicing the plasma separating method of the second embodiment separates plasma more efficiently than the conventional continuous separation method.

Figures 11(A) and 11(B) are block diagrams showing a modification of the second embodiment of Figures 7 and 8. Here the blood from the blood feed pump 7 does not flow directly into the blood reservoir 8. Figures 12(A) and 12(B) are block diagrams showing another modification of the second embodiment. Here the reservoir 8 is provided outside of the recirculating circuit, and the blood from the blood feed pump 7 does not flow directly into the blood reservoir 8. (A) in Figures 11 and 12 illustrates operation during blood collection, and (B) illustrates operation during blood return. The effects obtained with the arrangements of Figures 11 and 12 are similar to those obtained with the second embodiment shown in Figure 8. In the case of Figure 8, blood from the blood feed pump 7 and the concentrated blood from the plasma separator 1 mix in the blood reservoir 8, whereas in Figures 11 and 12 only the concentrated blood from the plasma separator 1 flows into the reservoir 8.

As many apparently widely different embodiments of the present invention can be made without departing from the spirit and scope thereof, it is to be understood that the invention is not limited to the specific embodiments thereof except as defined in the appended claims.

Concrete effects of the invention

According to the present invention as set forth above, plasma is separated from blood through a semicontinuous apparatus whereby a fixed amount of blood is repeatedly collected in and returned from a blood reservoir without requiring continuous circulation externally of a donor or patient. Therefore, unlike the conventional continuous arrangement that requires the donor or patient to be punctured at two locations, puncture at only one location is sufficient. Thus, a healthy donor is not subjected to the hazards of external circulation. Moreover, since plasma separation continues even during return of the blood and there is no need to operate the separator at less than peak performance as in the continuous system of the prior art, an equivalent or higher separation efficiency can be obtained, with one and the same plasma separator, as compared with the conventional external circulation-type continuous separation system heretofore considered to be the most outstanding in terms of effectiveness. The present invention therefore enables blood to be collected in a shorter period of time.

In the plasma separating apparatus of the present invention, the membrane-type plasma separating means is capable of having the cross-sectional area of its blood flow passages varied. This makes it possible to prevent hemolysis by suppressing a rise in pressure loss and stabilizing TMP even when blood viscosity changes. Since the blood reservoir means may comprise a sealed bag made of flexible synthetic

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resin, changes in pressure can be followed up automatically. Further, since the blood feed means for introducing and discharging blood may comprise a reversible roller pump, the cost of the apparatus can be lowered since only a single such roller pump need be used.

The plasma separating apparatus of the invention has at least two pumps, one for driving the blood feed means and the other for driving the circulating means. This enables a higher plasma separation efficiency to be achieved because the introduction, discharge and circulation of blood can be performed simultaneously.

Claims

1. An apparatus for separating plasma from blood comprising:

a single common needle (18) for introducing blood and returning blood, membrane-type plasma separating means (1) having an inlet port (4) for introducing blood therein and an outlet port (2) for discharging concentrated blood therefrom,

blood feed means which includes a reversibly rotatable blood feed pump (7) for introducing and discharging blood from said single common needle, and

blood reservoir means (8) connected to said plasma separating means for temporarily pooling or collecting concentrated blood, characterized in that

a blood circulating circuit is provided having one end which is connected to said inlet port (4) of said plasma separating means (1) and another end connected to said outlet port (2) of said plasma separating means (1), the blood concentrated by said plasma separating means (1) flowing through said blood circulating circuit;

circulating means (3) is provided for circulating the blood internally of said blood circulating circuit from said outlet port (2) to said inlet port (4) of said plasma separating means (1);

said blood reservoir means (8) is coupled to said blood circulating circuit on an outlet side thereof for temporarily pooling or collecting an excess amount of concentrated blood which overflows in said blood circulating circuit;

said blood feed means is coupled between said single common needle (18) and said blood circulating circuit; and

said plasma separating means (1) further includes means (19) for varying the cross-sectional area of blood flow passages defined therein.

2. The apparatus according to Claim 7, wherein said blood reservoir means (8) comprises a sealed bag made of a flexible synthetic resin.

3. The apparatus according to Claim 7, further comprising at least two pumps (7, 3), one (7) for driving said blood feed means and the other (3) for driving said circulating means.

4. The apparatus according to Claim 7, further comprising at least two liquid-containing vessels (10, 11), and liquid feed means operatively associated with said blood feed means (7) for selectively delivering to said blood feed means a liquid from said liquid-containing vessels at a predetermined ratio.

5. The apparatus according to Claim 12, wherein the liquid contained in one (10) of said liquid-containing vessels is an anticoagulant, and the liquid contained in the other (11) of said liquid containing vessels is a replacement liquid of an amount equivalent to an amount of separated plasma.

6. An apparatus for separating plasma from blood comprising:

a single common needle (18) for introducing blood and returning blood, membrane-type plasma separating means (1) having an inlet port (4) for introducing blood therein and an outlet port (2) for discharging concentrated blood therefrom,

blood feed means which includes a reversibly rotatable blood feed pump (7) for introducing and discharging blood from said single common needle, and

blood reservoir means (8) connected to said plasma separating means for temporarily pooling or collecting concentrated blood, characterized in that

a blood circulating circuit is provided having one end which is connected to said inlet port (4) of said plasma separating means (1) and another end which is connected to said outlet port (2) of said plasma separating means (1), the blood concentrated by said plasma separating means (1) flowing through said blood circulating circuit;

circulating means (3) is provided for circulating the blood internally of said blood circulating circuit from said outlet port (2) to said inlet port (4) of said separating means (1);

said blood reservoir means (8) is provided in said blood circulating circuit, for temporarily pooling or collecting blood introduced through said single common needle (18) and concentrated by said plasma separating means;

said blood feed means is coupled between said single common needle (18) and said blood reservoir means (8), and

said plasma separating means (1) further includes means for varying the cross-sectional area of blood flow passages defined therein.

7. The apparatus according to Claim 6, wherein said blood reservoir means (8) comprises a sealed bag made of a flexible synthetic resin.

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8. The apparatus according to Claim 6, further comprising at least two pumps (7, 3), one for driving said blood feed means and the other for driving said circulating means.

9. The apparatus according to Claim 6, further comprising at least two liquid-containing vessels (10, 11), and liquid feed means operatively associated with said blood feed means for selectively delivering to said blood feed means a liquid from said liquid-containing vessels at a predetermined ratio.

10. The apparatus according to Claim 9, wherein the liquid contained in one (10) of said liquid-containing vessel is an anticoagulant, and the liquid contained in the other (11) of said liquid containing vessels is a replacement liquid of an amount equivalent to an amount of separated plasma.

Patentansprüche

1. Vorrichtung zum Abtrennen von Blutplasma von Blut, welche aufweist:
eine einzelne gemeinsame Nadel (18) zum Zuführen und zum Rückführen von Blut,
eine membranartige Plasma-Trennvorrichtung (1) mit einer Einlaßöffnung (4) zum Einbringen von Blut in diese und einer Auslaßöffnung (2) zum Austragen von konzentriertem Blut aus dieser,
eine Blutfördereinrichtung, welche eine reversibel drehbare Blutförderpumpe (7) zum Einführen und Austragen von Blut von der einzelnen gemeinsamen Nadel enthält, und
einen Blutvorratsbehälter (8), welcher mit der Plasma-Trenneinrichtung verbunden ist, zum zeitweisen Speichern oder Sammeln von konzentriertem Blut, dadurch gekennzeichnet,
daß ein Blutumwälzkreislauf vorgesehen ist, welcher mit einem Ende an die Einlaßöffnung (4) der Plasmatrenneinrichtung (1) und mit einem anderen Ende an die Auslaßöffnung (2) der Plasmatrenneinrichtung (1) angeschlossen ist, wobei das durch die Plasmatrenneinrichtung (1) konzentrierte Blut durch den Blutumwälzkreislauf fließt,
daß eine Umwälzeinrichtung (3) vorgesehen ist, um das Blut innerhalb des Blutumwälzkreislaufes von der Ausgangsöffnung (2) zu der Eingangsöffnung (4) der Plasmatrenneinrichtung (1) umzuwälzen,
daß der Blutvorratsbehälter (8) an den Blutumwälzkreislauf an dessen Auslaßseite angeschlossen ist, um einen Überschußbetrag von konzentriertem Blut, welcher in dem Blutumwälzkreislauf in Übermenge vorhanden ist, zeitweise zu speichern bzw. zu sammeln,
daß die Blutfördereinrichtung zwischen den einzelnen gemeinsame Nadel (18) und dem Blutumwälzkreislauf eingeschaltet ist und
daß die Plasmatrenneinrichtung (1) außerdem eine Einrichtung (19) zur Veränderung der Querschnittsfläche der in ihr definierten Blut-Strömungsdurchgänge aufweist.

2. Vorrichtung nach Anspruch 1, dadurch gekennzeichnet, daß der Blutvorratsbehälter (8) einen aus flexiblem Kunstharzmaterial bestehenden abgedichteten Beutel umfaßt.

3. Vorrichtung nach Anspruch 1, dadurch gekennzeichnet, daß sie mindestens zwei Pumpen (7, 3), die eine (7) zum Antrieb der Blutfördereinrichtung und die andere (3) zum Antrieb des Umwälzkreislaufes, aufweist.

4. Vorrichtung nach Anspruch 1, dadurch gekennzeichnet, daß mindestens zwei Flüssigkeit enthaltende Behälter (10, 11) und eine mit der Blutfördereinrichtung (7) wirkungsmäßig verbundene Flüssigkeitsfördereinrichtung vorgesehen sind, um wahlweise eine Flüssigkeit von dem Flüssigkeit enthaltenden Behälter in einem vorgegebenen Verhältnis zu der Blutfördereinrichtung zu liefern.

5. Vorrichtung nach Anspruch 12, dadurch gekennzeichnet, daß die in einem (10) der Flüssigkeit enthaltenden Behälter enthaltene Flüssigkeit ein Antigerinnungsmittel ist und daß die in dem anderen (11) der Flüssigkeit enthaltenden Behälter enthaltende Flüssigkeit eine Ersatzflüssigkeit in einem dem Betrag des abgetrennten Plasmas äquivalenten Betrag ist.

6. Vorrichtung zum Abtrennen von Blutplasma von Blut, welche aufweist:
eine einzelne gemeinsame Nadel (18) zum Zuführen und Rückführen von Blut,
eine membranartige Plasmatrenneinrichtung (1) mit einer Einlaßöffnung (4) zum Einführen von Blut in diese und einer Auslaßöffnung (2) zum Austragen von konzentriertem Blut aus dieser,
eine Blutfördereinrichtung, welche eine reversibel drehbare Blutförderpumpe (7) zum Zuführen und Austragen von Blut von der einzelnen gemeinsamen Nadel umfaßt, und
eine Blutbehältereinrichtung (8), welche mit der Plasmatrenneinrichtung verbunden ist, zum zeitweiligen Speichern bzw. Sammeln von konzentriertem Blut, dadurch gekennzeichnet,
daß ein Blutumwälzkreislauf vorgesehen ist, welcher mit einem Ende an die Einlaßöffnung (4) der Plasmatrenneinrichtung (1) und mit einem anderen Ende an die Auslaßöffnung (2) der Plasmatrenneinrichtung angeschlossen ist, wobei das durch die Plasmatrenneinrichtung (1) konzentrierte Blut durch den Blutumwälzkreislauf fließt,
daß eine Umwälzeinrichtung (3) zum Umwälzen des Blutes innerhalb des Blutumwälzkreislaufes von der Auslaßöffnung (2) zu der Einlaßöffnung (4) der Plasmatrenneinrichtung (1) vorgesehen ist,
daß die Blutvorratsbehältereinrichtung (8) in dem Blutumwälzkreislauf vorgesehen ist, um zeitweilig durch die einzelne gemeinsame Nadel (18) eingeführtes und durch die Plasmatrenneinrichtung konzentriertes Blut zu speichern bzw. zu sammeln,
daß die Blutfördereinrichtung zwischen die einzelne gemeinsame Nadel (18) und die Blutvorratsbehältereinrichtung (8) eingeschaltet ist und
daß die Plasmatrenneinrichtung (1) außerdem eine Einrichtung zur Veränderung der Querschnittsfläche der in ihr definieren Blutströmungsdurchgänge aufweist.

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7. Vorrichtung nach Anspruch 6, dadurch gekennzeichnet, daß die Blutvorratsbehältereinrichtung (8) einen aus flexiblem Kunstharz bestehenden, verseigelten Beutel aufweist.

8. Vorrichtung nach Anspruch 6, dadurch gekennzeichnet, daß mindestens zwei Pumpen (7, 3), die eine zum Antrieb der Blutfördereinrichtung und die andere zum Antrieb der Umwälzeinrichtung, vorgesehen sind.

9. Vorrichtung nach Anspruch 6, dadurch gekennzeichnet, daß sie mindestens zwei Flüssigkeit enthaltende Behälter (10, 11) sowie eine mit der Blutfördereinrichtung wirkungsmäßig verbundene Flüssigkeitsfördereinrichtung zur wahlweisen Leiferung einer Flüssigkeit von den Flüssigkeit enthaltenden Behältern in einem vorgegebenen Verhältnis an die Blutfördereinrichtung aufweist.

10. Vorrichtung nach Anspruch 9, dadurch gekennzeichnet, daß die in einem (10) der Flüssigkeit enthaltenden Behälter enthaltene Flüssigkeit ein Antigerinnungsmittel ist und daß die in dem anderen (11) der Flüssigkeit enthaltenden Behälter enthaltene Flüssigkeit eine Ersatzflüssigkeit in einem dem Betrag des abgetrennten Plasmas äquivalenten Betrag ist.

Revendications

1. Appareil pour séparer le plasma du sang comprenant:

une aiguille commune (18) unique destinée à l'introduction du sang et au retour du sang, un moyen de séparation de plasma (1) du type membrane comportant un orifice d'entrée (4) pour y introduire le sang et un orifice de sortie (2) pour en évacuer le sang concentré,

un moyen de transport de sang qui comporte une pompe de transport (7) pour le sang susceptible de tourner de façon réversible, destinée à l'introduction du sang et à l'évacuation du sang par ladite unique aiguille commune et un moyen (8) formant réservoir pour le sang, relié audit moyen de séparation de plasma pour accumuler ou recueillir temporairement le sang concentré, caracterise en ce que:

un circuit pour la circulation du sang est aménagé, dont l'une des extrémités est reliée audit orifice d'entrée (4) dudit moyen de séparation de plasma (1) et dont l'autre extrémité est reliée audit orifice de sortie (2) dudit moyen (1) de séparation de plasma, le sang concentré par ledit moyen (1) de séparation de plasma s'écoulant dans ledit circuit destiné à la circulation du sang;

un moyen de circulation (3) est installé en vue de faire circuler le sang à l'intérieur dudit circuit destiné à la circulation du sang, dudit orifice de sortie (2) audit orifice d'entrée (4) dudit moyen (1) de séparation de plasma;

ledit moyen (8) formant réservoir de sang est relié audit circuit pour la circulation du sang du côté de la sortie de celui-ci pour accumuler ou recueillir une quantité excédentaire de sang concentré, qui dépasse la capacité d'écoulement dudit circuit destiné à la circulation du sang;

ledit moyen de transport de sang est raccordé entre ladite aiguille commune (8) unique et ledit circuit destiné à la circulation du sang;

et le moyen (1) de séparation de plasma comporte en outre un moyen (19) destiné à faire varier la surface de la section transversale des passages pour le sang, définis à l'intérieur.

2. Appareil selon la revendication 7, dans lequel ledit moyen (8) formant réservoir le sang comporte une poche étanche fabriquée en résine de synthèse souple.

3. Appareil selon la revendication 7, comprenant en outre au moins deux pompes (7, 3), l'une (7) destinée à entraîner ledit moyen de transport de sang et l'autre (3) destinée à entraîner ledit moyen de circulation.

4. Appareil selon la revendication 7, comprenant en outre aux moins deux récipients (10, 11) contenant du liquide, et un moyen d'alimentation en liquide associé fonctionellement audit moyen de transport de sang (7) pour fournir de façon sélective audit moyen de transport de sang un liquide provenant desdits récipients contenant du liquide selon un rapport prédéterminé.

5. Appareil selon la revendication 12, dans lequel le liquide contenu dans l'un (10) desdits récipients renfermant du liquide est un anticoagulant, et le liquide contenu dans l'autre (11) desdits récipients renfermant du liquide est un liquide de remplacement en quantité équivalente à la quantité de plasma qui a été séparé.

6. Appareil pour la séparation du plasma comprenant:

une aiguille commune (18) unique destinée à l'introduction du sang et au retour du sang, un moyen (1) de séparation de plasma, du type membrane, comportant un orifice d'entrée (4) pour y introduire le sang et un orifice de sortie (2) pour en évacuer le sang concentré,

un moyen de transport de sang qui comporte une pompe (7) de transport de sang, susceptible de tourner de façon réversible pour introduire et évacuer le sang par ladite unique aiguille commune,

et un moyen formant réservoir (8) relié audit moyen de séparation de plasma pour accumuler ou receuillir temporairement le sang concentré, caracterise en ce que

un circuit pour la circulation du sang est aménagé, dont l'une des extrémités est reliée audit orifice d'entrée (4) dudit moyen (1) de séparation de plasma et dont l'autre extrémité est reliée audit orifice de sortie (2) dudit moyen (1) de séparation de plasma, le sang concentré par ledit moyen (1) de séparation de plasma s'écoulant dans ledit circuit destiné à la circulation du sang;

un moyen de circulation (3) est installé en vue de faire circuler le sang à l'intérieur dudit circuit destiné à la circulation du sang, dudit orifice de sortie (2) audit orifice d'entrée (4) dudit moyen de séparation (1);

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ledit moyen (8) formant réservoir de sang est installé dans ledit circuit destiné à la circulation du sang pour accumuler ou recueillir temporairement le sang prélevé par ladite unique aiguille commune (18) et concentré par ledit moyen de séparation de plasma;

et ledit moyen de transport de sang est raccordé entre ladite unique aiguille commune (18) et ledit moyen (8) formant réservoir de sang

et ledit moyen (1) de séparation de plasma comporte en outre un moyen destiné à faire varier la surface de la section transversale des passages pour le sang, définis à l'intérieur.

7. Appareil selon la revendication 6, dans lequel ledit moyen (8) formant réservoir de sang comporte une poche étanche fabriquée en résine de synthèse souple.

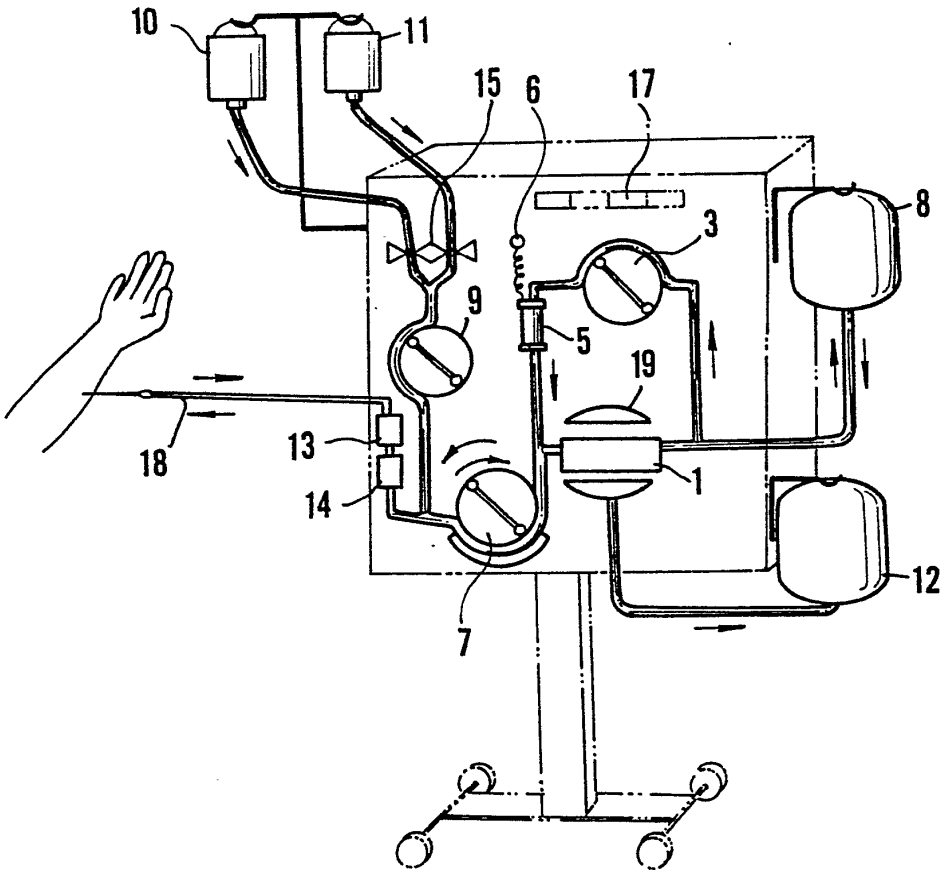
8. Appareil selon la revendication 6, comprenant en outre au moins deux pompes (7, 3), l'une destinée à entraîner ledit moyen de transport de sang et l'autre destinée à entraîner ledit moyen de circulation.

9. Appareil selon la revendication 6, comprenant en outre au moins deux récipients (10, 11) contenant du liquide et un moyen d'alimentation en liquide fonctionnellement associé audit moyen de transport de sang pour fournir de façon sélective audit moyen de transport de sang un liquide provenant desdits récipients contenant du liquide, selon un rapport prédéterminé.

10. Appareil selon la revendication 9, dans lequel le liquide contenu dans l'un (10) desdits récipients contenant du liquide est un anticoagulant, et le liquide contenu dans l'autre (11) desdits récipients contenant du liquide est un liquide de replacement en quantité équivalente à la quantité de plasma qui a été séparé.

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FIG. 1 (A)



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FIG. 1 (B)

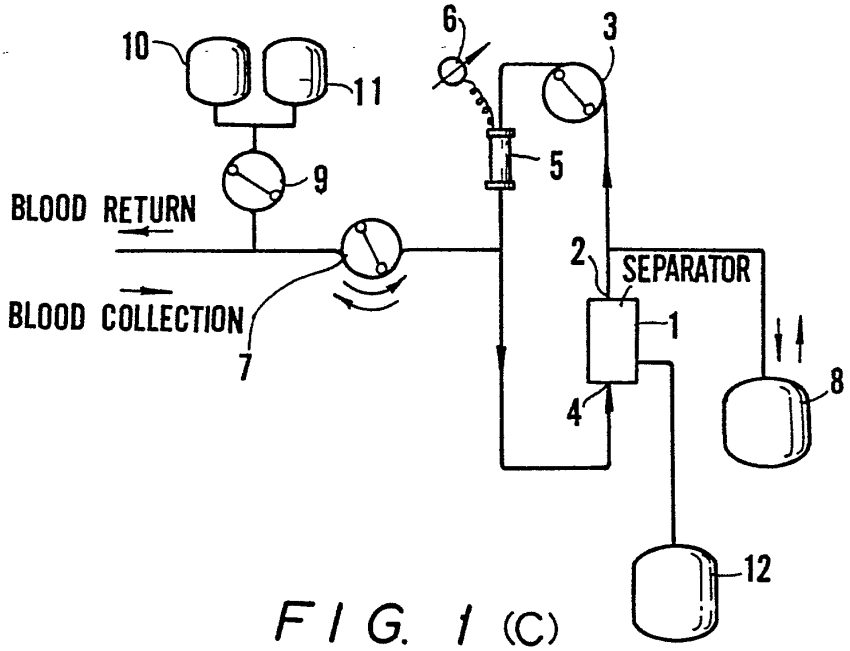
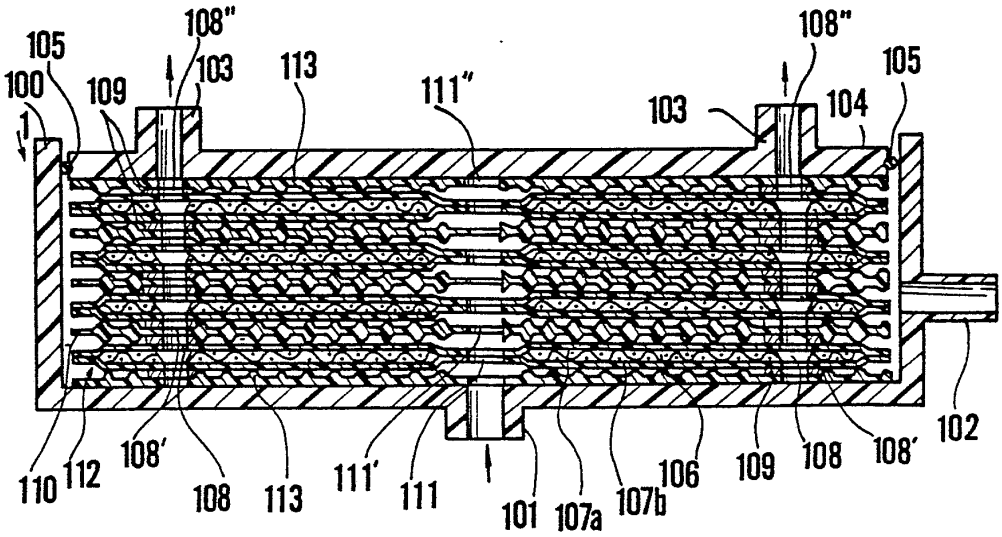
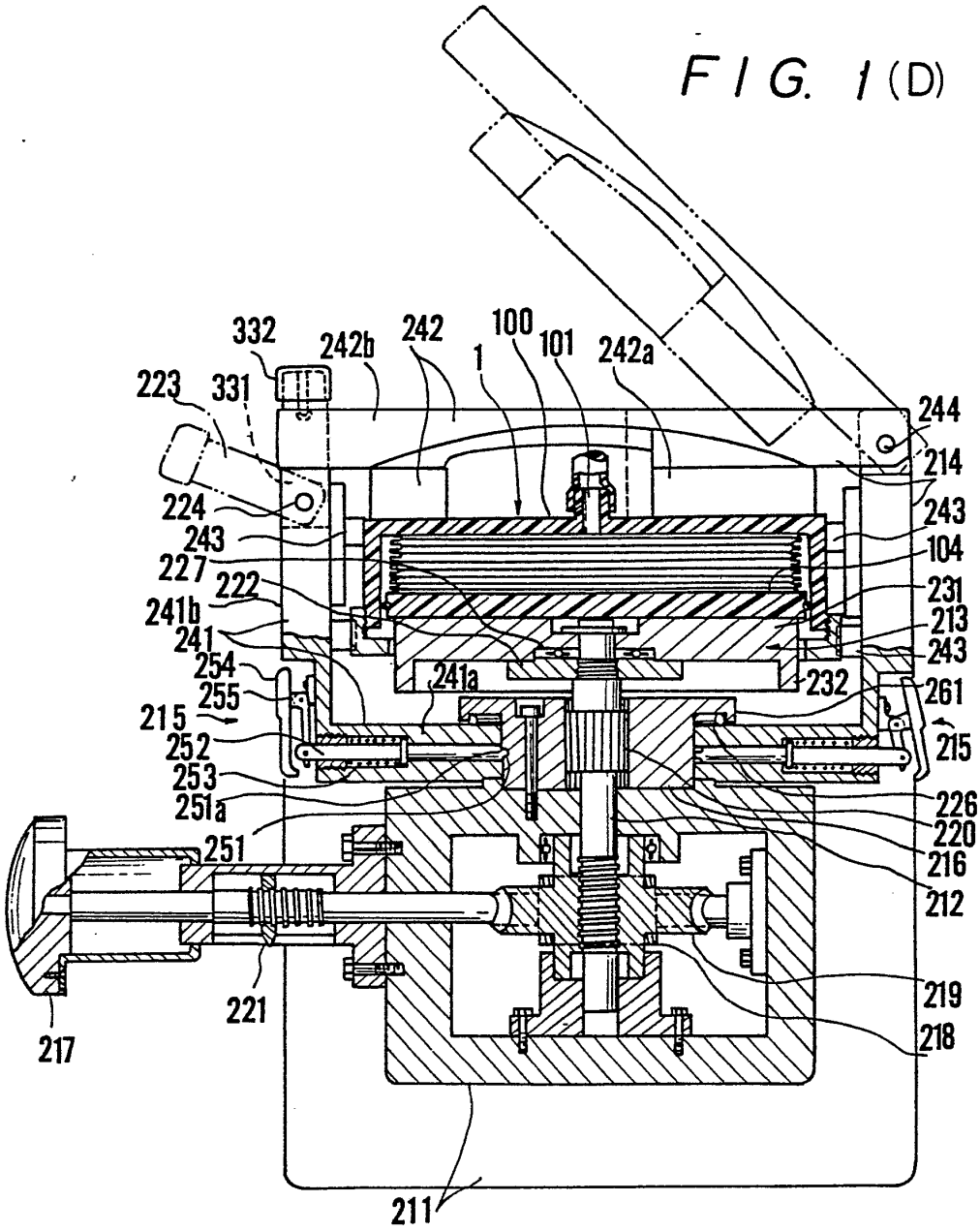


FIG. 1 (C)



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FIG. 1 (D)



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FIG. 2 (A)

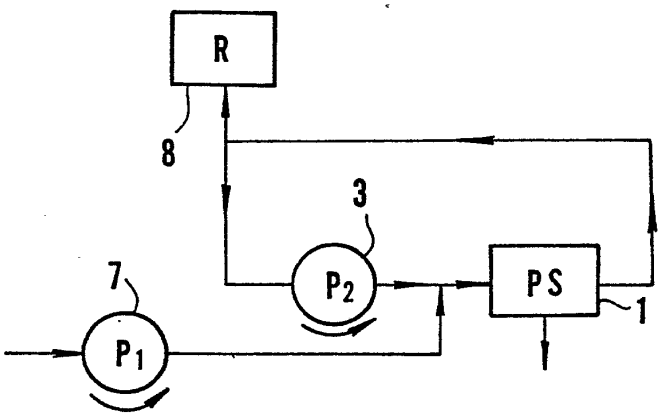
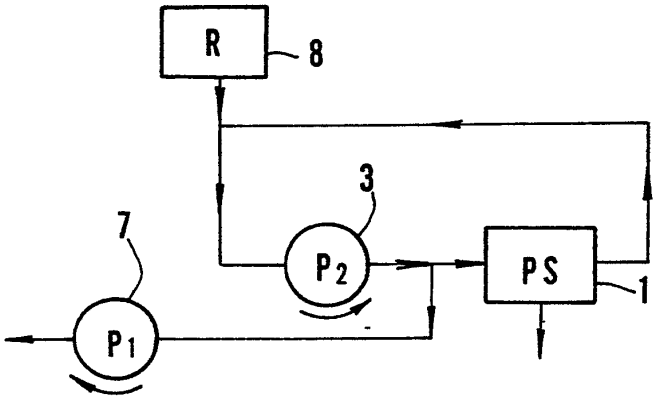
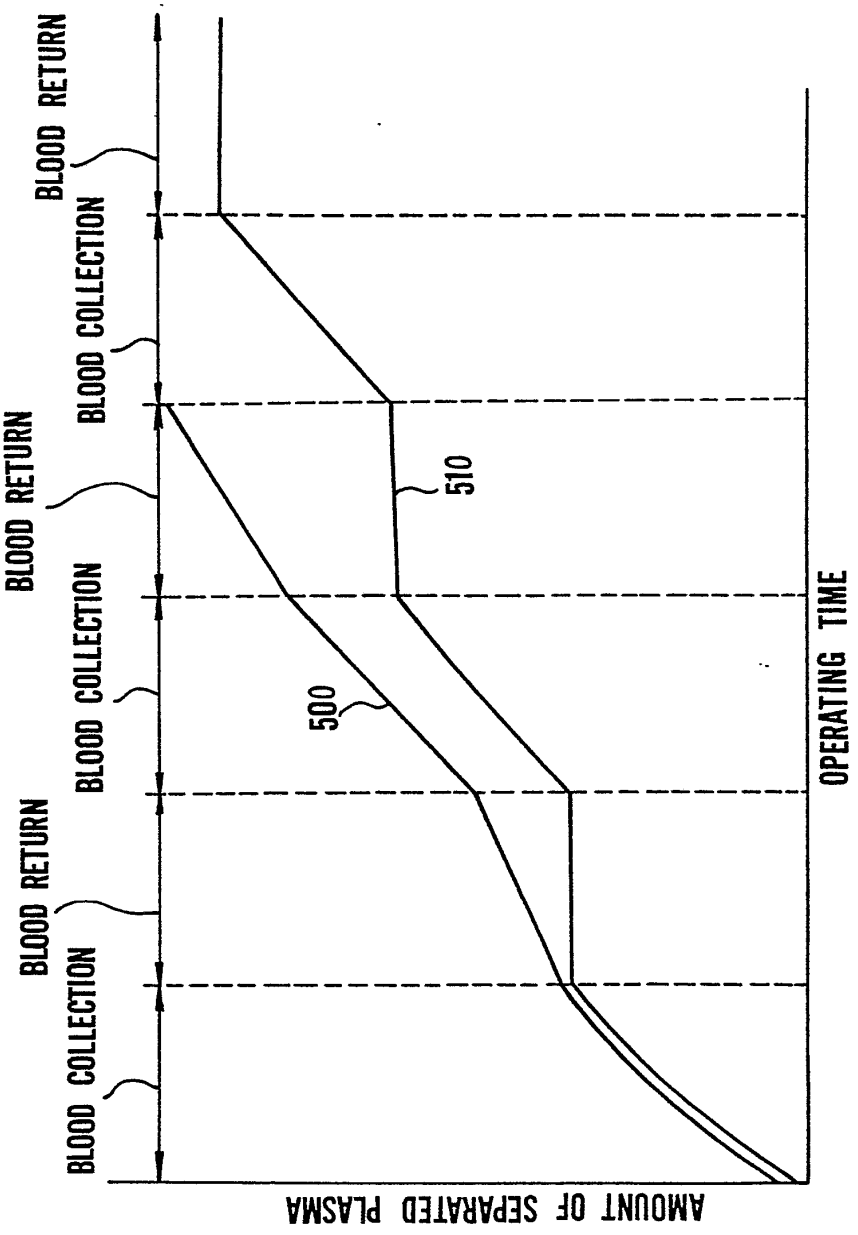


FIG. 2 (B)



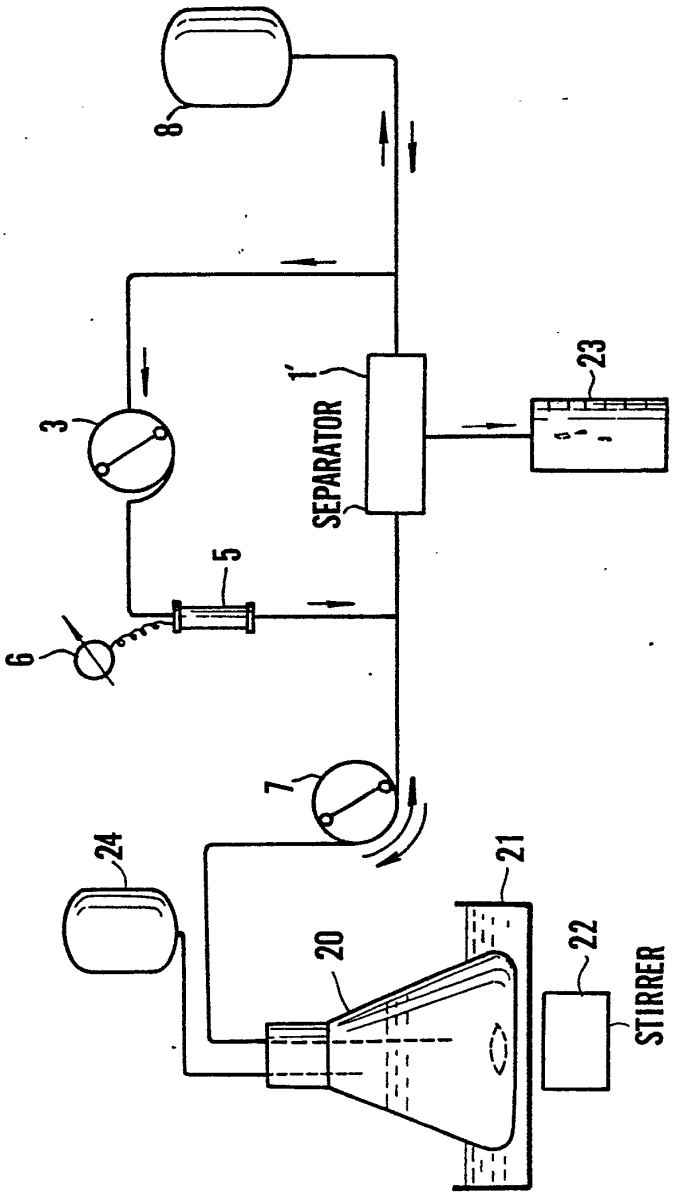
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FIG. 3



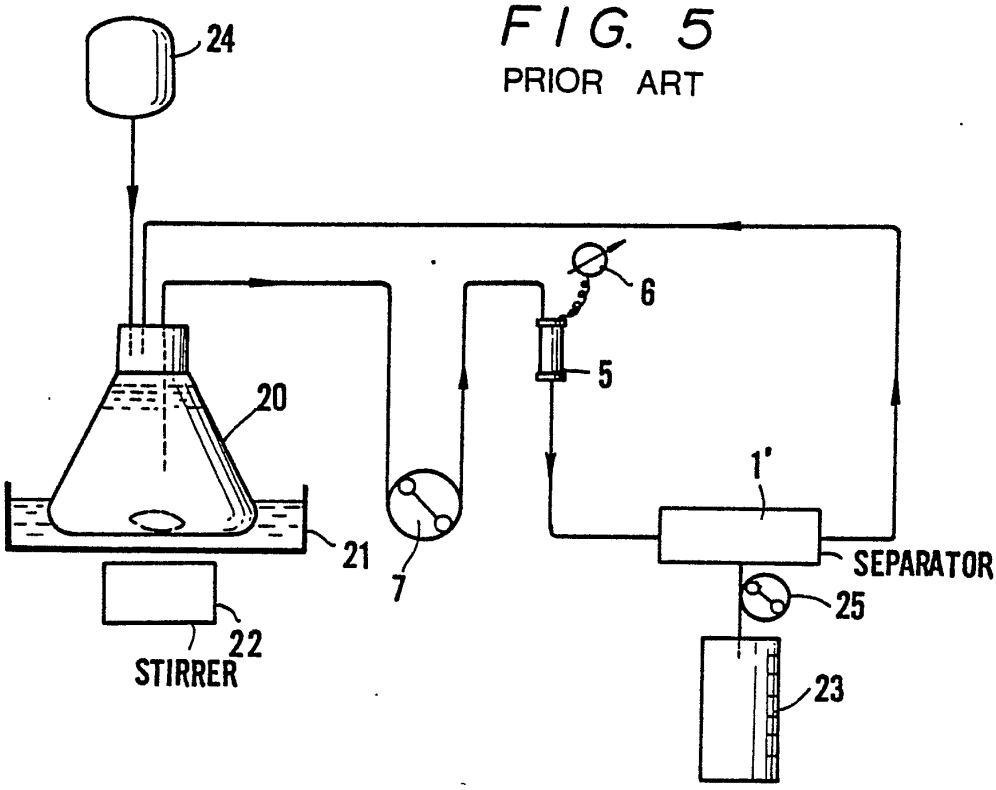
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FIG. 4



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FIG. 5
PRIOR ART



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FIG. 8(A)

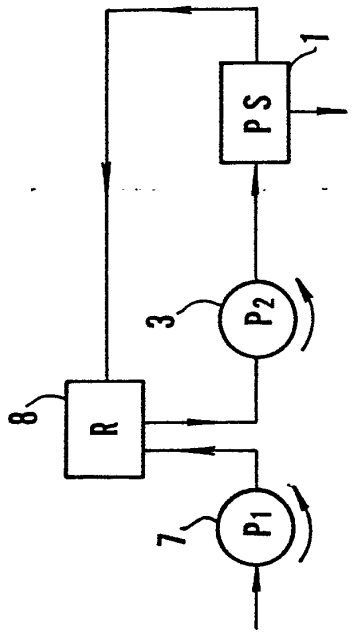


FIG. 8(B)

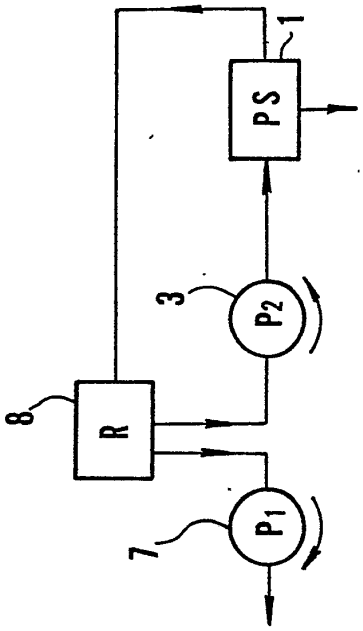


FIG. 6(A)

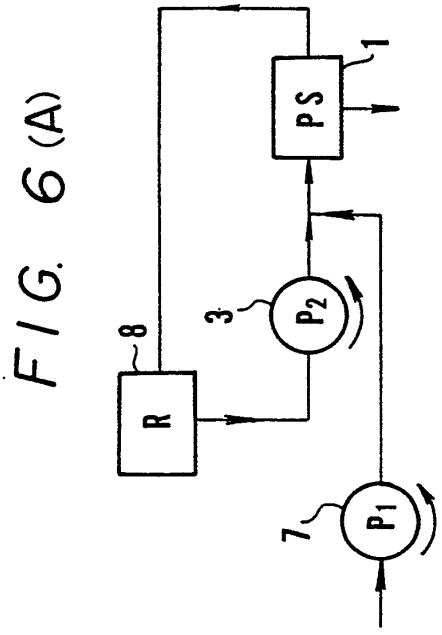
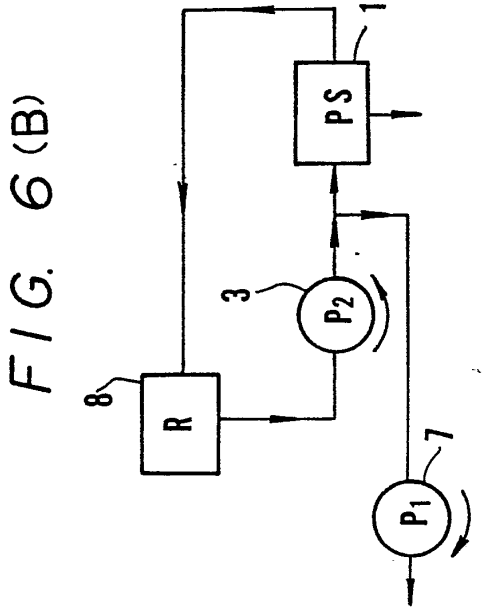
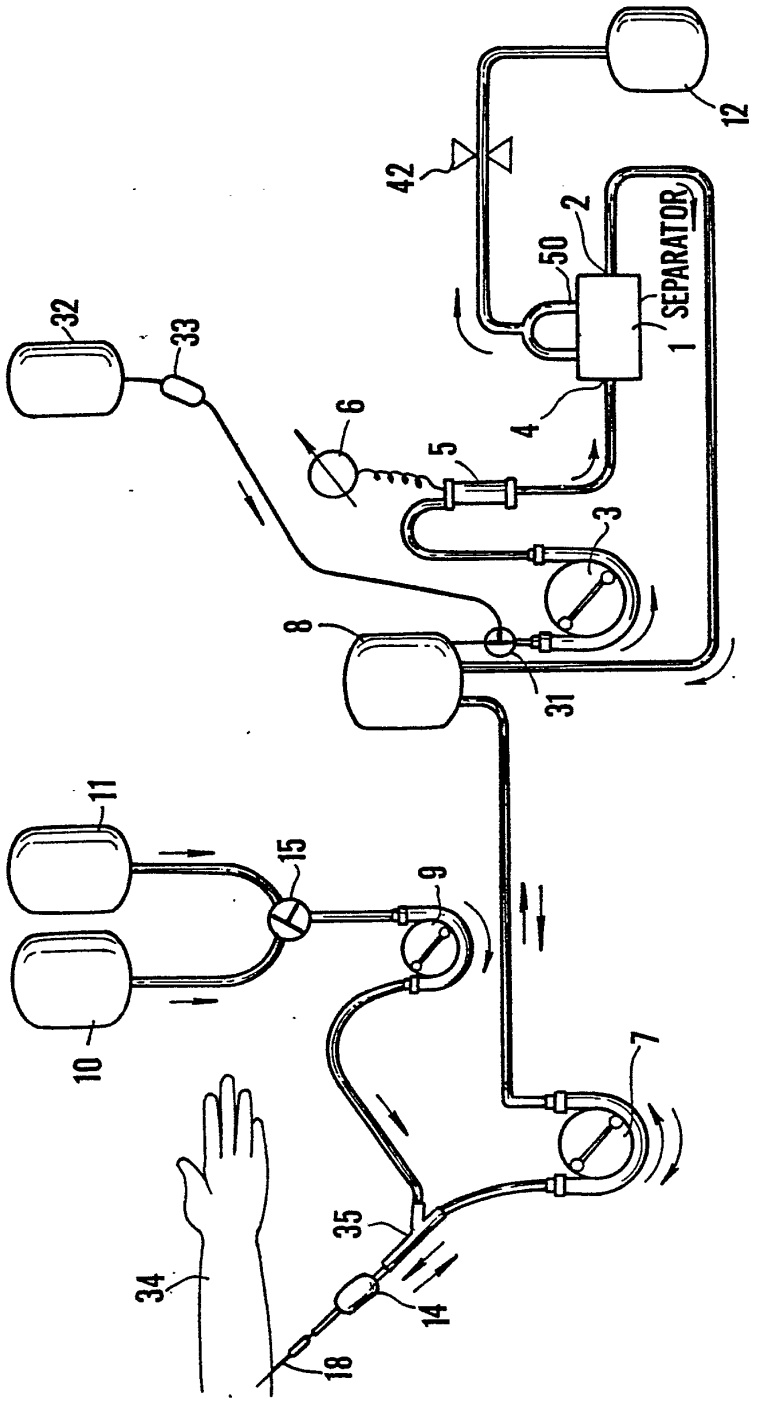


FIG. 6(B)



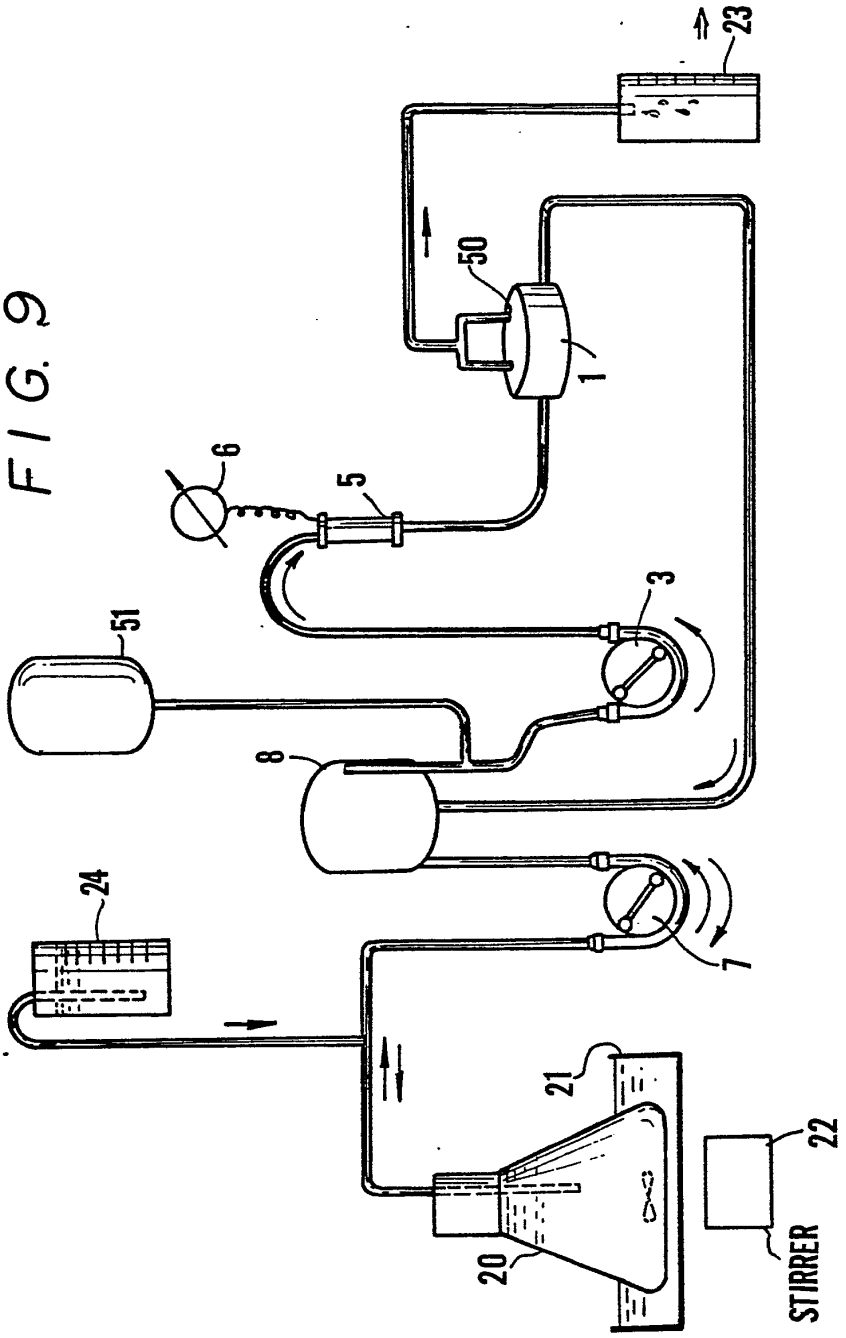
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FIG. 7



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FIG. 9



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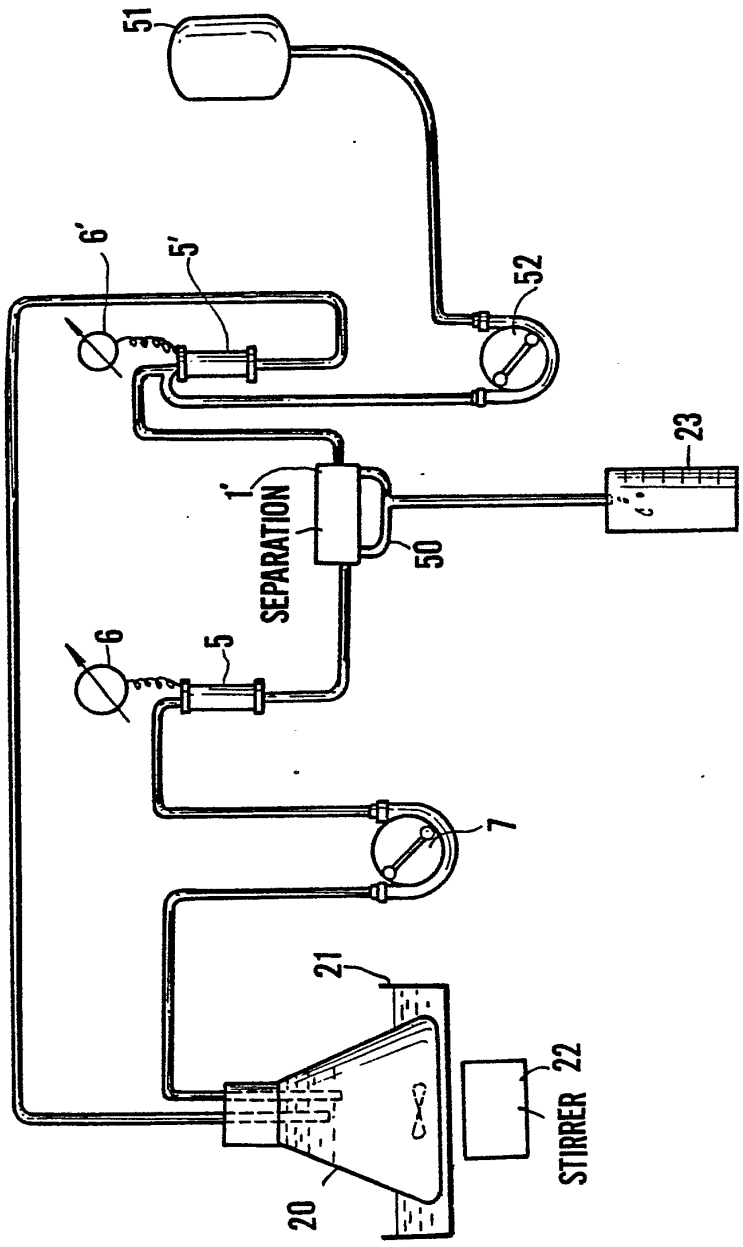


FIG. 10
PRIOR ART

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FIG. 12 (A)

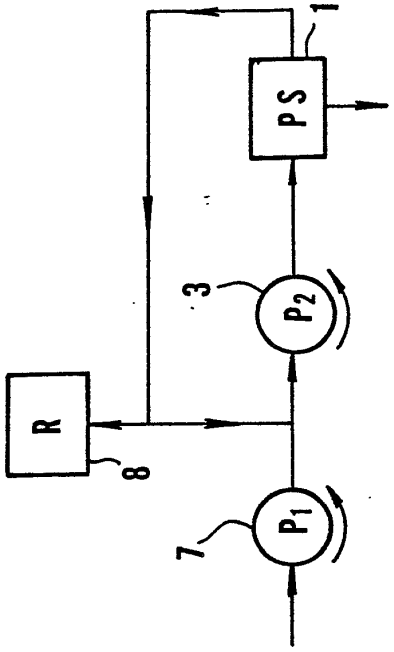


FIG. 12 (B)

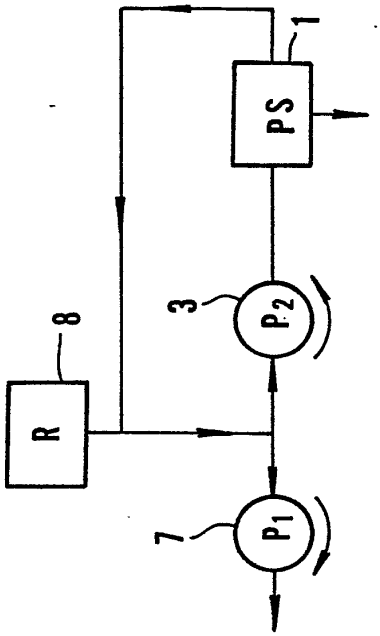


FIG. 11 (A)

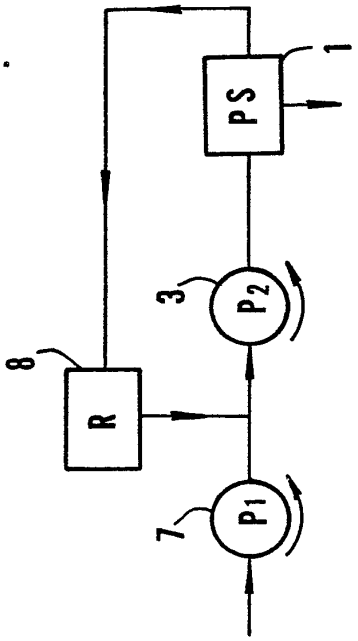
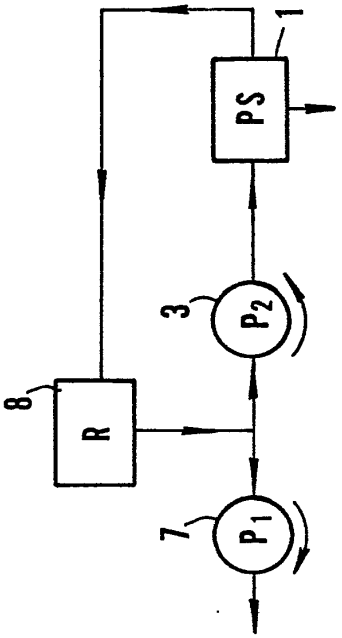


FIG. 11 (B)



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(54) Verfahren und Vorrichtung zur Gewinnung von Blutplasma.

(57) Ein System zur Gewinnung von Blutplasma bei einer Blutentnahme vom lebenden Körper mit Blutentnahmekanüle (1) nach Stauung der entnahmefähigen Blutgefäße unter zusätzlicher Ausnutzung von äußerem Druck und Schwerkraft mit Hilfe einer Plasmafiltereinheit (4) als Trennvorrichtung bietet ein Optimum an Sicherheit für den Spender und an Funktionstüchtigkeit, wenn man Vorfüllungs-Lösung - (10) mit Hilfe eines separaten Anschlusses (2) zugibt, das gespendete Blutvolumen mißt, die Stabilisatorlösung (7) mit Hilfe einer Pumpe (8) entsprechend dem gemessenen gespendeten Blutvolumen zudosiert, das Blut durch eine zwischen Blutentnahmestelle (1) und Plasmafiltereinheit (4), jedoch nach dem Anschluß (11) für die Stabilisatorlösung (7) liegende Tropfkammer (6) mit eingebautem Transfusionsfilter führt und die Sammelstelle (5) für Plasma während des ganzen Verfahrens tiefer als Sammelstelle (3) für Blut anordnet, oder Blut in einen mit Stabilisatorlösung gefüllten Beutel (13) spendet, den vom Beutelsystem (12) abgetrennten Beutel (13) an oberes Ende eines Transfusionssystems (20) anschließt und Blut über Plasmafiltereinheit (4) und Tropfkammer (6) mit Transfusionsfilter retransfundiert und während der Retransfusion Plasma sammelt.

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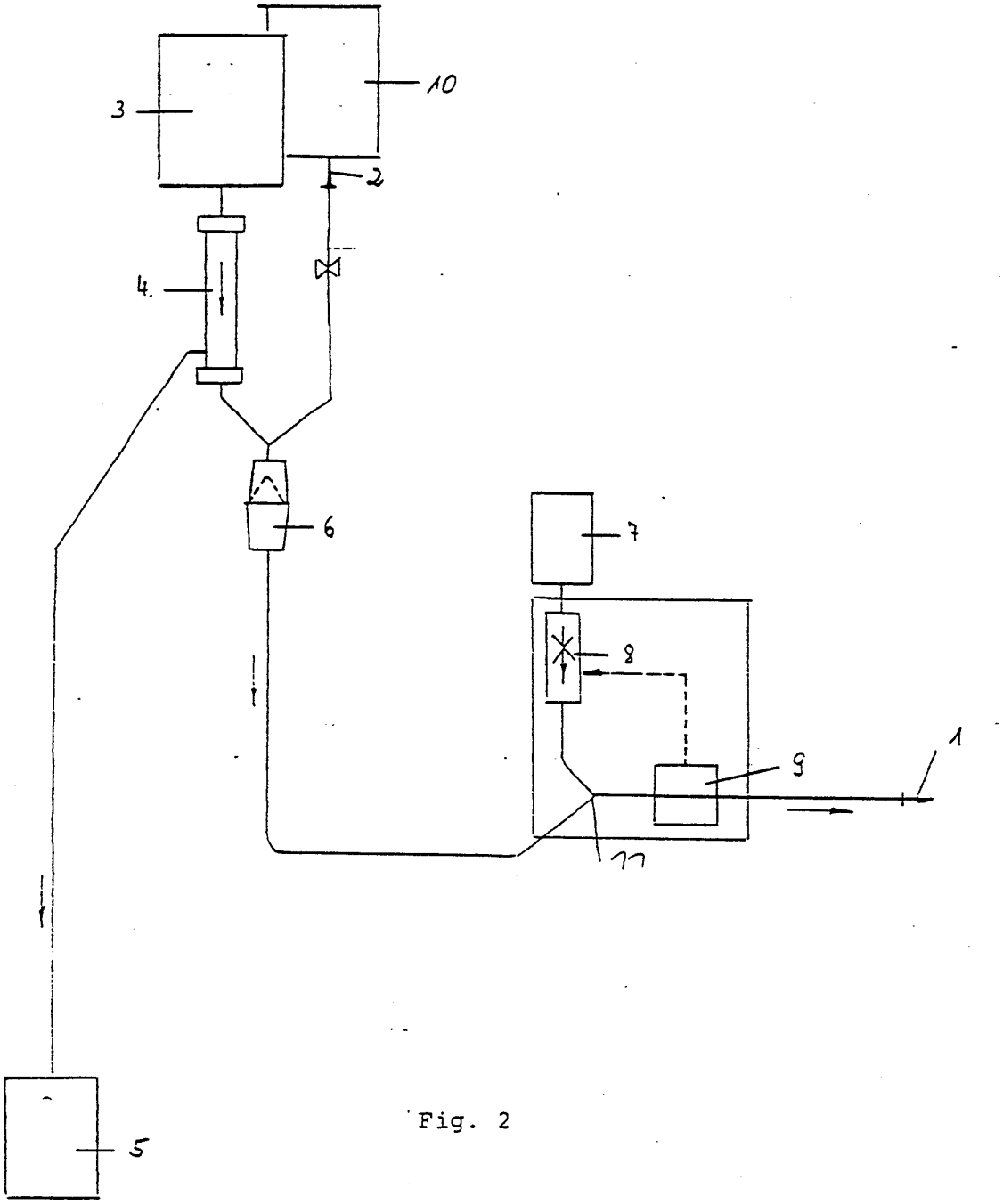


Fig. 2

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Verfahren und Vorrichtung zur Gewinnung von Blutplasma

Die Erfindung betrifft ein Verfahren zur Gewinnung von Blutplasma nach dem Oberbegriff des Anspruchs 1 bzw. 4 sowie eine Vorrichtung zur Durchführung des Verfahrens.

Bei der routinemäßig mit Beutel durchgeführten Plasmaspende spendet der Spender eine bestimmte Menge Blut in einen Beutel, in dem eine auf die Blutmenge abgestimmte Menge Stabilisatorlösung bzw. Antikoagulanzlösung für Blut vorliegt. Nach der Spende wird der Beutel abgetrennt und die Bildung von Gerinnsel in der Venenkanüle im Arm des Spenders durch langsames Infundieren von isotoner NaCl-Lösung über ein Infusionsbesteck verhindert. Der Beutel wird dann zentrifugiert, um das Plasma von den Blutzellen abzutrennen, was meist in einem separaten Raum erfolgt. Anschließend werden die Blutzellen mit etwas isotoner NaCl-Lösung verdünnt und dem Spender über das Infusionsgerät retransfundiert. Dies wird in der Regel zweimal hintereinander durchgeführt, und man erhält so etwa 500 -600 ml Plasma. - ("Richtlinien fur Plasmapheresen", Deutsches Ärzteblatt, Heft 5 (1977) 305-314; "Handbuch der Blutkomponenten-Therapie" American Association of Blood Banks (1969) 24-33)

Die Zentrifugen fur das Zentrifugieren des Plasmas sind sehr groß und schwer und brauchen zur Energieversorgung einen Netzstromanschlu8. Somit kann eine Plasmaspende nur in einem eingerichteten Spendezentrum durchgefuhrt werden.

Da zum Zwecke des Zentrifugierens das gespendete Blut vom Spender entfernt werden muß, kann es trotz aller Vorsichtsmaßnahmen zu Verwechslungen kommen, und dem Spender können falsche Blutzellen retransfundiert werden ("Manuel of Blood Component Preparation", American Association of Blood Banks (1969) 39-44).

Es war nun wünschenswert, auch bei Blutspendeterminen, die nicht in den Spendezentren stattfinden, Plasmaspenden durchführen zu können. Der Bedarf an Plasma ist größer als durch Blutspenden abgedeckt werden kann. Außerdem belastet eine Plasmaspende das blutbildende System weniger als eine Blutspende, so daß eine wöchentliche Spende von 500 ml Plasma möglich ist, während eine Blutspende von 500 ml Blut nur alle 12 Wochen erfolgen kann. Man versuchte ferner ein Verfahren zu finden, das das Wegtransportieren des Spenderblutes nicht mehr erforderlich macht.

Es wurden deshalb Verfahren und Vorrichtungen zur Gewinnung von Blutplasma bei einer Blutentnahme am lebenden Körper unter Verwendung einer Plasmafiltereinheit entwickelt, bei denen das Spenderblut mit Hilfe von Schlauchpumpen zur Plasmafiltereinheit und durch diese hindurchgepumpt werden. Derartige Systeme sind jedoch sehr aufwendig und erfordern an mehreren Stellen Überwachungseinrichtungen für Drücke, Strömungen und Luftblasen.

Aus der DE-OS 33 02 383 bzw. Lysaght, M. et al.: "Plasmapheresis without pumps..."; Int.Workshop Plasma Separation and Plasma Fractionation 17.-19. März 1983, Rottach-Egern, Seiten 1-14, sind ein Verfahren zur Gewinnung von Blutplasma bei einer Blutentnahme nach dem Oberbegriff des Anspruchs 1 bzw. 4 und eine Vorrichtung nach dem Oberbegriff des Anspruchs 7 bzw. 8 bekannt..

Dieses Verfahren arbeitet ohne Blutpumpen, Tropfkammern oder andere Apparaturen, sondern unter Ausnutzung der Schwerkraft und ist somit wesentlich einfacher und weniger aufwendig als bisherige mit Pumpen und anderen Apparaturen arbeitende Verfahren. Es wird dort lediglich unter Verwendung einer Blutentnahmekanüle nach einer Stauung der entnahmefähigen Blutgefäße Spenderblut mittels eines Schlauches zu einer tiefer gelegenen Plasmafiltereinheit geleitet, worin Plasma und Blut getrennt und einer Sammelstelle für Plasma und einer davon getrennten Sammelstelle für Blut zugeleitet werden. Zwischen Blutentnahmestelle und Plasmafiltereinheit befindet sich ein Anschluß für eine Antikoagulanzlösung.

Bei diesem System braucht der Blutbeutel nicht zum Zwecke des Zentrifugierens wegtransportiert zu werden, sondern bleibt bei der Spende, wodurch eine geringere Verwechselungsgefahr besteht.

Neben dem Vorteil der einfachen Handhabung und der geringeren Verwechselungsgefahr weisen dieses Verfahren und die Vorrichtung jedoch einige Nachteile auf.

Das System sieht keine Messung des Spendevolumens vor, wobei die Gefahr besteht, daß ein zu großes Blutvolumen sich außerhalb des Körpers des Spenders befindet, wobei es zu einem Kreislaufkollaps kommen kann. Die Antikoagulanzlösung wird dem System in einer konstanten Menge zugeführt, jedoch unabhängig vom Blutfluß, nachdem dieser nicht gemessen wird. Der zu erwartende Blutfluß ist vor der Spende nicht bekannt und kann sich außerdem während der Spende ändern. Aus diesem Grunde kann Überdosierung oder Unterdosierung der Antikoagulanzlösung erfolgen. Überdosierung bedeutet bei der Retransfusion fur den Spender eine zusätzliche, möglicherweise mit Komplikationen verbundene Belastung. Sehr unangenehm kann es für den Spender werden, wenn der Blutfluß stoppt wegen einer Verstopfung nach

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der Antikoagulanz-Zufuhrstelle. In diesem Falle läuft die Antikoagulanz-Zufuhr weiter, und zwar in die Vene des Spenders. Es wird also reine Antikoagulanzlösung infundiert, wovor auf dem Aufdruck von Behältern mit Antikoagulanzlösung ausdrücklich gewarnt wird. Unterdosierung fördert die Bildung von Mikroaggregat und birgt die Gefahr der Gerinnungsaktivierung in sich, was bei Einsatz von Membranfiltern zur Plasmaabtrennung insofern besonders kritisch ist, als hier eine große Fremdoberfläche für das Blut vorliegt und die Gefahr einer Gerinnungsaktivierung besonders gegeben ist.

Vor Beginn der Spende muß das System mit isotoner Lösung vorgefüllt werden. Ist das System nicht von Anfang an vorgefüllt, so kann der Transmembrandruck (TMP) sogar negativ sein, wenn bei langsamem Blutfluß das für die Strömung notwendige Druckgefälle zwischen Plasmafiltereinheit und Blutsammelbeutel kleiner wird als die hydrostatische Druckdifferenz. Es findet dann keine Plasmafiltration statt. Es muß daher die Leitung zum Plasmabeutel mit Flussigkeit gefüllt sein, um einen zusätzlichen Unterdruck aufgrund der Höhendifferenz zwischen Plasmafiltereinheit und Plasmabeutel sicherzustellen, so daß auf jeden Fall ein positiver TMP vorliegt, d.h. daß der Druck auf der Blutseite der Membran großer ist als auf der Plasmaseite.

Die Luft muß aus den Schlauchleitungen weitgehend entfernt werden, um bei der Retransfusion die Gefahr einer Luftembolie zu vermeiden. Beim bekannten System wird deshalb vor der Spende mit isotoner NaCl-Lösung über die Entnahmekanüle gespült. Beim Vorfüllen des Systems über die Blutentnahmekanüle kann letztere jedoch beim Einstechen in den Stopfen einer Flasche mit NaCl-Lösung verändert werden und eine Venenpunktion dann erschwert werden.

Wie bereits vorstehend ausgeführt, arbeitet das System ohne Tropfkammer und ohne Infusionsfilter, was, wie nachstehend genauer erläutert wird, sehr gefährlich sein kann.

Schließlich befinden sich die Sammelstelle für Plasma und die Sammelstelle für Blut bei der Blutspende praktisch auf einer Ebene. Mit einer solchen Anordnung kann über die kommunizierenden Schlauchleitungen bei Stillstand des Blutflusses das Plasma über die Plasmafiltereinheit in die Sammelstelle für Blut fließen, falls der Plasmabeutel geringfügig über dem Blutbeutel hängt, was sehr leicht auftreten kann.

Der Erfindung liegt die Aufgabe zugrunde, ein Verfahren und eine Vorrichtung zur Gewinnung von Blutplasma bei einer Entnahme vom lebenden Körper bereitzustellen, die leicht zu handhaben und einfach sind und sich keiner aufwendigen Blutpumpen und sonstiger Apparaturen bedienen, sondern unter Ausnutzung der Schwerkraft arbeiten, dabei jedoch ein Optimum an Sicherheit für den Spender bieten und keine Funktionsmängel aufweisen.

Diese Aufgabe wird bei einem gattungsgemäßen Verfahren durch die kennzeichnenden Merkmale des Anspruchs 1 bzw. 4 und bei einer gattungsgemäßen Vorrichtung durch die kennzeichnenden Merkmale des Anspruchs 7 bzw. 8 gelöst.

Nach einer Ausführungsform der Erfindung wird die Stabilisator-bzw. Antikoagulanzlösung mit Hilfe einer Dosierpumpe entsprechend dem gemessenen Blutvolumen genau dosiert, wodurch ein optimales Stabilisator/Blut-Verhältnis eingehalten wird und weder durch Unterdosierung die Gerinnungsaktivierung begünstigt wird, noch durch Überdosierung der Spender bei der Spende gefährdet oder bei der Retransfusion zusätzlich belastet wird.

Um zu vermeiden, daß ein zu großes Volumen an Blut sich außerhalb des Körpers befindet und es somit zu einem Kreislaufkollaps kommen kann, wird erfindungsgemäß das gespendete Blutvolumen laufend gemessen. Die Messung erfolgt vorzugsweise mit einem Ultraschalldetektor an der Außenseite des blutführenden Schlauches. Eine geeignete Meßmethode wird in der EP-OS 83 100 079 beschrieben. Eine weitere, jedoch nicht so bevorzugte Meßmethode besteht in der Verwendung einer elektronischen Waage.

Als Dosierpumpe für Antikoagulanzlösung läßt sich jede Art von auf dem Markt befindlichen Dosierpumpen verwenden. Besonders brauchbar sid Peristaltikpumpen, wie sie für diesen Zweck in der EP-OS 83 100 079 beschrieben werden.

Als ganz besonders brauchbar erwies sich ein Blutentnahmegerät (BEG 404) der Fa.Doltron AG. Bei diesem Gerät wird der Blutfluß mit einem Ultraschalldetektor gemessen und die Antikoagulanzlösung über eine Perestaltikpumpe dem Blutfluß entsprechend zudosiert. Aus dem Blutfluß wird das Blutvolumen berechnet und angezeigt, wenn ein vorbestimmtes Volumen erreicht ist.

Es ist ferner nicht unbedingt erforderlich, die Vorfüllungs-Lösung am Anfang des Systems mit Hilfe der Blutentnahmekanüle einzufüllen, sondern dies ist auch mit Hilfe eines separaten Anschlusses an irgendeiner Stelle des Systems möglich. Erfindungsgemä8 ist deshalb ein separater Anschluß für die Vorfullungs-Lösung vorgesehen. Dadurch wird die Entnahmekanüle geschont, und die Venenpunktion wird nicht durch eine bereits vorher schon einmal eingestochene Kanüle erschwert.

Der Anschluß für die Vorfüllungs-Lösung kann mit einer Kanüle oder einem Dorn versehen sein zum Einstechen in eine mit Vorfüllungs-Lösung gefullte Flasche oder einen Beutel.

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Während der Retransfusion können sich aus dem System Luftblasen lösen, die beim Einfüllen mit isotoner Lösung und während der Blutspende nicht vollständig entfernt wurden (Gefahr der Luftembolie). Zum anderen besteht immer die Möglichkeit, daß im System trotz ausreichender Zugabe von Antikoagulanzlösung Gerinnungsvorgänge ablaufen, die zur Bildung von Mikroaggregaten führen können. Diese müssen bei der Retransfusion der Erythrozyten herausgefiltert werden (Gefahr der Thrombose). Aus Sicherheitsgründen, um diese Gefahren auszuschließen, ist erfindungsgemäß eine Luftblasenfalle mit eingebautem Transfusionsfilter vorgesehen. Diese Falle befindet sich hinter dem Anschluß für die Antikoagulanzlösung und vor der Plasmafiltereinheit, bezogen auf den Blutfluß während der Blutspende. Eine solche Luftblasenfalle mit Transfusionsfilter liegt in Form einer Tropfkammer mit Filter für Blut und Blutbestandteile vor, beispielsweise wie sie gemäß DIN 58 360 Teil 1 beschrieben wird.

Schließlich wurde gefunden, daß es zur Vermeidung eines Überfließens von Plasma aus der Sammelstelle für Plasma zur Sammelstelle für Blut, bei Stillstand des Blutflusses, der z.B. bei Verlegen der Venenkanüle durch die Venenwand eintritt, erforderlich ist, sowohl während der Blutspende als auch während der Retransfusion die Sammelstelle für Plasma tiefer als den Blutbeutel zu hängen.

Nach einer weiteren, bevorzugten Ausführungsform der Erfindung erfolgt die Abtrennung des Plasmas nicht mehr während der Blutspende, sondern nur noch während der Retransfusion.

Dabei erfolgt die Spende in einen Blutbeutel, dem eine bestimmte, auf die zu spendende Blutmenge abgestimmte Stabilisatorlösung vorliegt, auf ähnliche Weise, wie in der vorstehend genannten Literatur zur Plasmapherese beschrieben wird. Danach wird der Beutel vom Beutelsystem abgetrennt und an das obere Ende eines Transfusionsgerätes angeschlossen, das mehrere Einstichdorne am oberen Ende, eine Plasmafiltereinheit, eine Sammelstelle für Plasma und eine Tropfkammer mit eingebautem Transfusionsfilter enthält und mit dem unteren Ende mit dem Beutelsystem und somit der Spenderkanüle verbunden ist.

Das gespendete Blut kann nun über die Plasmafiltereinheit dem Spender retransfundiert werden. Während das Blut durch die Plasmafiltereinheit fließt, wird das Plasma abgetrennt und in einem Plasmasammelbeutel aufgefangen.

Diese bevorzugte Ausführungsform ist noch sicherer und noch einfacher als die vorstehend beschriebene Ausführungsform der Erfindung.

Sicherer deshalb, weil beim Durchströmen des Transfusionsfilters in beiden Richtungen Stoffe, z.B. Mikroaggregate, die bei der Blutentnahme im Filter zurückgehalten wurden, beim umgekehrten Durchströmen doch mal in den Spender retransfundiert werden können und weil diese Gefahr beim einfachen Durchströmen, d.h. nur beim Retransfundieren, ausgeschlossen ist.

Einfacher deshalb, weil kein Dosiersystem für die Stabilisatorlösung erforderlich ist und jeglicher apparativer Aufwand, wie die Dosierpumpe als solche und Leitungs-oder Batteriestrom, entfallen. Das Stabilisator-bzw. Antikoagulanzproblem ist mit dieser Ausführungsform total gelöst.

Zur Gewinnung einer gewissen Plasmamenge sind zwar mehr Zyklen erforderlich als bei der ersten Ausführungsform, weil nur während der Retransfusion Plasma gewonnen wird, d.h. die Plasmaextraktion pro Volumeneinheit Blut ist etwas geringer, dafür ist aber die Zykluszeit kürzer, weil der Hämatokritwert niedriger ist.

Die Retransfusionszeit kann außerdem noch dadurch verkürzt werden, daß man um den gefüllten Beutel eine Druckmanschette legt, wie sie bei Drucktransfusion üblich ist.

Das Verfahren kann mehrere Male wiederholt werden, bis eine ausreichende Plasmamenge gespendet worden ist.

Am Beutelsystem befindet sich mindestens ein Blutbeutel, vorzugsweise drei, jedoch sind bis zu fünf Beutel möglich. Dementsprechend sollte auch die Anzahl der Einstichdorne am oberen Ende des Transfusionsgerätes sein. D.h. es sollten mindestens so viele Einstichdorne vorhanden sein, wie anzuschließende Blutbeutel vorgesehen sein können plus ein Einstichdorn für den Anschluß der Vorfüllungs-Lösung.

Als Vorfüllungs-Lösung wird vorzugsweise eine isotone NaCl-Lösung verwendet.

Stabilisatorlösungen werden in der Literatur beschrieben. Zu den üblichen Lösungen gehören beispielsweise Na-Citrat-und CPD-(Citrat-Phosphat-Dextrose)Lösungen.

Als Plasmafiltereinheit lassen sich Module sowohl mit Flachmembranen als auch mit Hohlfasermembranen verwenden. Die Porengröße der Membranen sollte zweckmäßigerweise 0,2 bis 0,8 µm, vorzugsweise maximal 0,65 µm betragen. Bei einer zu kleinen Porengröße, z.B. unter 0,2 µm, könnten Proteine zurückgehalten werden. Der Innendurchmesser von Hohlfasermembranen kann

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beliebig sein, jedoch werden durch das extrakorporale Blutvolumen Grenzen gesetzt. Deshalb sollte der Innendurchmesser nicht kleiner als 100 µm und nicht größer als 500 µm sein.

Eine brauchbare Plasmafiltereinheit mit Hohlfasermembran ist die Plasmapur(®)-Patrone, wie sie im Firmenprospekt "Pure plasma..... Plasmapur(®)" der Firma Organon Technika beschrieben wird. Ebenfalls brauchbar ist das Travenol CPS-10 Plasmafilter mit einer aktiven Hohlfaserlänge von 21 cm, wie es in der DE-OS 33 02 383 beschrieben wird.

Eine geeignete Plasmafiltereinheit mit Flachmembran wird beispielsweise in der DE-PS 29 25 143 beschrieben.

Als Sammelstelle für Blut und für Plasma lassen sich Blutflaschen oder Blutbeutel aus Kunststoff verwenden, wie sie allgemein zur Aufbewahrung von Blut üblich sind. Die Verbindungsschläuche zwischen den einzelnen Elementen der erfindungsgemäßen Vorrichtung können ebenfalls übliche Kunststoff-oder Gummischläuche sein, wie sie bei Transfusionsgeräten üblich sind und z.B. den Forderungen gemäß DIN 58 360 oder DIN 58 367 entsprechen. Derartige Schläuche haben einen Innendurchmesser von mindestens 3 mm.

Nachstehende Zeichnungen dienen der weiteren Erläuterung der Erfindung.

Es zeigen:

Fig. 1 eine erfindungsgemäße Vorrichtung in erfindungsgemäßer Anordnung zur Blutspende;

Fig. 2 eine erfindungsgemäße Vorrichtung in erfindungsgemäßer Anordnung zur Retransfusion;

Fig. 3 eine Vorrichtung ohne Anschluß an eine Vorfüllungs-Lösung in Anordnung zur Blutspende, wobei die Sammelstelle für Blut tiefer hängt als die Sammelstelle für Plasma;

Fig. 4 eine Vorrichtung ohne Anschluß an eine Vorfüllungs-Lösung in Anordnung zur Retransfusion, wobei die Sammelstelle für Blut höher hängt als die Sammelstelle für Plasma;

Fig. 5 eine bevorzugte Vorrichtung gemäß der Erfindung;

Fig. 6 eine stark vereinfachte Vorrichtung zur Effektivitätsmessung des bevorzugten Systems.

In Fig. 1 wird Blutentnahmekanüle (1) gezeigt, von der aus Blut durch ein Schlauchsystem, das mit einer Meßvorrichtung (9) für gespendetes Blutvolumen versehen ist, durch Tropfkammer mit eingebautem Transfusionsfilter (6) zur Plasmafiltereinheit (4) fließt. Zwischen Tropfkammer (6) und Blutentnahmekanüle (1) befindet sich der Anschluß (11) an Stabilisatorlösung (7), die mit Hilfe der Dosierpumpe (8) dem System in Abhängigkeit vom gespendeten Blutvolumen zudosiert wird. Beim Durchströmen durch die Plasmafiltereinheit (4) wird Plasma vom Blut getrennt und fließt zur Sammelstelle für Plasma (5), während Blut zur Sammelstelle für Blut (3) fließt. Der Anschluß (2) für die Vorfüllungs-Lösung (10) befindet sich bei dieser Ausführungsform zwischen Tropfkammer (6) und Plasmafiltereinheit (4), kann sich jedoch an jeder anderen beliebigen Stelle des Systems befinden, vorzugsweise zwischen Blutentnahmekanüle (1) und Plasmafiltereinheit (4). Ebenso kann sich die Meßvorrichtung (9) an irgendeiner beliebigen Stelle zwischen (1) und (4) befinden. Bei der Blutspende sind Blutentnahmekanüle (1) und Anschluß (11) mit Stabilisatorlösung (7) und Dosierpumpe (8) oberhalb der übrigen Elemente des Systems angeordnet, damit Blut mit Hilfe der Schwerkraft fließen kann. Die Sammelstelle für Plasma (5) befindet sich unterhalb der Sammelstelle für Blut (3).

In Fig. 2 haben alle Elemente die gleiche Bedeutung wie in Fig. 1. Die Fig. 2 unterscheidet sich von Fig. 1 lediglich dadurch, daß zum Zwecke der Retransfusion diesmal Sammelstelle für Blut (3), Plasmafiltereinheit (4) und Tropfkammer (6) höher als die Blutentnahmekanüle angeordnet sind, damit das nur zum Teil vom Plasma befreite Blut mit Hilfe der Schwerkraft zum Spender zurückfließen kann. Bei diesem Zurückfließen passiert das partiell deplasmatisierte Blut zum zweiten Mal die Plasmafiltereinheit (4) und eine weitere Plasmamenge wird vom Blut abgetrennt. Während der Retransfusion fördert die Dosierpumpe (8) keine Stabilisatorlösung (7).

In Fig. 3 haben ebenfalls alle Elemente die gleiche Bedeutung wie in Fig. 1. Fig. 3 unterscheidet sich von Fig. 1 dadurch, daß kein Anschluß (2) für Vorfullungs-Lösung (10) vorgesehen ist und die Sammelstelle fur Blut (3) tiefer angeordnet ist als die Sammelstelle für Plasma (5).

In Fig. 4 haben ebenfalls alle Elemente die gleiche Bedeutung wie in Fig. 1. Fig. 4 unterscheidet sich von Fig. 2 dadurch, daß kein Anschluß (2) fur Vorfullungs-Lösung (10) vorgesehen ist.

In Fig. 5 wird eine bevorzugte Vorrichtung gezeigt, bei der die Plasmagewinnung nur während der Retransfusion erfolgt.

Es wird dort Blutentnahmekanüle (1) gezeigt, von der das Spenderblut in das Beutelsystem (12) und in die Beutel (13, 13a, 13b) fließt. Es wird ferner das Transfusionsgerät (20) gezeigt, das die Plasmafiltereinheit (4), Sammelstelle für Plasma (5), Tropfkammer mit eingebautem Transfusionsfilter (6), Einstichdorne (14,14a,14b) zum Anschluß an die Blutbeutel (13,13a,13b), Einstichdorn (14c) zum Anschluß an die Vorfüllungs-Lösung (10) und Rollklemmen (15,15a,15b,16,17) enthält. Blutbeutelsystem (2) und Transfusionsgerät (20) weisen jeweils an einem Ende ein Verbindungssystem (18) auf, mit Hilfe dessen sie miteinander verbunden werden

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können.

Nachdem diese Verbindung erfolgt ist, wird das gesamte System über Einstichdorn (14c) mit der Vorfullungs-Lösung (10) vorgefüllt. Danach beginnt die Punktierung des Spenders mit Hilfe der Blutentnahmekanüle (1). Nachdem die mit Stabilisatorlösung vorgelegten Blutbeutel (13) mit Spenderblut gefüllt sind, werden sie vom Beutelsystem - (12) abgeklemmt und abgetrennt und mit Hilfe der Einstichdorne (14,14a,14b) an das höher liegende Transfusionssystem angeschlossen. Nun erfolgt die Retransfusion, bei der das Blut mit Hilfe von äußerem Druck und Schwerkraft durch Plasmafiltereinheit (4) fließt, wobei das Plasma abgetrennt und in der Sammelstelle fur Blutplasma (5) gesammelt wird. Das deplasmatisierte Blut fließt dann weiter durch die Tropfkammer mit eingebautem Transfusionsfilter (6) zurück zum Spender.

In Fig. 6 wird eine stark vereinfachte Vorrichtung gezeigt, die dazu dienen soll, die Effektivität des bevorzugten Systems beim Durchströmen des stabilisierten Blutes durch eine Plasmafiltereinheit zu messen, ohne direkte Verbindung mit dem Spender.

Man sieht dort einen mit stabilisiertem Blut gefüllten Blutbeutel (13), Einstichdorn (14), Rollklemme (15), Plasmafiltereinheit (4), Sammelstelle für Plasma (5) und einen ca. 150 cm tiefer als der Blutbeutel (13) angeordneten Leerbeutel (21) zum Sammeln des durch die Plasmafiltereinheit (4) geflossenen Blutes.

Nachstende Beispiele dienen der weiteren Erläuterung der Erfindung.

Beispiel 1

Ein System bestehend aus:

Kanüle (Plasmapheresekanüle Fa. Biotest)

Tropfkammer mit Transfusionsfilter (TNSB-Gerät Fa.Biotest)

Hollow fiber Modul zur Plasmaabtrennung - (Plasmapur der Fa. Organon Technika)

Blutbeutel zum Sammeln des Blutes (Leerbeutel 500 ml Fa. Biotest)

Plasmabeutel zum Sammeln des Plasma - (Leerbeutel 500 ml Fa. Biotest)

Beutel mit Blutstabilisator (Na-Zitrat pH = 7. Fa. Biotest) wurde gemäß Fig. 3 mit PVC-Schläuchen verbunden.

Die Dosierung der Stabilisatorlösung erfolgte mit einem Blutentnahmegerät (BEG 404) der Fa. Doltron.

Der Blutbeutel hing tiefer als der Plasmabeutel. Ein Blutspender spendete 500 ml Blut direkt durch die Trenneinheit in den Blutsammelbeutel, ohne daß das System mit isotoner NaCl-Lösung vorgefüllt war. Das System füllte sich zu Beginn nur sehr langsam mit Blut, da die Schläuche nicht mit Flüssigkeit gefüllt waren, so daß das hydrostatische Druckgefälle noch nicht den Blutfluß unterstützen konnte.

Sobald das Blut die Trenneinheit gefullt hatte, begann Plasma durch die Membrane zu treten und sammelte sich im Plasmabeutel. Der Blutfluß wurde zeitweilig durch Verlegen der Kanüle unterbrochen. Das Plasma strömte aus dem Plasmabeutel über die Trenneinheit in den Blutbeutel. Die Plasmaleitung war dann mit der Luft des Plasmabeutels gefüllt. Nach Korrektur der Lage der Kanüle in der Vene konnte der Blutfluß zwar wieder hergestellt werden, es trat jedoch keine Plasmafiltration mehr auf, da in der Plasmaleitung keine Flüssigkeitssäule mehr vorhanden war.

Beispiel 2

Es wurde das Beispiel 1 wiederholt, jedoch wurde das System mit isotoner NaCl-Lösung vorgefüllt und der Plasmasammelbeutel tiefer als der Blutsammelbeutel angebracht. Das Füllen des Systems mit isotoner NaCl-Lösung gestaltete sich - schwierig, da keine entsprechenden Anschlüsse hierfur vorgesehen waren. Es mußten Verbindungen geöffnet werden, um die Vorfüllungs-Lösung anschließen zu können und nach dem Fullen wieder umgesteckt werden.

In 8 Minuten wurden 500 ml Blut gespendet und dabei 160 ml Plasma gesammelt. Der Rückfluß des Blutes bei geänderter Schwerkraftlage (Fig. 4) in einen anstelle der Venenkanüle angeschlossenen Leerbeutel dauerte 7 Minuten, und es wurden weitere 80 ml Plasma gesammelt. In einem Zyklus konnten somit aus 500 ml Blut 240 ml Plasma gewonnen werden.

Beispiele 3 und 4

In das Schlauchsystem der Fig. 3 bzw. 4 wurde ein Anschluß für die Vorfüllungs-Lösung gemäß Fig. 1 bzw. 2 eingebaut. Die Komponenten entsprachen den Beispielen 1 bzw. 2.

Das System wurde mit isotoner NaCl gefüllt. Bei dieser Anordnung konnte durch Drücken auf die Tropfkammer die Tropfkammer selbst, die Plasmafiltereinheit und der Schlauch zwischen der Plasmafiltereinheit und dem Plasmasammelbeutel

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gefüllt werden, ohne das System an einer Stelle öffnen zu mussen. Die restliche Luft, die sich im Schlauch zwischen der Blutentnahmekanüle und der Tropfkammer befand, sammelte sich bei der Blutspende in der Tropfkammer. Die Beispiele wurden analog des Beispiels 2 durchgeführt.

	Beispiel 3	Beispiel 4
Spendezeit für 500 ml Blut	9 Min.	11 Min.
gesammeltes Plasma	140 ml	125 ml
Zeit für den Rückfluß des Blutes in einen Leerbeutel	8 Min.	8 Min.
zusätzlich gesammeltes Plasma	80 ml	75 ml
gesamte Plasmamenge	220 ml	200 ml

Aus den Beispielen 1 und 2 ist ersichtlich, daß es zwingend notwendig ist, das System mit einer Vorfüllungs-Lösung zu beschicken und daß auch bei der Blutspende der Plasmasammelbeutel tiefer angebracht sein muß als der Blutsammelbeutel.

Um eine einfachere Handhabung zu ermöglichen, wurde das Schlauchsystem für die Beispiele 3 und 4 modifiziert.

Diese Versuche dienen gleichzeitig der Feststellung, ob bei der Zugabe der Vorfullungs-Lösung gemäß der Erfindung an einer separaten Anschlußstelle sich das System leichter handhaben läßt.

Wie aus diesen Beispielen ersichtlich ist, arbeitete unter Verwendung einer separat eingefüllten Vorfüllungs-Lösung und damit bei einfacherer Handhabung des Vorfüllvorganges sowie bei Anbringung des Plasmasammelbeutels tiefer als der Blutsammelbeutel dieses System einwandfrei.

Beispiel 5

Ein System bestehend aus:

Hollow fiber Modul zur Plasmatrennung (Plasmapur der Fa. Organon Technika)

Plasmabeutel zum Sammeln des Plasma - (Leerbeutel 500 ml Fa. Biotest)

wurde gemäß Fig. 6 installiert. Das System wurde mit isotoner NaCl-Lösung vorgefüllt. Ein mit stabilisiertem Blut gefüllter Beutel wurde über den Einstichdorn oberhalb der Plasmafiltereinheit angeschlossen und eine "Retransfusion" in einen Leerbeutel mit gleichzeitiger Plasmaabtrennung durchgeführt. Bei einem Höhenunterschied von 150 cm zwischen dem Blutbeutel und dem Leerbeutel wurden folgende Zeiten und Volumina gemessen:

	Versuch A	Versuch B
"Retransfusionszeit", Min.	12	10
Abgetrennte Plasmamenge,ml	145	132

Wird die Spendezeit für Blut berücksichtigt, so ergibt sich eine Effektivität wie folgt:

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Spendezeit für 500 ml Blut	5 Min.
Zeit für Retransfusion und Abtrennung des Plasmas	11 Min.
Handhabung des Gerätes	1 Min.
gesammeltes Plasma	140 ml

Dieser Zyklus kann z.B. 3 x wiederholt werden, so daß man in ca. 50 Minuten einschließlich Retransfusion 420 ml Plasma erhält.

Ansprüche

1. Verfahren zur Gewinnung von Blutplasma bei einer Blutentnahme vom lebenden Körper, bei dem man nach einer Stauung der entnahmefähigen Blutgefäße mit Hilfe einer Blutentnahmekanüle Blut entnimmt und unter Ausnutzung von äußerem Druck und Schwerkraft und gegebenenfalls unter Verwendung einer Vorfüllungs-Lösung sowie nach Zusatz einer Stabilisatorlösung mit Hilfe eines Schlauches durch eine tiefer als die Blutquelle liegende Plasmafiltereinheit leitet, in der man Plasma vom Blut trennt, das abgetrennte Plasma einer Sammelstelle für Plasma und das partiell deplasmatisierte Blut einer davon getrennten Sammelstelle für Blut zuführt und gegebenenfalls das partiell deplasmatisierte Blut zum lebenden Körper in geänderter Schwerkraftlage durch dieselbe Plasmafiltereinheit retransfundiert, **dadurch gekennzeichnet**, daß man im Falle der Verwendung einer Vorfüllungs-Lösung diese mit Hilfe eines separaten Anschlusses zugibt, das gespendete Blutvolumen mißt, die Stabilitsatorlösung mit Hilfe einer Pumpe entsprechend dem gemessenen gespendeten Blutfluss bzw. Blutvolumen zudosiert, das Blut durch eine zwischen Blutentnahmestelle und Plasmafiltereinheit, jedoch nach dem Anschluß für die Stabilisatorlösung liegende Tropfkammer mit eingebautem Transfusionsfilter führt und die Sammelstelle für Plasma während des ganzen Verfahrens tiefer als die Sammelstelle für Blut anordnet.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Messung des gespendeten Blutvolumens laufend erfolgt.

3. Verfahren nach einem der Ansprüche 1 oder 2, dadurch gekennzeichnet, daß die Messung des gespendeten Blutvolumens an der Schlauchaußenseite mit Hilfe eines Ultraschalldetektors erfolgt.

4. Verfahren zur Gewinnung von Blutplasma bei einer Blutentnahme vom lebenden Körper, bei dem man das System mit einer Vorfüllungs-Lösung vorfüllt, nach einer Stauung der entnahmefähigen Blutgefäße mit Hilfe einer Blutentnahmekanüle Blut entnimmt, mit Stabilisatorlösung vermischt und unter Ausnutzung von äußerem Druck und Schwerkraft mit Hilfe mindestens eines Schlauches durch eine tiefer als die Blutquelle liegende Plasmafiltereinheit leitet, in der man Plasma vom Blut trennt, das abgetrennte Plasma einer Sammelstelle für Plasma zuführt und das partiell deplasmatisierte Blut zum lebenden Körper retransfundiert, dadurch gekennzeichnet, daß eine bestimmte Menge Blut in mindestens einen Beutel, der eine auf die Blutmenge abgestimmte Menge Stabilisatorlösung enthält, gespendet wird, der Beutel mit dem stabilisierten Blut vom Beutelsystem abgetrennt und an das obere Ende eines Transfusiionsgerätes angeschlossen wird, das mit seinem unteren Ende mit dem Beutelsystem und der Spenderkanüle verbunden ist und das die Plasmafiltereinheit und die Sammelstelle für Plasma sowie eine Tropfkammer mit Transfusionsfilter enthält, das Blut über die Plasmafiltereinheit und die Tropfkammer dem Spender retransfundiert wird und während der Retransfusion das Plasma gesammelt wird.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß die Vorfüllungs-Lösung mit Hilfe eines Einstichdorns am oberen Ende des Transfusionsgerätes dem System zugeführt wird.

6. Verfahren nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß man die Spende und die Retransfusion mehrere Male durchführt.

7. Vorrichtung zur Durchführung des Verfahrens nach einem der Ansprüche 1 bis 3, enthaltend eine Plasmafiltereinheit (4) zwischen einer Blutentnahmekanüle (1) und einer Sammelstelle für Blutplasma (5) sowie einer davon getrennten Sammelstelle für das partiell deplasmatisierte Blut (3) und einen Anschluß (11) für Stabilisatorlösung, dadurch gekennzeichnet, daß außerdem zwischen Injektionskanüle (1) und Plasmafiltereinheit (4) eine Tropfkammer mit eingebautem Transfusionsfilter (6), eine Dosierpumpe (8) zur Dosierung von Stabilisatorlösung (7), die mit einer Meßvorrichtung (9) fur das gespendete Blutvolumen gekoppelt ist, und ein Anschluß (2) an Vorfüllungs-Lösung (10) angeordnet sind, wobei Anschluß (11) mit Dosier-

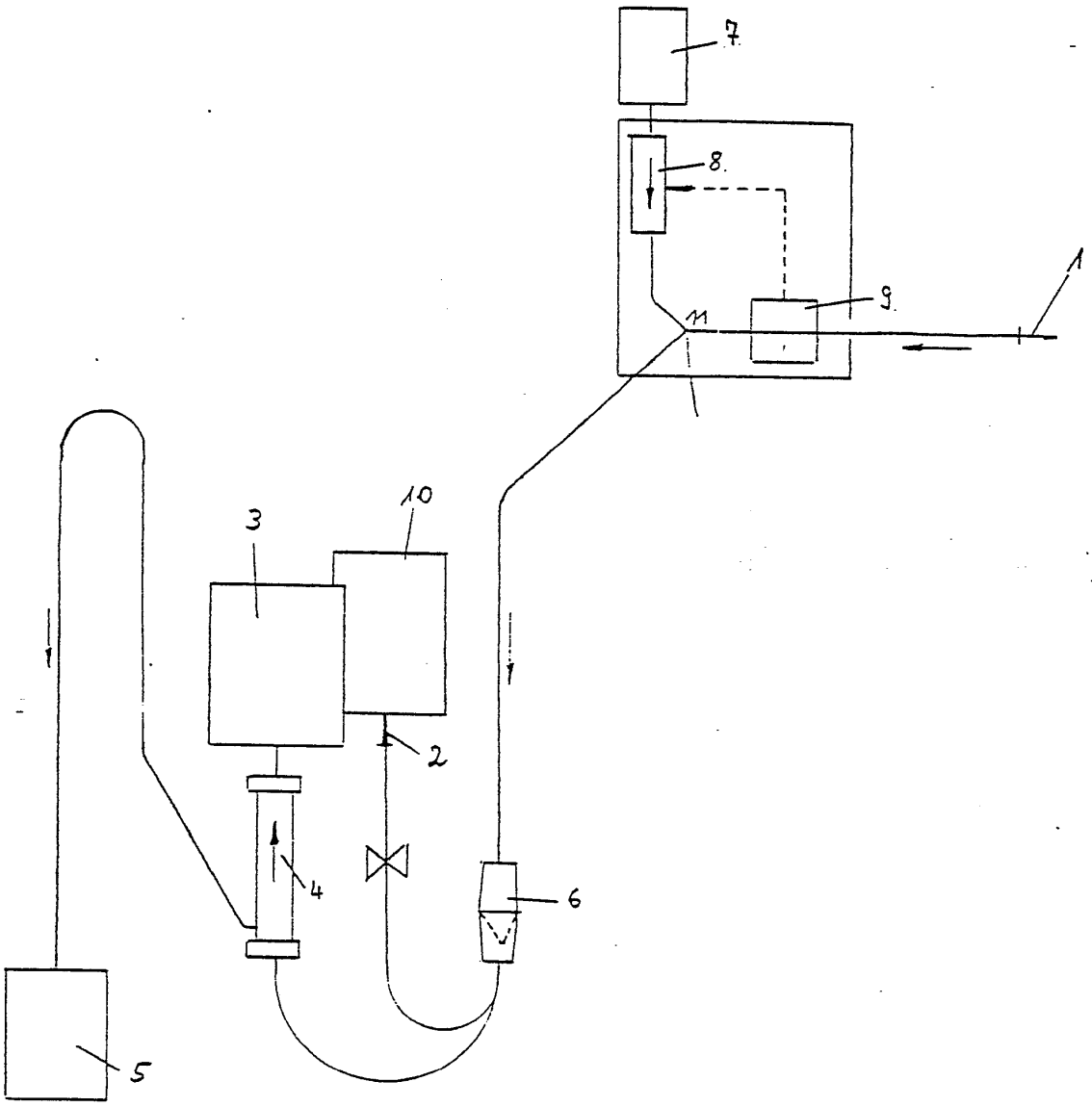
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pumpe (8) und Stabilisatorlösung (7) sich vor der Tropfkammer mit eingebautem Transfusionsfilter - (6), bezogen auf die Richtung des Blutflusses bei der Spende, befinden.

8. Vorrichtung zur Durchführung des Verfahrens nach einem der Ansprüche 4 bis 6, enthaltend eine Blutentnahmekanüle (1), eine Plasmafiltereinheit (4) und eine Sammelstelle für Plasma (5), dadurch gekennzeichnet, daß sich die Blutentnahmekanule am Ende eines Beutelsystems (12) befindet, das mindestens einen mit Stabilisatorlösung zu füllenden Blutbeutel (13) enthält, und die Plasmafiltereinheit (4) sowie die Sammelstelle für Plasma - (5) sich innerhalb eines Transfusionsgerätes (20) befinden, das am oberen Ende einen oder mehrere Einstichdorne (14), im Anschluß an die Plasmafiltereinheit (4) in Richtung des Retransfundierungsflusses eine Tropfkammer mit eingebautem Transfusionsfilter (6) und am unteren Ende ein Verbindungssystem (18) zum Anschluß an das Beutelsystem (12) aufweist.

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Fig. 1



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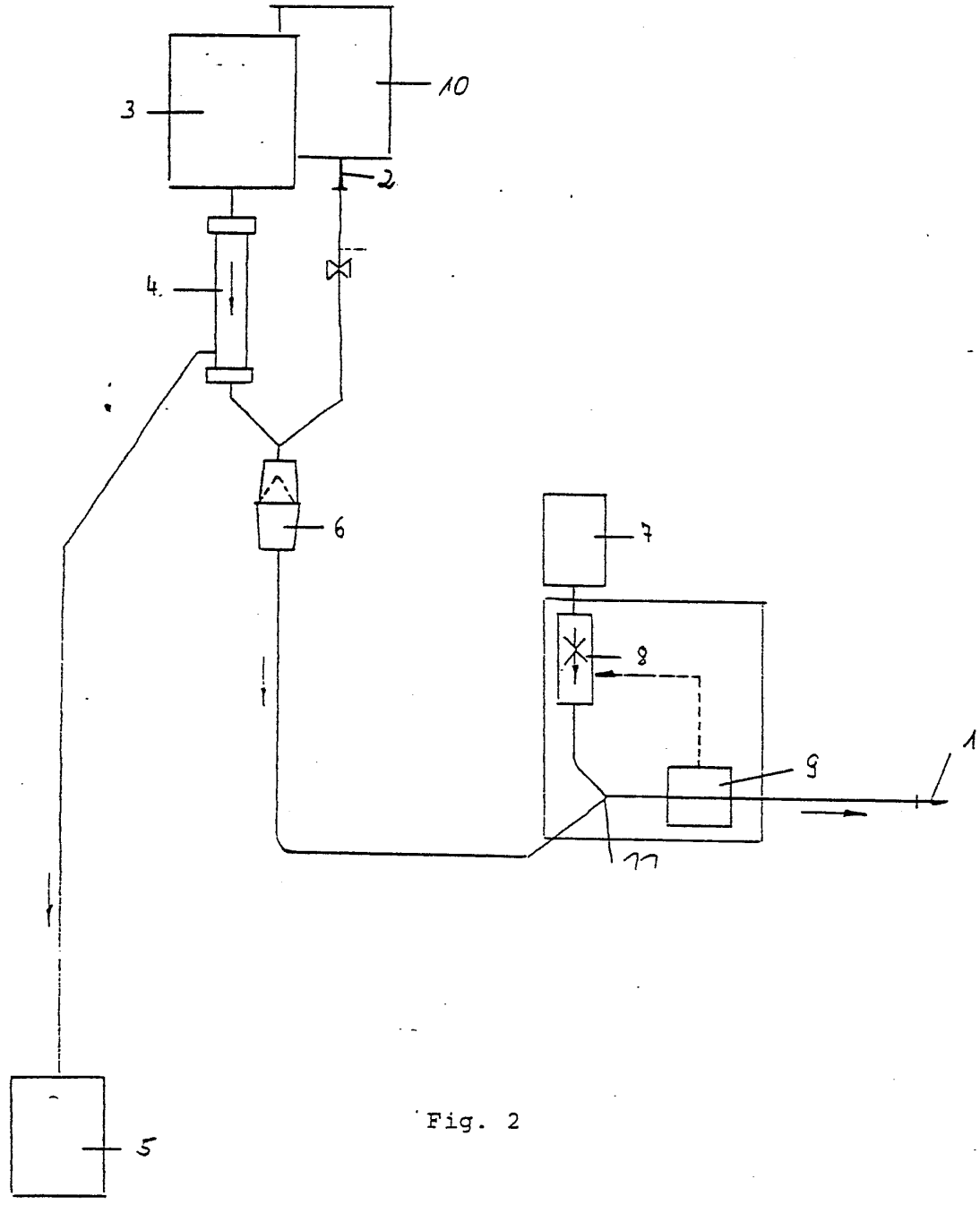
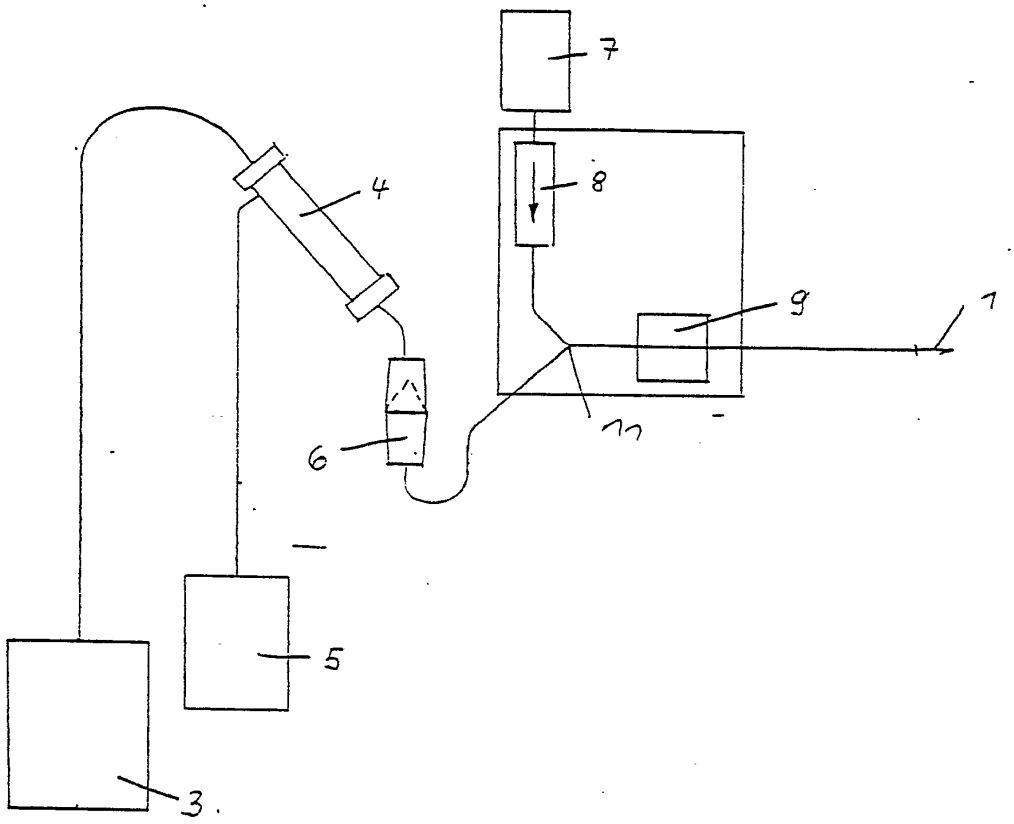


Fig. 2

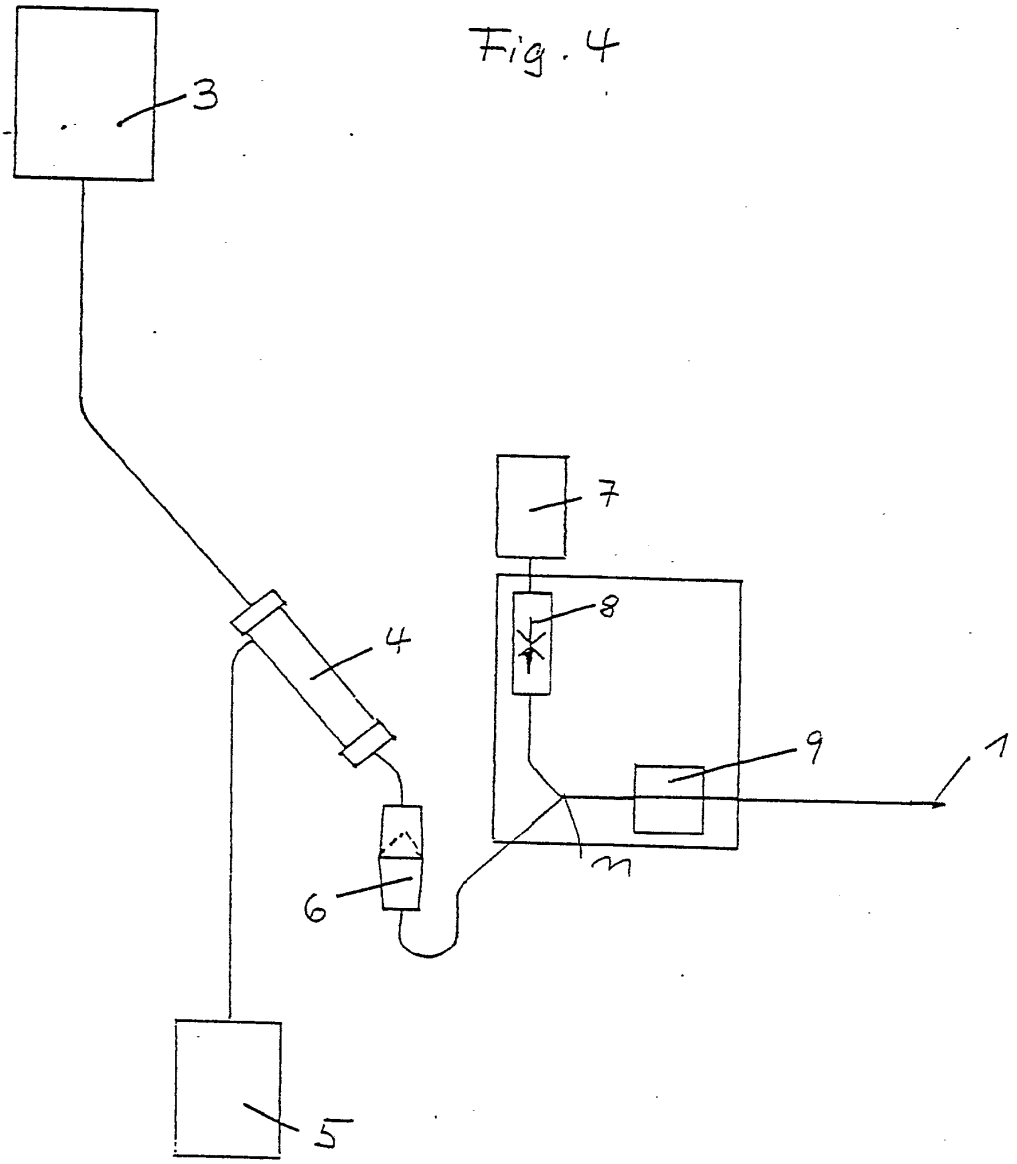
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Fig. 3



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Fig. 4



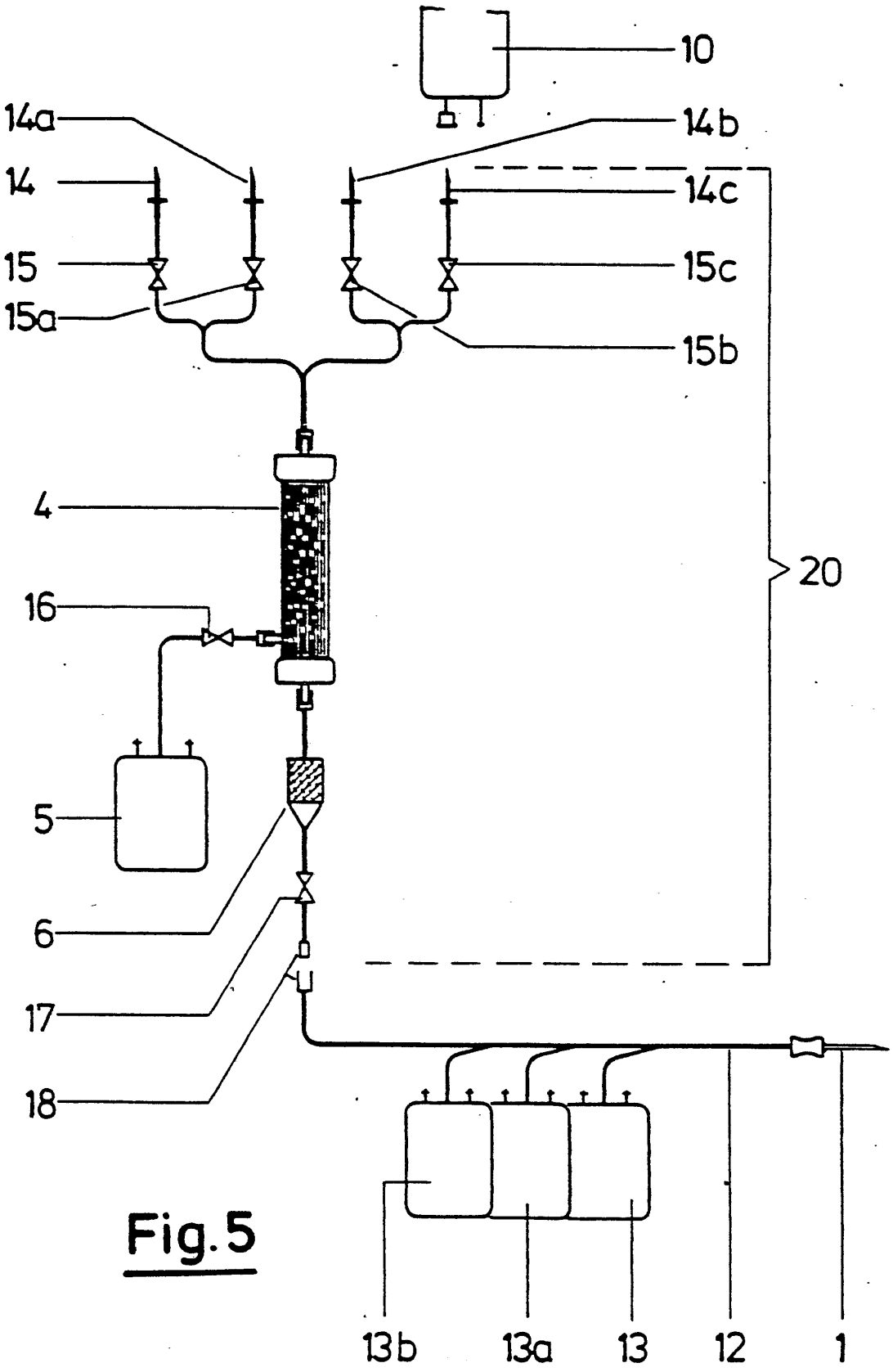
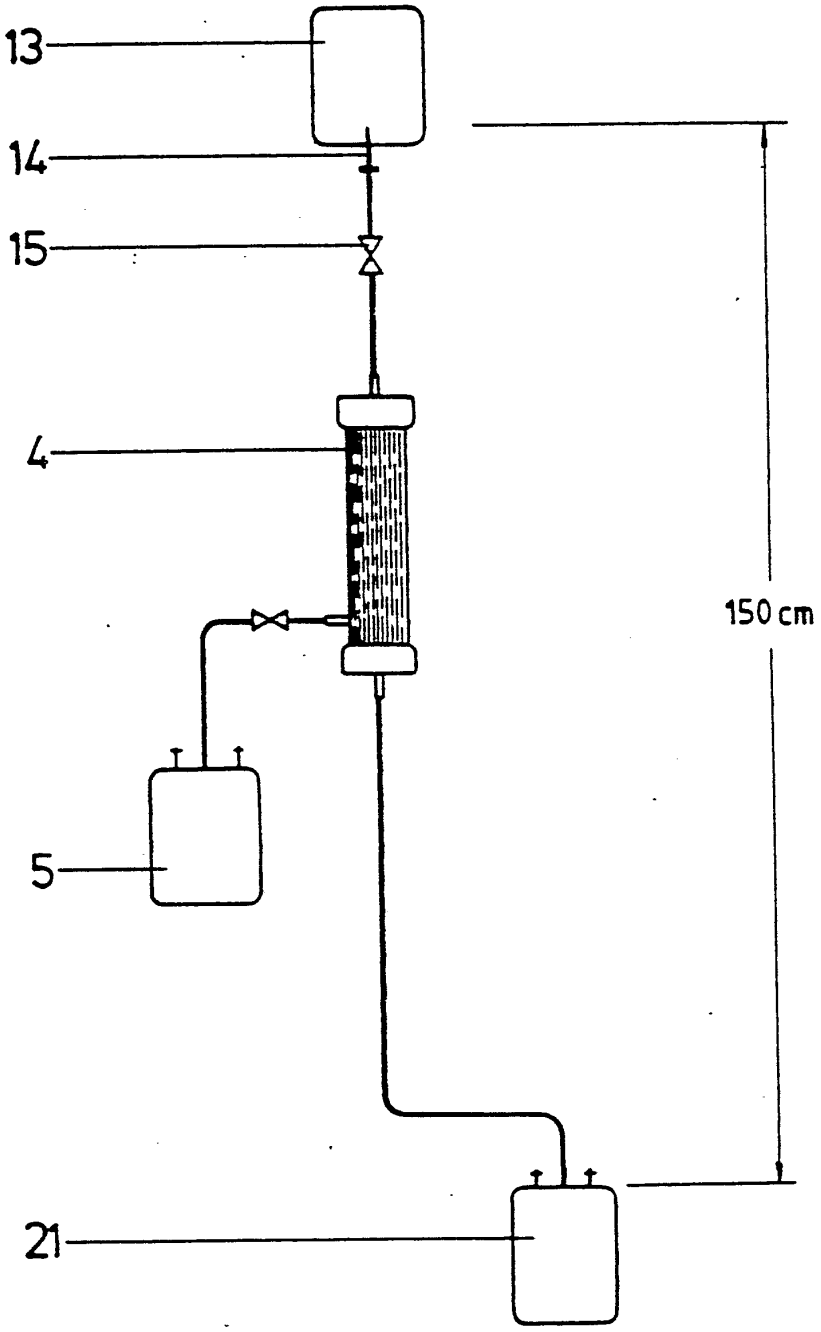


Fig.5

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Fig. 6



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Europäisches Patentamt

EUROPÄISCHER TEILRECHERCHENBERICHT,

der nach Regel 45 des Europäischen Patentübereinkommens für das weitere Verfahren als europäischer Recherchenbericht gilt

Nummer der Anmeldung: EP 86104316.4

EINSCHLÄGIGE DOKUMENTE

Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl.4)
A	US - A - 4 498 983 (A.C.JILSTAD et al.) * Gesamt; insbesondere Fig. 1,2, 9a,b; Spalte 4, Zeile 54 - Spalte 5, Zeile 63; Spalte 6, Zeilen 18-49; Spalte 13, Zeile 21 - Spalte 14, Zeile 56 * --	7,8	A 61 M 1/34 A 61 M 1/36
A	EP - A1 - 0 085 016 (RHONE POULENC S.A.) * Gesamt; insbesondere Fig. 2; Seite 7, Zeile 31 - Seite 12, Zeile 3 * --	7,8	
D,A	DE - A1 - 3 302 383 (M. LYSAGHT et al.) * Gesamt * --	7,8	

RECHERCHIERTE SACHGEBIETE (Int. Cl.4)

A 61 M 1/00
A 61 M 5/00

UNVOLLSTÄNDIGE RECHERCHE

Nach Auffassung der Recherchenabteilung entspricht die vorliegende europäische Patentanmeldung den Vorschriften des Europäischen Patentübereinkommens so wenig, daß es nicht möglich ist, auf der Grundlage einiger Patentansprüche sinnvolle Ermittlungen über den Stand der Technik durchzuführen.

Vollständig recherchierte Patentansprüche: 7,8
Unvollständig recherchierte Patentansprüche: -
Nicht recherchierte Patentansprüche: 1-6
Grund für die Beschränkung der Recherche:

(in Anwendung des Art. 52 (4))

Recherchenort	Abschlußdatum der Recherche	Prüfer
WIEN	17-09-1986	LUDWIG

KATEGORIE DER GENANNTEN DOKUMENTEN

X : von besonderer Bedeutung allein betrachtet
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EP 86104316.4

EINSCHLÄGIGE DOKUMENTE			KLASSIFIKATION DER ANMELDUNG (Int. Cl. 4)
Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	betrifft Anspruch	
A	GB - A - 2 112 293 (COBE LAB. INC.) * Gesamt; insbesondere Fig. 1; Seite 2, Zeile 94 - Seite 3, Zeile 8 * --	7,8	
A	EP - A1 - 0 096 973 (KURARAY CO.) * Gesamt; insbesondere Fig. 4; Seite 11, Zeile 18 - Seite 12, Zeile 15 * --	7,8	
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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

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(21) Application number: **93110259.4**

(22) Date of filing: **28.06.1993**

(54) **Apparatus and method for transferring separated components in liquid**

Gerät und Methode zur Transferierung einer in einer Flüssigkeit abgetrennten Komponente

Appareil et méthode pour transférer un composant séparé d'un liquide

(84) Designated Contracting States:
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(30) Priority: **30.06.1992 JP 19789892**

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US-A- 4 447 220
US-A- 4 539 005
US-A- 4 663 032

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Description

[0001] This invention relates generally to apparatus and method for transferring a separated component in a liquid, and more particularly to apparatus and method for transferring or taking out a centrifugally separated component in a liquid such as blood contained in a blood bag.

[0002] In carrying out blood transfusion, recently, blood collected from a donor is centrifuged with a centrifugal separator for separating the collected blood into blood components, and then only the component required for a patient is transfused, in order to utilize the blood effectively and to reduce a burden on the patient who receives a blood transfusion. Owing to this component transfusion, it has become possible to utilize blood more effectively, as compared with the whole blood transfusion so far adopted.

[0003] In the above-mentioned component transfusion, connected bags (referred to as "multiple bag system") composed of a blood collecting bag and one or more bags are used.

[0004] As one of the multiple bag systems, there is known a triple bag system, which comprises a blood collecting bag, a platelet concentrate preserving bag (hereinafter, referred to as "PC bag") and a plasma preserving bag (hereinafter, referred to as "plasma bag") which are connected to each other through tubes. The blood collected into the blood collecting bag is centrifuged at least once to separate the blood into three components of erythrocyte concentrate, platelet concentrate, and platelet-poor plasma (hereinafter, referred to as "PRP method"), and the separated components are preserved in the blood bag, the PC bag and the plasma bag, respectively.

[0005] In the multiple blood bag system as described above, the respective bag is formed by laminating flexible polyvinyl chloride sheets and further fusing the periphery thereof. The reasons why the flexible polyvinyl chloride is used is that this material has an appropriate gas penetrability, and further that this material is excellent in preservation of cells such as erythrocyte, platelet, etc., in heat-resistance in autoclave sterilization, and in flexibility endurable to centrifugal separation and suitable for shake preservation. Further, the material is also low in manufacturing cost.

[0006] The blood collected into a blood collecting bag is centrifuged by placing the blood collecting bag in a centrifugal cup formed of a hard material and formed into a cup-shaped container and mounting the centrifugal cup with the blood collecting bag to a centrifugal separator. Further, the separated components are collected in accordance with the following steps, that is, first the blood collecting bag is removed from the centrifugal cup; the blood collecting bag is then set to an automatic separating stand; and thereafter the blood collecting bag is pressed, so that the supernatant plasma layer is discharged. As the automatic separating stand, for example, one disclosed in U.S. Patent No. 4,976,851 can be used.

[0007] In the method as described above, however, after the centrifugal separation, the following operations are required, that is, the blood collecting bag is removed from the centrifugal cup, the removed bag is then transferred to the separating stand, and thereafter the bag is set to the separating stand. Therefore, there are various problems in that the blood collecting bag is shaken or vibrated during the above-mentioned operations and further the bag is likely to be deformed because of its flexibility. With this result, the interfaces between the respective two layers of the three separated components are likely to be disturbed during the operations, thus leading to the problem that yield (quantity of collection or purity) of each of the separated components is deteriorated. When the yield of each of the separated components is lowered as described above, the quality of blood products is also degraded, and therefore there exists such a case that the blood collecting bag must be centrifuged again as occasion demands.

[0008] In addition, since it takes a long time to take out the blood collecting bag from the centrifugal cup and further to set the bag to the separating stand. In particular, if these operations are carried out carefully so as not to disturb the interfaces between the respective separated components, a further long time is required.

[0009] US-A-4,447,220 discloses an apparatus for separating blood components which comprises a centrifuge cup having two chambers. In a first chamber there is placed an elastically deformable inset cup tightly enclosing a blood bag filled with blood fluid. A deformable pressure pad is disposed in said first chamber between the inset cup and the inner surface of the first chamber.

[0010] During centrifuging the pressure pad is inflated and the inset cup is thus compressed to transfer blood component into an empty bag disposed in the second chamber.

[0011] The object of the present invention is to provide apparatus and method which can transfer a centrifugally separated component in a liquid contained in a flexible bag in which the number of the necessary components and steps are reduced and with improved yield for each separated component.

[0012] A further object of the present invention is to provide apparatus and method which can collect the centrifugally separated component from the liquid with high yield, without removing out the flexible bag in which the liquid is contained from the centrifugal cup,

[0013] As claimed the apparatus of the invention for transferring a separated component in a liquid contained in a flexible bag in airtight condition comprises a deformable centrifugal container for removably accommodating the flexible bag therein and pressing means provided outside said centrifugal container for pressing the flexible bag accommodated in said centrifugal container to increase the inner pressure of said flexible bag while the bag is released from the airtight

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condition, so that a predetermined separated component can be discharged from the bag.

[0014] According to the invention, the centrifugal container includes a frame portion and a soft material part and the pressing means comprises a pair of opposing push members at least one of which is movable toward the other by a reciprocal motion driving mechanism. The push members are adapted for pressing the soft material part of said centrifugal container which is therefore deformed, so as to project in the inner direction of the centrifugal container, thus discharging the separated component of the liquid contained in the flexible bag.

[0015] Further, the present invention is also directed to a method of transferring a separated component in a liquid contained in a flexible bag under airtight condition; which comprises the steps of:

accommodating the flexible bag in which the liquid is contained under airtight condition into a centrifugal container which is removably attached to a centrifugal separator, said centrifugal container having a soft material part formed in at least one portion thereof;
centrifuging the flexible bag accommodated in the centrifugal container by the centrifugal separator to separate the liquid in the flexible bag into the components thereof;
removing said centrifugal container from the centrifugal separator together with the flexible bag contained therein and then fixing the centrifugal container to a fixing means, and
pressing the soft material part of the centrifugal container from the outside of said centrifugal container using a movable push member provided outside of the container for pushing said soft material part of said centrifugal container to increase inner pressure of the bag while releasing the airtight condition, thereby taking out a predetermined component in the liquid which has been separated by the centrifugation outside the flexible bag.

[0016] When the apparatus and method as described above are used to transfer separated blood components, the following steps are taken place.

[0017] A required amount of blood is collected into a flexible blood collecting bag. This bag is placed in the centrifugal container, and then the container in which the bag is accommodated is set to the centrifugal separator for centrifugal separation. The blood in the blood collecting bag is separted by the centrifugal separation into three layers, namely a plasma layer, a buffy coat layer, and an erythrocyte layer.

[0018] After completion of the centrifugal separation, the centrifugal container is removed from the centrifugal separator, and thereafter is fixed to a separating stand for instance. Then, the blood collecting bag accommodated in the centrifugal container is pressed by actuating at least one of the opposing push members. Since the inner pressure of the blood collecting bag increases, the upper plasma layer is discharged through a tube connected to the blood collecting bag, so that the plasma can be transferred to another bag or the like and collected therein.

[0019] In this case, since the plasma is transferred and collected, after centrifugal separation, without removing the blood collecting bag from the centrifugal container and further without setting the blood collecting bag to a separating stand, the time and labor required for the operation can be reduced. Further, the disturbance at the respective interfaces between two of the three separated component layers will not occur due to vibration or bag deformation which are likely to be caused when the blood collecting bag is removed, transferred or hanged. In addition, the yield of the collected plasma can be improved.

[0020] Further, in the present invention, since the upper plasma layer is raised and then discharged under the condition that the inner pressure of the blood collecting bag is kept increased and further the respective interfaces between the layers are kept stationary, it is possible to avoid that the other component in the lower layer below the plasma layer is mixed to the plasma, thereby enabling to increase the yield for the plasma. In addition, when the separated buffy coat layer is transferred and further collected, the yield therefore can be also improved in the same way as in the case of the plasma collection. In this regard, it should be noted that the liquid to be contained in the flexible bag is no limited to blood. Bone marrow fluid can be used instead of blood.

[0021] According to the invention, the push members are for pushing the soft material part of the centrifugal container in such a manner that the soft material part is deformed inwardly to project inside the container, and a reciprocal motion driving mechanism for driving the push member.

[0022] Further, in the apparatus and method according to the present invention, it is possible to use sucking means for sucking the separated component in the bag in addition to the pressing means. If the sucking means is provided in addition to the pressing means, it becomes possible to maintain high yield which is the same rate as that where the pressing means is used alone and shorten the time required for collecting the separated component.

[0023] Other objects, structures and advantages of the present invention will become apparent from the following descriptions of the preferred embodiments when taken in conjunction with the accompanying drawings.

Fig. 1 is a plan view showing an example of the connected bags to which the present invention is applied;
Fig. 2 is a side cross-sectional view showing an apparatus for transferring a centrifugally separated component in a liquid which is not according to the present invention but illustrating the general principles for such a transfer.

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Fig. 3 is a perspective view showing a cuff as pressing means of the apparatus of figure 2;
Fig. 4 is a perspective view showing an embodiment of the apparatus according to the present invention; and
Fig. 5 is a side cross-sectional view showing the example in which a sucking means which can be used in the present invention is additionally provided to the apparatus of figure 2.

[0024] An apparatus and a method for transferring a separated component in a liquid according to the present invention will be described in detail hereinbelow with reference to the attached drawings.

[0025] First, the typical multiple bag system used for the apparatus according to the present invention will be explained. Fig. 1 is a plan view showing an example of the multiple bag system. The multiple bag system shown in Fig. 1 is constituted as quadruple (four-connection) bags which are composed of a blood collecting bag, a PC bag, a plasma bag, and a sub-bag (buffy coat bag).

[0026] The blood collecting bag 1 shown on the right side in Fig. 1 is formed into a closed bag by laminating flexible sheets of a resin material such as soft polyvinyl chloride and further fusing a peripheral sealing portion 2 thereof in accordance with fusing method (e.g., thermal fusion, high frequency fusion, etc.) or bonding the portion 2. In the space defined by the two sheets and enclosed by the sealing portion 2, there is formed a blood component accommodating section 3 to which collected blood or erythrocyte concentrate obtained by centrifuging the blood is to be contained.

[0027] In the upper portion of the blood collecting bag 1, there is formed two opening portions 4 provided with a peeling tub, respectively. Further, a blood outlet 5 is formed between the two opening portions 4 so as to be connected to another bag. One end of a tube 14 is connected to this outlet 5 via a connecting member 15.

[0028] Further, a bifurcated connector 20 is connected to the other end of the tube 14. Another tube 21 is connected to this bifurcated connector 20. Further, another bifurcated connector 22 is connected to the other end of this tube 21.

[0029] Further, it is preferable to constitute the connecting member 15 so as to provide with a path closing member (not shown) inside thereof. The path closing member is adapted to be broken by bending the connecting member 15 to allow fluid communication in the connecting member 15. Accordingly, the closing member functions in such a way that fluid communication in the connecting member 15 is kept impossible before broken, but the fluid communication therein becomes allowed after breaking. As such a closing member, it is possible to use a Click Chip which is a product name of TERUMO Kabushiki Kaisha, for instance. In this invention, alternatively, it is possible not to provide the connecting member 15 as described above. In this case, it is preferable to close or open the tube 14 appropriately with the use of a clamp.

[0030] Further, one end of a flexible tube 6 communicating with the blood component accommodating section 3 is connected to the upper portion of the blood collecting bag 1. To the other end of this tube 6, a blood collecting needle 8 is attached via a hub 7. Further, there is provided a cap 9 which is attached to the hub 7 to cover the needle 8.

[0031] The plasma bag 10 shown at the second position from the left side in Fig. 1 is also formed into a closed bag by laminating flexible sheets of a resin material such as soft polyvinyl chloride and further bonding a peripheral sealing portion 11 thereof in accordance with fusing method (e.g., thermal fusion, high frequency fusion, etc.). In the space defined by the sheets and enclosed by the sealing portion 11, a plasma accommodating section 12 is formed to accommodate plasma (platelet-poor plasma, in particular) separated from the blood in the blood collecting bag 1.

[0032] In the upper portion of the plasma bag 10, there are formed two opening portions 13 provided with a peeling tub, respectively.

[0033] Further, one end of a flexible tube 23 communicating with the plasma accommodating section 12 is connected to the side of the opening portion 13 of the upper portion of the bag 10. The other end of this tube 23 is connected to thebifurcated end of the bifurcated connector 21. Therefore, the blood component accommodating portion 3 of the blood collecting bag 1 communicates with the plasma accommodating portion 12 of the plasma bag 10 through the tubes 14, 21 and 23 and the bifurcated connectors 20 and 22.

[0034] The PC bag 16 shown on the left side in Fig. 1 is also formed into a closed bag by laminating flexible sheets of resins such as soft polyvinyl chloride and further bonding a peripheral sealing portion 17 thereof in accordance with fusing method (e.g., thermal fusion, high frequency fusion, etc.). In the space defined by the sheets and enclosed by the sealing portion 17, a platelet accommodating section 18 is formed to accommodate platelet (platelet concentrate plasma) obtained by centrifuging the blood.

[0035] In the upper portion of the blood PC bag 16, there are formed two opening portions 19 which are provided with a peeling tub, respectively. Further, an outlet 25 is formed on the side of the opening portion 19 of the upper portion of the bag 16. This outlet 25 is connected to one end of the flexible tube 24 through another connecting member 15 in the same way as the blood collecting bag described above. The other end of this tube 24 is connected to the bifurcated end of the bifurcated connector 22. Therefore, the platelet accommodating section 18 of the PC bag 16 communicates with the blood component accommodating section 3 of the blood collecting bag 1 and the plasma accommodating section 12 of the plasma bag 10, respectively, through the tubes 14, 21, 23 and 24 and the bifurcated connectors 20 and 22.

[0036] Between the blood collecting bag 1 and the plasma bag 10, there is provided a buffy coat bag 27 which is

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used to accommodate buffy coat temporarily. The buffy coat bag 27 is also formed into a closed bag by laminating flexible sheets of a resin material such as soft polyvinyl chloride and further bonding a peripheral sealing portion 28 thereof in accordance with fusing method (e.g., thermal fusion, high frequency fusion, etc.). In the space defined by the sheets and enclosed by the sealing portion 28, a buffy coat accommodating section 29 is formed to accommodate buffy coat separated from the blood in the blood collecting bag 1.

[0037] On the upper portion of the buffy coat bag 27, one end of another flexible tube 26 is connected so as to communicate with the buffy coat accommodating section 29 of the buffy coat bag 27. The other end of this tube 26 is connected to the bifurcated end of the bifurcated connector 20. Therefore, the buffy coat accommodating section 29 of the buffy coat bag 27 communicates with the blood component accommodating section 3 of the blood collecting bag 1, the plasma accommodating section 12 of the plasma bag 10, and the platelet accommodating section 18 of the PC bag 16, respectively, through the tubes 14, 21, 23, 24 and 26 and the bifurcated connectors 20 and 22.

[0038] In use of the multiple bag system as described above, the blood collecting needle 8 is first inserted into a vein of a donor, and the blood is introduced into the blood component accommodating section 3 of the blood collecting bag 1 through the tube 6 and then stored therein. When the blood within the blood component accommodating section 3 reaches a predetermined quantity, the needle 8 is pulled out from the vein of the donor. Thereafter, the midway portion of the tube 6 is fused for instance to seal it, and the tube 6 on the side of the blood collecting needle 8 is cut off for removal. Under these conditions, the blood is accommodated within the blood collecting bag 1 in airtight condition.

[0039] In the above description, explanation is made with reference to the quadruple bag system. However, the multiple bag system to which the present invention is applied is not limited to only the quadruple bag system. That is, this invention can be applied to various bags, such as a single bag only having a blood collecting bag; a double bag system composed of a blood collecting bag and a plasma bag; a triple bag system composed of a blood collecting bag, a PC bag and a plasma bag; and a quadruple bag for use in the different purpose from that of the afore-mentioned quadruple bag. Further, this invention can also be applied to a double bag system, a triple bag system and a quadruple bag system connected to another bag for collecting cryo-precipitate (AHF), for instance.

[0040] Furthermore, this invention can also be applied to a multiple bag system having the blood collecting bag 1 in which a first discharge port and a second discharge port which are communicated with the upper portion and the bottom portion of the blood collecting bag, respectively, are formed in such a manner that the plasma in the upper layer is discharged from the first discharge port, the erythrocyte in the lower layer is discharged from the second port, and the buffy coat in the middle layer remains in the bag. As one of the examples of such a multiple bag system, one disclosed in US-A-5,102,407 can be used.

[0041] Moreover, a multiple bag system as disclosed in EP-A-484,751 or Japanese Laid-open Patent Publication No. 4-350556 can be used in particular with reference to the embodiment shown in Figs. 5 and 6 of this application which are described later.

[0042] Fig. 2 is a side cross-sectional view showing a separated component transferring apparatus which is not according to the present invention but useful for describing transfer of reparated component. As shown in the drawing, the apparatus 30 is provided with a centrifugal container (inner cup) 40 in which connected bags of the multiple bag system is to be placed. This centrifugal container 40 is formed into a cylindrical configuration having a bottom and adapted to be removably attached to a centrifugal separator. The bottom 41 of this cup 40 is formed into a semispherical shape.

[0043] The centrifugal container 40 is formed of a material having a rigidity of such an extent as not to be deformed easily even when it is centrifuged or even when the blood collecting bag 1 accommodated in the container 40 is pressed by the pushing means (described later). Preferably, the material is formed of an acrylic resin such as hard polyvinyl chloride, polyethylene, polypropylene, polycarbonate, polymethylmethacrylate (PMMA), or the like; a metal such as stainless steel or aluminum; various glasses or ceramics; or appropriate combinations of any of these materials.

[0044] In the centrifugal container 40 as described above, the connected bags having the blood collecting bag in which blood is stored are placed, and then centrifuged. The connected bags are put into the centrifugal container 40 by stacking the respective bags 1, 10, 16 and 27 and by directing the upper portion of the respective bag, that is the side on which the opening portion is formed toward the upper opening portion side of the centrifugal container 40.

[0045] When the connected bags are placed in the centrifugal container 40, it is not necessary to place all the bags in the centrifugal container 40. That is, it is possible to separate'the blood collecting bag 1 from the remaining connected bags and then to place only the blood collecting bag 1 in the centrifugal container 40. For this reason, hereinafter, description is made based on a case where only the blood collecting bag 1 is placed in the centrifugal container 40.

[0046] Further, the method of removably setting the centrifugal container 40 to the centrifugal separator is not particularly limited. For example, the centrifugal container 40 may be constructed such that the container 40 is supported at opposite two portions of the upper annular edge thereof (not shown) so as to be rotatable with respect to the axis extending through the two supported portions.

[0047] The separated component transferring apparatus 30 is provided with a pressing means for pressing the blood collecting bag 1 in which blood is contained. In the apparatus shown in Fig. 2, the pressing means is composed of an

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expansible and contractible cuff 50 to be interposed between the inner surface of the centrifugal container 40 and the outer surface of the blood collecting bag 1, and a fluid supplying means 51 for supplying a fluid such as air into the cuff 50 for expansion thereof.

[0048] The cuff 50 is formed into an annular tubular shape so as to be able to push or press the outer circumferential surface of the blood collecting bag 1 roughly uniformly. As shown in Fig. 3, the cuff 50 is constituted so as to provide a central space under the contracted condition thereof into which the blood collecting bag 1 containing the blood can be passed therethrough.

[0049] The cuff 50 is formed of a sheet material made of various rubbers (e.g., silicone rubber. etc.), various resins (e.g., soft polyvinyl chloride, polyethylene, polypropylene, etc.), cloth, and any appropriate combinations of these materials.

[0050] The dimensions of the cuff 50 are not limited to specific values. However, it is preferable to determine the width W of the cuff 50 within a range between 50 mm and 100 mm, in particular between 70 mm and 90 mm.

[0051] Further, the cuff 50 may be fixed to either the inner surface of the centrifugal container 40 or the outer surface of the blood collecting bag 1. Alternatively, the cuff 50 is simply interposed between the centrifugal container 40 and the blood collecting bag 1. Further, the shape of the cuff 50 is not limited only to the annular shape as shown. For instance, it is possible to arrange a pair of flat bags on the front and rear sides of the blood collecting bag 1, respectively.

[0052] The fluid supplying means 51 is composed of an air feeding tube 52 communicating with the inner side of the cuff 50; an air supply source 55 such as air cylinder, air compressor, compressed gas cylinder, etc.; another air feeding tube 53 connected to the air supply source 55; a pair of male and female connectors 54 connected between the two air feeding tubes 52 and 53; and open and close valve 56 disposed midway of the air feeding tube 53 to control the air supplied into the cuff 50. In this case, the open and close valve 56 may be constructed into the type in which the air pressure supplied to the cuff 50 can be adjusted by adjusting the opening rate thereof.

[0053] Further, the fluid for expanding the cuff 50 is not limited to only air, and other gas or water can be used.

[0054] The operation of the separated component transferring apparatus as described above will be described hereinbelow.

[0055] In order to place the blood collecting bag 1 in the bag accommodating container 40 or centrifuge the blood collecting bag 1, first, the connector 54 is removed from the cuff 50 to contract the cuff 50.

[0056] Next, The blood collecting bag 1 in which blood is contained is placed in the centrifugal container 40, and the centrifugal container 40 accommodating the blood collecting bag 1 is then set to the centrifugal separator (not shown) for centrifugal separation. Therefore, the blood in the blood collecting bag 1 is separated into three layers i.e. a plasma layer, a buffy coat layer, and an erythrocyte layer in this order from the above.

[0057] After the centrifugal separation, under the condition that the blood collecting bag 1 is kept placed in the centrifugal container 40, the centrifugal container 40 is removed from the centrifugal separator, and further fixed to a fixing means (not shown) such as a stand or a mounting base. In this state, since the blood collecting bag 1 is not removed from the centrifugal container 40, the interfaces between two of the respective separated components are not disturbed. In this case, it should be noted that in the case where all the connected bags in the double, triple, or quadruple bag system are placed in the centrifugal container 40 for centrifugal separation, the bag or bags other than the blood collecting bag 1 are removed from the centrifugal container 40.

[0058] Successively, the plasma in the upper layer is collected from the separated components. In this case, the connecting member 15 of the upper portion of the blood collecting bag 1 is broken to allow the fluid communication and further the tube 26 is closed by a clamp or an electrically actuated solenoid pinch valve or the like. On the other hand, the connector 54 is connected. The air supply source 55 is actuated and the valve 56 is opened, to feed air into the cuff 50 through the air feeding tubes 52 and 53, so that the cuff 50 is expanded. In accordance with the expansion of the cuff 50, the blood collecting bag 1 is pressed and thereby the inner pressure thereof increases. With this result, the upper plasma layer is discharged through the outlet 5, and further fed into the plasma bag 10 through the tubes 14, 21 and 23, respectively. When the plasma is being discharged, the blood collection bag 1 is kept under the expanded condition, as already explained. Therefore, the lower components will not mixed with the plasma now being discharged and fed, thus improving the yield for the collection of the plasma.

[0059] In this case, the discharging speed of the plasma from the blood collecting bag 1 is preferably set in the rate under which no eddy that is likely to disturb the interface between the respective separated components is caused in the blood-collecting bag 1 and the time required for the collection of the plasma can be shortened as much as possible. The control of the discharging speed of the plasma can be conducted, for example, by controlling the pressure of the actuating fluid to be supplied to the cuff 50.

[0060] It is possible to use a sucking means (not shown) together with the pressing means for pressing the blood collecting bag 1. In this case, since the quantity of plasma discharged per unit time can be increased while keeping the high yield, it is possible to shorten the time required to collect the separated components.

[0061] Fig. 5 is a cross-sectional view showing one example of the sucking means. The sucking means 90 shown in the drawing comprises a vacuum chamber 91, a vacuum pump 92, a pipe 93 connected between the vacuum chamber

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91 and the vacuum pump 92. On the middle portion of the pipe 93, there is formed a branch pipe 94, on which a valve 95 is provided.

[0062] The plasma bag 10 which is a container for collecting the separated plasma is adapted to be placed in the vacuum chamber 91. The tube 23 connected to the plasma bag 10 passes through a wall portion of the vacuum chamber 91 by means of a seal member. With this structure, the vacuum chamber 91 can be kept air-tight.

[0063] With valve 95 closed, when the vacuum pump 92 is actuated, the air in the vacuum chamber 91 is discharged through the pipe 93, and therefore the inner pressure of the vacuum chamber 91, that is, the atmosphere around the plasma bag 10 is reduced to be a negative pressure. Due to this reduced pressure, the plasma is sucked into the plasma bag 10. In this case, it is preferable to maintain the inner pressure of the vacuum chamber 91 to a constant value or within a predetermined value during the sucking operation. The adjustment of the inner pressure of the vacuum chamber 91 is made for example by on-off operation of the vacuum pump 92, open-close operation of the valve 95, or adjustment of the opening rate of the valve 95. The reduced inner pressure of the vacuum chamber 91 during the sucking operation is for example set to the rate between -0.133 bar (-100 mmHg) and -0.399 bar (-300 mmHg) (here, 0 mmHg is equal to the atmospheric pressure).

[0064] As an alternative for the sucking means, it is possible to provide a roller pump provided on the midway of the tube 14 connected to the blood collecting bag 1. The roller pump is adapted to squeeze the tube 14 so as to transfer the liquid within the tube to the side of the plasma bag 10.

[0065] In these cases, it is preferable that the quantity of air to be sucked is set to such an extent that a rising in the inner pressure of the blood collecting bag 1 by the pressing means is not reduced markedly.

[0066] Further, after almost all the quantity of the plasma is discharged from the blood collecting bag 1, the tube 21 is closed by a clamp or a solenoid pinch valve, while the tube 26 is opened. When the blood collecting bag 1 is further pressed under this condition in the same way as above, the intermediate buffy coat layer can be discharged. The buffy coat layer is fed into the buffy coat bag 27 through the tubes 14 and 26, respectively.

[0067] Upon discharging the buffy coat layer from the blood collecting bag 1, it is also possible to additionally provide such a sucking means as described above. In this case, the buffy coat bag 27 which is a container for collecting the buffy coat layer is placed inside the vacuum chamber 91 of the sucking means 90.

[0068] In this embodiment, it is possible to provide an optical sensor 80 at the midway of the tube 14 to detect the fact that almost all the quantity of the plasma in the blood collecting bag 1 has been discharged. This optical sensor 80 is constituted by light emitting element and light receiving element which are disposed on the opposite sides of the tube 14. When almost all the quantity of the plasma has been discharged from the blood collecting bag 1 and therefore the liquid flowing within the tube 14 is changed from the plasma to the buffy coat, the transmissibility of the light emitted from the light emitting element is reduced and therefore the amount of the light received by the light receiving element is also reduced. At this point of time, the fact that almost all the quantity of the plasma in the blood collecting bag 1 has been discharged is detected.

[0069] When the fact that almost all the quantity of the plasma is discharged from the blood collecting bag 1 is detected by the way described above, the transfer of the plasma to the plasma bag 10 is stopped by closing the tube 21 by clamping the midway of the tube 21 by a clamp or by actuating the solenoid pinch valve through the control performed by a micro computer (not shown). Thereafter, by opening the fluid path to the buffy coat bag 27, fluid communication is changed so as to allow the buffy coat is fed or transferred into the buffy coat bag 27. In this state, the actuating fluid from the fluid supply means 51 to the cuff 50 is supplied continuously, so that the buffy coat is being discharged from the blood collecting bag 1.

[0070] The weight of the buffy coat bag 27 is kept monitored by a weight sensor such as a load cell (not shown). When the weight sensor detects the fact that the weight of the buffy coat stored in the buffy coat bag 27 reaches a predetermined value, the transfer of the buffy coat from the blood collecting bag 1 to the buffy coat bag 27 is stopped.

[0071] The discharge of the buffy coat from the blood collecting bag 1 is stopped by stopping the supply of the actuating fluid from the fluid supply means 51 to the cuff 50 or closing the tube 14 or 26 with a clamp or the like. The supply of the actuating fluid is stopped by closing the valve 56 or stopping the operation of the air supply source 55.

[0072] As stated in the foregoings, if the apparatus is constituted such that the discharge of the blood component from the blood collecting bag 1 can be stopped or changed so as to direct toward a different bag in good timing based on the detected information by the optical sensor 80 or the weight sensor, the yield for the component is further improved.

[0073] Fig. 4 is a perspective view showing a separated component transferring apparatus according to the present invention. In the apparatus 32 shown in Fig. 4, at least one part of the centrifugal container 40, that is, the side portion 42 thereof is formed of a soft material to provide a soft material part 48. When this soft material part 48 is pressed by a movable push member 57, the soft material part 48 is deformed so as to project in the inner direction of the centrifugal container 40.

[0074] The movable push member 57 is composed of a movable piston 58 and a head 59 fixed to an end of the piston 58, and driving means (not shown) are provided for driving the movable push member 57.

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[0075] The pressing means of this embodiment is composed of a pair of opposing push members 57 and the driving means (not shown) for driving the push members 57 both roughly in the horizontal direction. When two opposing pistons 58 are moved in the direction that both the heads 59 approach each other, the soft material part 48 of the centrifugal container 40 is pressed by the two heads 59 and then deformed in the inner direction of the centrifugal container 40. As a result, the blood collecting bag 1 placed in the centrifugal container 40 is also compressed, so that the plasma in the upper layer is discharged from the blood collecting bag 1.

[0076] In this embodiment, it should be noted that the pressing means is constructed such that one of the push members 57 is not movable and only the other push member 57 is movable so as to press the soft material part 48 of the centrifugal container 40.

[0077] The soft material part 48 of the centrifugal container 40 is formed of a soft synthetic resin like a polyester such as soft polyvinyl chloride, polyethylene, polypropylene, polyethyleneterephtalate, or a combination of these materials. Further, the soft material part 48 can be formed at a bottom portion 41 of the centrifugal container 40, without being limited to only the side portion 42 thereof as described in the drawing.

[0078] As one of the example of the centrifugal container 40 used in the apparatus 32 of this embodiment, a portion excepting a frame portion 401, that is, a cylindrical portion thereof can be formed of the soft material as described above.

[0079] Further, any types of the pressing means such as rollers, fastening members, etc. can be used instead of the pair of the heads 59 as described above, as far as the soft material part 48 of the centrifugal container 40 can be deformed inwardly.

[0080] In accordance with the separated component transferring apparatus 32 as shown in Fig. 4, there are advantages such as follows. Namely, the blood collecting bag 1 can be pressed from the front and rear side thereof, the interfaces between the respective component layers are kept more stationary when the separated component is being discharged, thus leading to improvement of the yield for the blood component. Further, since the driving means of this embodiment is formed from the mechanism which merely perform reciprocal motion, the mechanism can be constructed with simple structure.

[0081] Further, it should be noted that the sucking means described with reference to Fig. 5 can also be applied to the apparatus according to the present invention.

[0082] Furthermore, it should be also noted that this invention can be applied to the case other than the transfer of the centrifugally separated blood component. For example, this invention can be used for collecting or taking out a layer including the effective component of eupyrene cells from a bone marrow fluid, for instance.

[0083] Hereinafter, practical experiments will be described hereinbelow.

[Experiment 1]

[0084] A quadruple bag system (four-connected bags) as shown in Fig. 1 was manufactured as follows: a blood collecting bag (400 ml in volume), a PC bag (60 ml in volume), a plasma bag (300 ml in volume) and a buffy coat bag (60 ml in volume) are all manufactured by use of a soft polyvinyl chloride sheet with a thickness of 0. 39 mm. Further, these bags are connected through soft polyvinyl chloride tubes as shown in Fig. 1.

[0085] On the other hand, a centrifugal container 40 as shown in Fig. 2 was manufactured by use of polypropylene. The wall thickness of the container 40 was 2. 5 mm, the inner diameter thereof was 95 mm, and the maximum depth thereof was 130 mm.

[0086] As the pressing means for pressing the blood collecting bag, an annular cuff (width (W) = 80 mm) was formed of soft polyvinyl chloride so as to be expandable and contractible. The annular cuff was placed on an inner surface of the centrifugal container 40 at a position 30 mm away from the bottom of the container 40, and further connected to an air supplying source (i.e. air compressor) through an air feeding tube.

[0087] A whole blood was collected in the blood collecting bag of the above-mentioned connected bags, and the blood collecting bag was placed in the centrifugal container under the condition that the annular cuff was contracted together with other bags. Then, the centrifugal container was set to a centrifugal separator (MODEL: DPR-6000 MODEL made by IEC Corp.), and centrifuged under 420rpm for 5 minutes.

[0088] Thereafter, the centrifugal container 40 was removed from the centrifugal separator, and further the bags other than the blood collecting bag were also removed from the centrifugal container 40. The connecting member 15 was then broken to effect the fluid communication therethrough, and further the tube 26 is closed by a clamp. Successively, the compressor was actuated, and compressed air of 0. 6 Kg/cm2 is fed into the annular cuff to expand the annular cuff gradually, so that the blood collecting bag in the centrifugal container was pressed to discharge the plasma in the upper layer through the tube 14. The discharged plasma was then transferred and collected into the plasma bag 10.

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[Experiment 2]

[0089] In this experiment, the connected bags, the centrifugal container and the pressing means which are all the same as with those of the Experiment 1 were used, by which the whole blood was centrifuged under the same conditions as those in Experiment 1.

[0090] After the centrifugal separation, the blood collecting bag accommodated in the centrifugal container was pressed in the same way as in Experiment 1, while the plasma bag 10 was placed in a pressure reducing chamber kept at a vacuum of - 0.239 bar (- 180 mmHg), to suck the plasma in the upper layer in the blood collecting bag in order to transfer and collect it into the plasma bag 10 through the tube 14.

[Comparative Experiment]

[0091] The connected bags and the centrifugal container which are the same as those used in the Experiment 1 were used, but no pushing means was used. Further, the whole blood was centrifuged under the same conditions as those in Experiment 1.

[0092] Thereafter, the connected bags were removed from the centrifugal container 40, and only the blood collecting bag was set between a pair of plates of a separator stand by hanging a small hole formed in the blood collecting bag on a hook of the separator stand. Then, the blood collecting bag was sandwiched between the two plates of the separator stand for pressurization, to discharge the plasma in the upper layer and transfer and collect it to the plasma bag 10.

[0093] The quantities of the blood and the collected plasma, and the time-required to collect the plasma were measured. Table 1 below lists these measured results.

TABLE 1

	QUANTITY OF BLOOD [g]	QUANTITY OF PLASMA [g]	TIME REQUIRED TO COLLECT PLASMA [sec]
EXPRMT 1	426. 2	318. 4	36. 0
EXPRMT 2	428. 3	320. 2	27. 5
COMPAR	424. 2	314. 0	97. 4

[0094] As indicated in Table 1, the yield for plasma collection (purity) is high in Experiments 1 and 2, as compared with Comparative Experiment. In particular, in the case of Experiment 2 in which the plasma is collected under the condition that the suction is performed in addition to the pressing motion, the time required to collect plasma can be shortened.

[0095] In addition, in the case of Experiment 1 or 2, even when the pressing means for pressing the blood collecting bag was replaced with another means as shown in Fig. 4 similar results were obtained.

[0096] In this connection, as the method of discharging each of the separated components without removing the blood collecting bag from the centrifugal container, it may be possible to use only the sucking method as described above which sucks the supernatant plasma layer through a tube connected to the upper end portion of the blood collecting bag and discharge it, without using the pressing means.

[0097] However, it has been found that the above-mentioned method is not appropriate due to the following reasons. That is to say, where the above-mentioned method is adopted alone, the inner pressure of the blood collecting bag is reduced into a vacuum pressure. For this reason, when the plasma layer is being discharged with the advance of pump suction, the two opposing inner surfaces of the bag are brought into contact with each other in particular at the upper portion of the bag. In addition, since gaps (channels) are produced between the inner surfaces of the bag so as to extendfrom the upper end discharge port 5 (outlet) of the bag to the vicinity of the fused edge portions of the bag, the separated component lower than the plasma layer, in particular the lowermost erythrocyte layer is sucked upwardly along the produced gaps. As a result, the erythrocyte is likely to be mixed with the plasma, thus causing another problem in that the yield for plasma collection is lowered.

[0098] Further, when the lower buffy coat layer is required to be collected after the plasma layer has been collected, the quantity of liquid within the blood collecting bag is further reduced, so that the two opposing inner surfaces of the bag are brought into further tight contact with each other. Therefore, a great quantity of erythrocyte is likely to be discharged through the gaps formed between the inner surfaces of the bag. In other words, the collection of the buffy coat layer must be stopped before the erythrocyte is mixed. This means that a quantity of the buffy coat layer remains within the blood collecting bag. As a result, it is difficult to separate the buffy coat layer from the erythrocyte layer effectively.

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[0099] In contrast with this, if the suction motion for the separated component by the sucking means is taken place in addition to the pressing motion for the blood collecting bag 1, the two opposing inner surfaces of the bag are not brought into contact with each other at the upper portion of the bag and further any channel is not be produced between the opposite two sheets, so that it becomes possible to transfer and collect the separated component with high yield.

[0100] As described above, in the separated component transferring apparatus and method according to the present invention, it is possible to improve the yield for the blood component obtained by the centrifugal separation, and further to reduce the time and labor required for separation.

Claims

1. An apparatus (32) for transferring a separated component in a liquid contained in a flexible bag (1) in airtight condition comprising :

   a deformable centrifugal container (40) for removably accommodating the flexible bag (1) therein;
   pressing means provided outside said centrifugal container (40) for pressing the flexible bag (1) accommodated in said centrifugal container (40) to increase the inner pressure of said flexible bag (1) while the bag (1) is released from the airtight condition, so that a predetermined separated component can be discharged from the bag (1),

   characterized in that said centrifugal container (40) includes a frame portion (401) and a soft material part (48);
   said pressing means comprises a pair of opposing push members (57), at least one of which is movable toward the other by a reciprocal motion driving mechanism, said push members (57) being adapted for pressing the soft material part of said centrifugal container (40) which is therefore deformed, so as to project in the inner direction of the centrifugal container, thus discharging the separated component of the liquid contained in the flexible bag.

2. The apparatus of claim 1, wherein each of said pushing members includes a roller for pushing the soft material part.

3. The apparatus as claimed in anyone of claims 1 to 2, wherein the apparatus further comprises sucking means (90) for sucking the separated component in the bag (1).

4. The apparatus of claim 3 which further comprises a container (10) for receiving the separated component, wherein said sucking means (90) includes means for reducing the pressure of an atmosphere in which said separated component receiving container (10) is placed.

5. A method of transferring a separated component in a liquid contained in a flexible bag (1) under airtight condition, which comprises the steps of:

   accommodating the flexible bag in which the liquid is contained under airtight condition into a centrifugal container (40) which is removably attached to a centrifugal separator, said centrifugal container having a soft material part formed in at least one portion thereof;
   centrifuging the flexible bag (1) accommodated in the centrifugal container (40) by the centrifugal separator to separate the liquid in the flexible bag (1) into the components thereof;
   removing said centrifugal container (40) from the centrifugal separator together with the flexible bag contained therein and then fixing the centrifugal container to a fixing means; and
   pressing the soft material part of the centrifugal container (40) from the outside of said centrifugal container (40) using a movable push member (57) provided outside of the container (40) for pushing said soft material part of said centrifugal container (40) to increase inner pressure of the bag (1) while releasing the airtight condition, thereby taking out a predetermined component in the liquid which has been separated by the centrifugation outside the flexible bag (1).

6. The method as claimed in claim 5, further comprising the step of sucking the separated component in the flexible bag (1) while pressing the flexible bag (1).

7. The method as claimed in claim 5, further comprising the step of sucking the separated component in the flexible bag (1) by reducing the pressure of an atmosphere in which a separated component receiving container (10) is put, while pressing the flexible bag (1).

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Patentansprüche

1. Vorrichtung (32) zum Übertragen eines getrennten Bestandteils in einer Flüssigkeit, welche in einem flexiblen Beutel (1) in luftdichtem Zustand enthalten ist, umfassend:

   einen verformbaren Zentrifugalbehälter (40) zum lösbaren Aufnehmen des flexiblen Beutels (1) darin;

   eine außen an dem Zentrifugalbehälter (40) vorgesehene Drückeinrichtung zum Drücken des in dem Zentrifugalbehälter (40) aufgenommenen flexiblen Beutels (1), so daß der Innendruck des flexiblen Beutel (1) erhöht wird, während der Beutel (1) aus dem luftdichten Zustand freigegeben wird, so daß ein vorbestimmter getrennter Bestandteil aus dem Beutel (1) abgegeben werden kann,

   dadurch gekennzeichnet, daß der Zentrifugalbehälter (40) einen Rahmenabschnitt (401) und einen Abschnitt (48) aus weichem Material umfaßt;
   wobei die Drückeinrichtung ein Paar gegenüberliegender Druckelemente (57) umfaßt, wobei mindestens eines davon hin zu dem anderen durch eine Reziprokbewegungs-Antriebsvorrichtung bewegbar ist, wobei die Druckelemente (57) angepaßt sind, den Abschnitt aus weichem Material des Zentrifugalbehälters (40) zu drücken, welcher dadurch verformt wird, so daß dieser in die Innenrichtung bezüglich des Zentrifugalbehälters vorsteht, wodurch der getrennte Bestandteil der in dem flexiblen Beutel enthaltenen Flüssigkeit abgegeben wird.

2. Vorrichtung nach Anspruch 1 , wobei jedes der Druckelemente eine Rolle zum Drücken des Abschnitts aus weichem Material umfaßt.

3. Vorrichtung nach einem der Ansprüche 1 bis 2, wobei die Vorrichtung ferner eine Saugeinrichtung (90) zum Saugen des getrennten Bestandteils in dem Beutel (1) umfaßt.

4. Vorrichtung nach Anspruch 3, welche ferner einen Behälter (10) zum Aufnehmen des getrennten Bestandteils umfaßt, wobei die Saugeinrichtung (90) eine Einrichtung zum Verringern des Drucks einer Atmosphäre umfaßt, in welcher der Behälter (10) zum Aufnehmen des getrennten Bestandteils angeordnet ist.

5. Verfahren zum Übertragen eines getrennten Bestandteils in einer in einem flexiblen Beutel (1) in luftdichtem Zustand enthaltenen Flüssigkeit, folgende Schritte umfassend:

   Aufnehmen des flexiblen Beutels, in welchem die Flüssigkeit in luftdichtem Zustand enthalten ist, in einem Zentrifugalbehälter (40), welcher abnehmbar an einer Trennzentrifuge angebracht ist, wobei der Zentrifugalbehälter einen Abschnitt aus weichem Material umfaßt, welcher in mindestens einem Abschnitt davon ausgebildet ist;

   Zentrifugieren des in dem Zentrifugalbehälter (40) aufgenommenen flexiblen Beutels (1) durch die Trennzentrifuge, so daß die Flüssigkeit in dem flexiblen Beutel (1) in die Bestandteile davon getrennt wird;

   Entfernen des Zentrifugalbehälters (40) von der Trennzentrifuge zusammen mit dem darin enthaltenen flexiblen Beutel und anschließendes Befestigen des Zentrifugalbehälters an einer Befestigungseinrichtung; und

   Drücken des Abschnitts aus weichem Material des Zentrifugalbehälters (40) ausgehend von dem Äußeren des Zentrifugalbehälters (40) unter Verwendung eines beweglichen Druckelements (57), welches außen an dem Behälter (40) vorgesehen ist, zum Drücken des Abschnitts aus weichem Material des Zentrifugalbehälters (40), so daß der Innendruck des Beutels (1) erhöht wird, während der luftdichte Zustand freigegeben wird, wodurch ein vorbestimmter Bestandteil in der Flüssigkeit entnommen wird, welcher durch die Zentrifugierung außerhalb des flexiblen Beutels (1) getrennt wurde.

6. Verfahren nach Anspruch 5, ferner umfassend den Schritt des Saugens des getrennten Bestandteils in dem flexiblen Beutel (1), während der flexible Beutel (1) gedrückt wird.

7. Verfahren nach Anspruch 5, ferner umfassend den Schritt des Saugens des getrennten Bestandteils in dem flexiblen Beutel (1) durch Verringern des Drucks einer Atmosphäre, in welcher ein Behälter (10) zum Aufnehmen eines getrennten Bestandteils angeordnet wird, während der flexible Beutel (1) gedrückt wird.

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Revendications

1. Appareil (32) servant à transférer un composant séparé dans un liquide contenu dans une poche souple (1) sous condition étanche à l'air comprenant :

   un récipient centrifuge déformable (40) destiné à recevoir, de manière amovible, la poche souple (1);
   un moyen de pressage prévu à l'extérieur dudit récipient centrifuge (40) pour presser la poche souple (1) logée dans ledit récipient centrifuge (40) pour accroître la pression interne de ladite poche souple (1) tandis que la poche (1) est libérée de la condition étanche à l'air, de sorte qu'un composant séparé prédéterminé peut être déchargé de la poche (1),

   caractérisé en ce que ledit récipient centrifuge (40) comprend une partie cadre (401) et une partie en matériau mou (48);
   ledit moyen de pressage comprend une paire de poussoirs opposés (57), au moins l'un d'entre eux pouvant être déplacé vers l'autre par un mécanisme d'entraînement à mouvement de va-et-vient, lesdits poussoirs (57) étant adaptés pour presser la partie en matériau mou dudit récipient centrifuge (40) qui est par conséquent déformée, afin de faire saillie vers l'intérieur du récipient centrifuge, en déchargeant de ce fait le composant séparé du liquide contenu dans la poche souple.

2. Appareil selon la revendication 1, dans lequel chacun desdits poussoirs comprend un rouleau servant à pousser la partie en matériau mou.

3. Appareil selon la revendication 1 ou 2, l'appareil comprenant en outre un moyen d'aspiration (90) servant à aspirer le composant séparé dans la poche (1).

4. Appareil selon la revendication 3 qui comprend en outre un récipient (10) destiné à recevoir le composant séparé, ledit moyen d'aspiration (90) comportant un moyen servant à réduire la pression de l'atmosphère dans laquelle est placé ledit récipient (10) de réception du composant séparé.

5. Procédé de transfert d'un composant séparé dans un liquide contenu dans une poche souple (1) sous condition étanche à l'air, qui comprend les étapes consistant à :

   placer la poche souple contenant le liquide sous condition étanche à l'air dans un récipient centrifuge (40) qui est attaché de manière amovible à un séparateur centrifuge, ledit récipient centrifuge comportant une partie en matériau mou formée dans au moins une portion de celui-ci;
   centrifuger la poche souple (1) logée dans le récipient centrifuge (40) au moyen du séparateur centrifuge pour séparer le liquide contenu dans la poche souple (1) en ses composants;
   retirer ledit récipient centrifuge (40) du séparateur centrifuge en même temps que la poche souple contenue dedans puis fixer le récipient centrifuge à un moyen de fixation; et
   presser la partie en matériau mou du récipient centrifuge (40) depuis l'extérieur dudit récipient centrifuge (40) en utilisant un poussoir mobile (57) prévu à l'extérieur du récipient (40) pour pousser ladite partie en matériau mou dudit récipient centrifuge (40) pour accroître la pression interne de la poche (1) tout en libérant la condition étanche à l'air, pour extraire de ce fait un composant prédéterminé du liquide qui a été séparé par la centrifugation hors de la poche souple (1).

6. Procédé selon la revendication 5, comprenant en outre l'étape consistant à aspirer le composant séparé dans la poche souple (1) tout en pressant la poche souple (1).

7. Procédé selon la revendication 5, comprenant en outre l'étape consistant à aspirer le composant séparé dans la poche souple (1) en réduisant la pression de l'atmosphère dans laquelle est placé un récipient (10) de réception de composant séparé, tout en pressant la poche souple (1).

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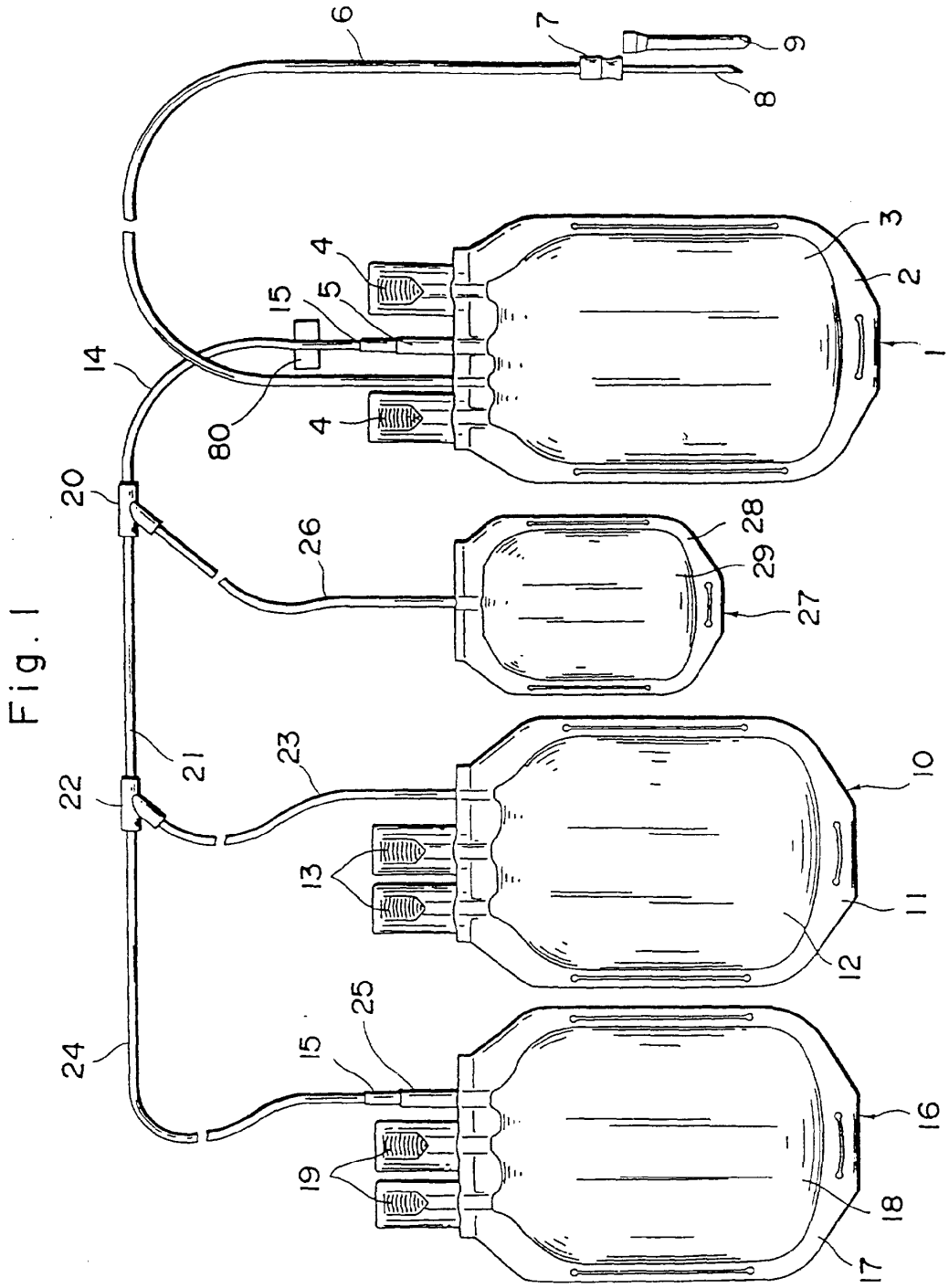


Fig. 1

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Fig.2

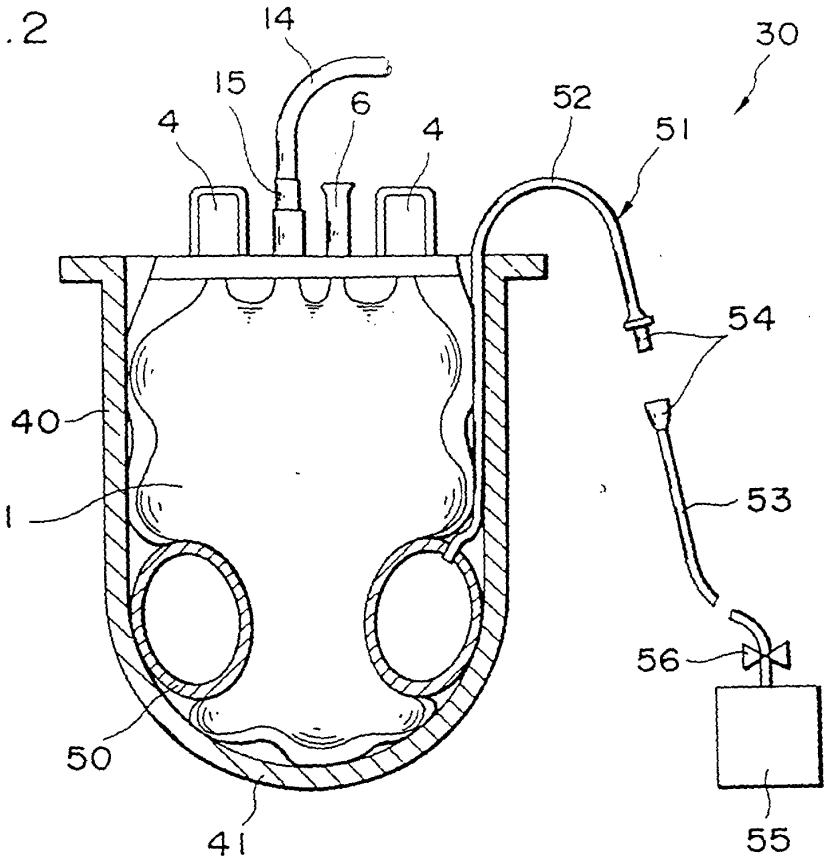
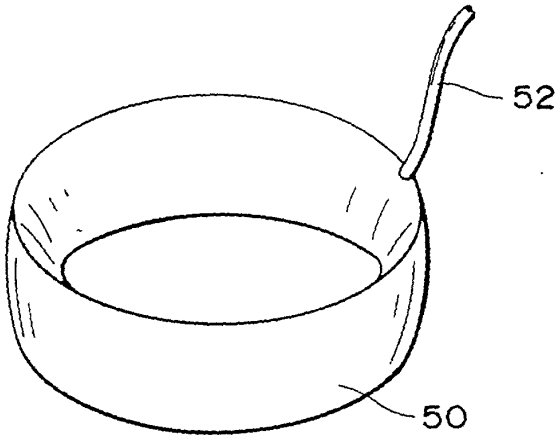
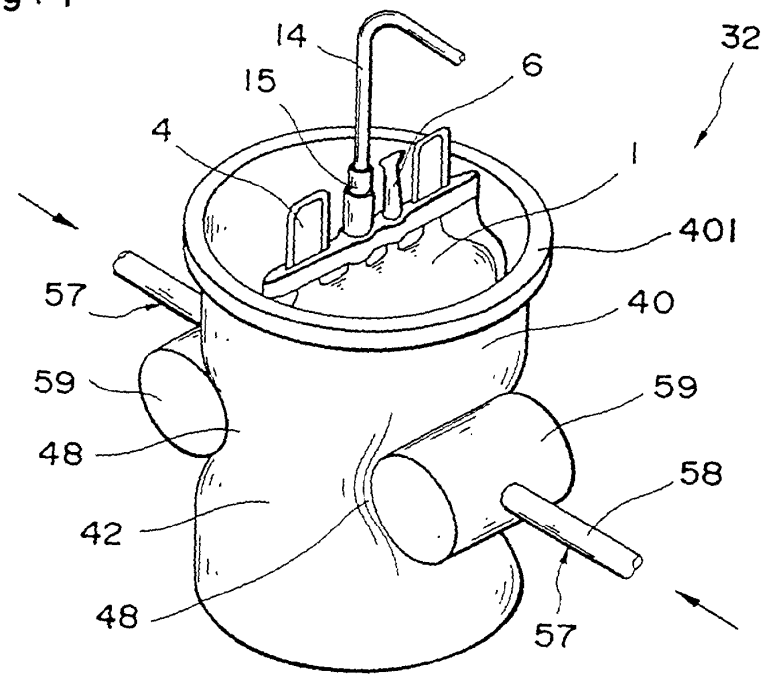


Fig.3



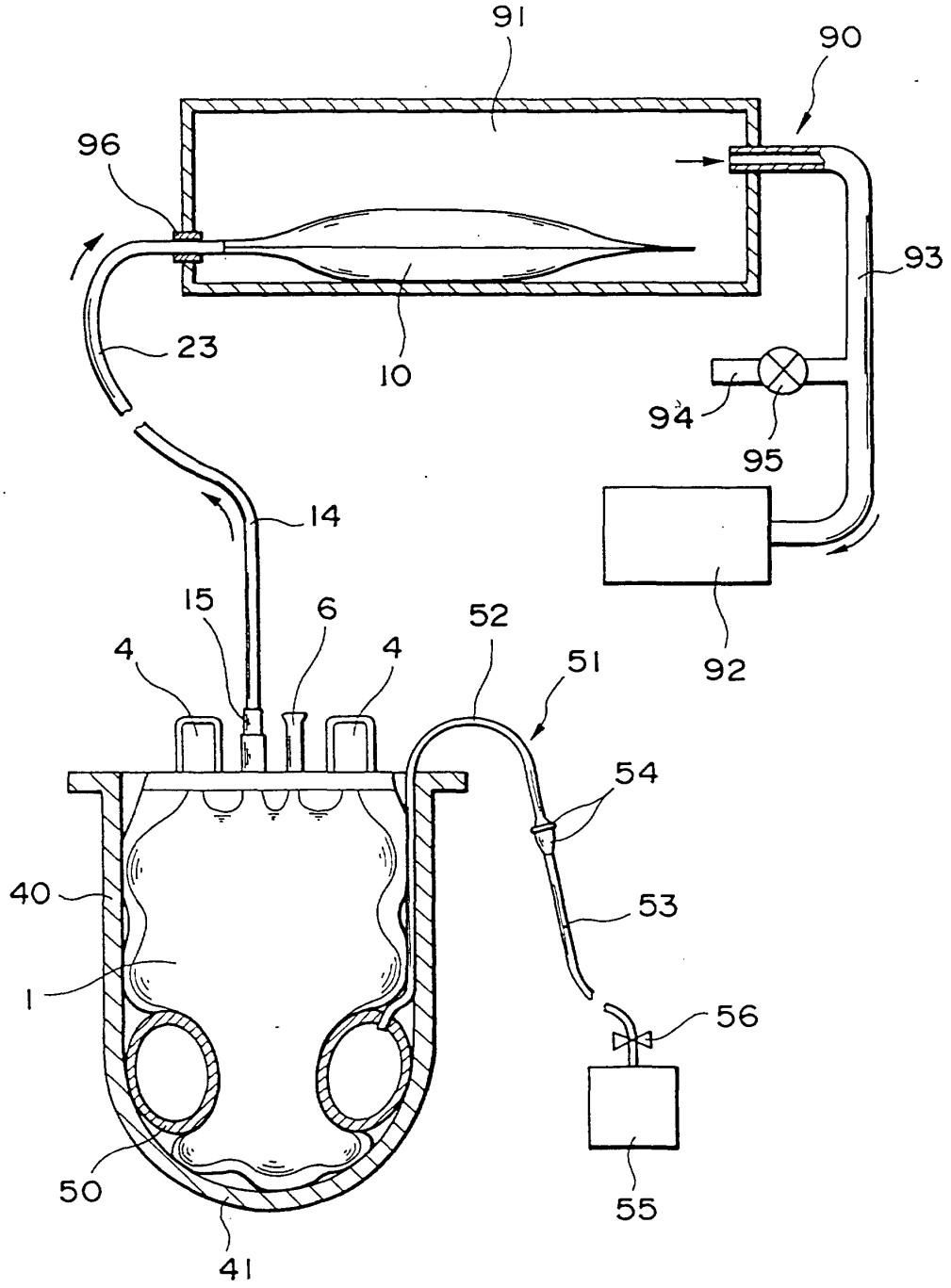
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Fig. 4



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Fig. 5



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Espacenet

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Optimized blood component collection system

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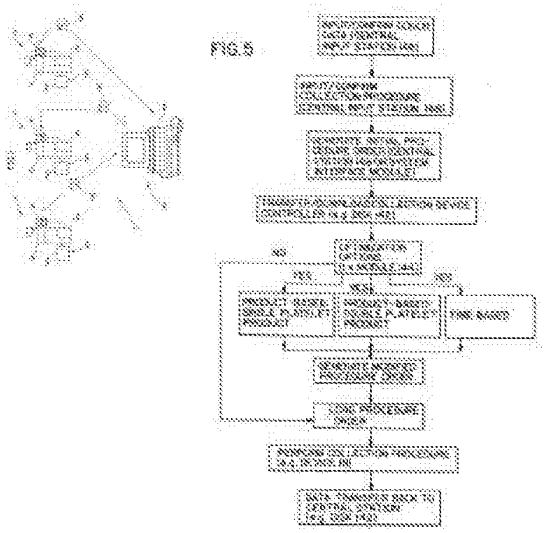
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Abstract of EP0654277 (A1)

A blood component collection system with optimization capabilities. In one embodiment, process parameters are derived from an input/configured predetermined blood component yield and which is based upon the maximization of at least one process parameter. Thereafter, the blood component collection procedure is performed with these derived process control parameters. In another embodiment, process parameters are derived from an input total procedure time from a maximized value for at least one of the other process control parameters so as to maximize blood component yield in this fixed time. Thereafter, the blood component collection procedure is performed with these derived parameters.

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(54) Blood component collection system with optimizer.

(57) A blood component collection system with optimization capabilities. In one embodiment, process parameters are derived from an input/configured predetermined blood component yield and which is based upon the maximization of at least one process parameter. Thereafter, the blood component collection procedure is performed with these derived process control parameters. In another embodiment, process parameters are derived from an input total procedure time from a maximized value for at least one of the other process control parameters so as to maximize blood component yield in this fixed time. Thereafter, the blood component collection procedure is performed with these derived parameters.

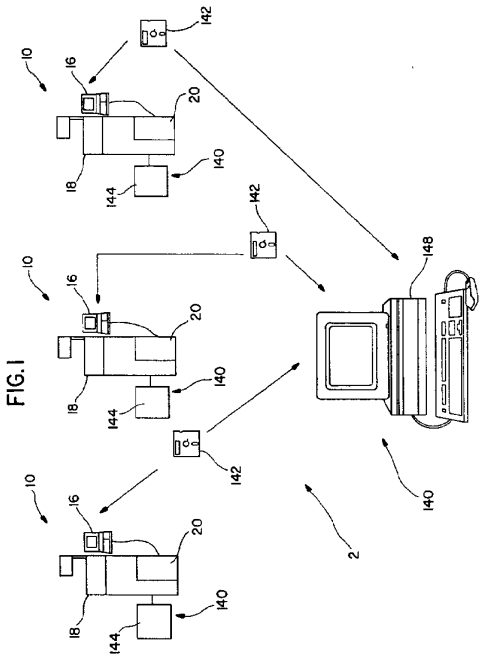
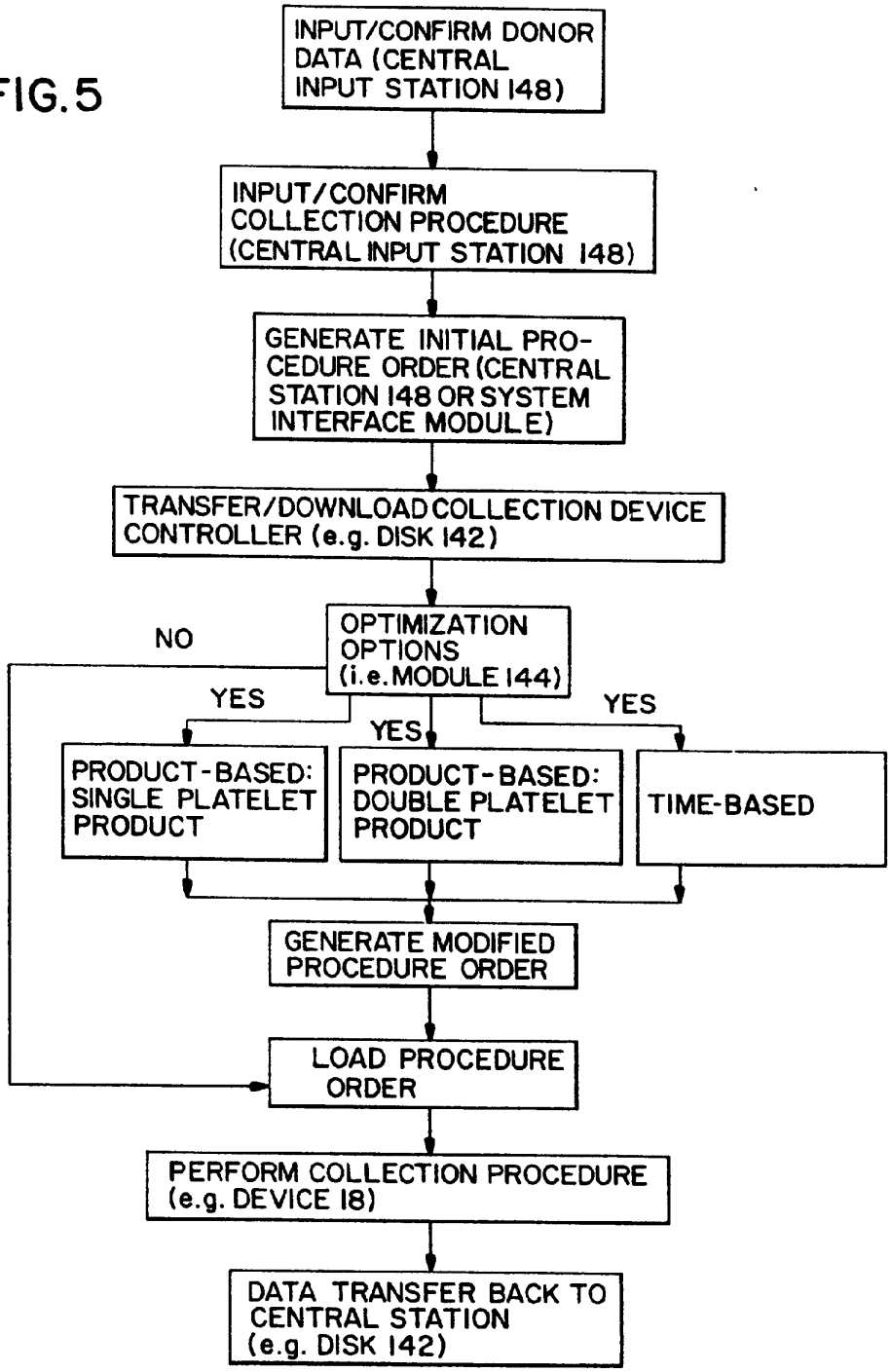


FIG. 1

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FIG.5



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Field of the Invention

The present invention generally relates to the field of blood component collection systems and, more particularly, to providing management capabilities by incorporating optimization principles into such systems.

Background of the Invention

The utilization of blood taken from donors and infused into recipients is well known for purposes of treating medical emergencies and other conditions. More recently, selected blood components have been separated and collected from blood for subsequent infusion into recipients requiring blood component therapy. The primary blood components include platelets, red blood cells, white blood cells, and plasma.

In order to collect blood components, blood is removed from a donor by a needle assembly or other blood access device and is thereafter processed utilizing centrifugation or other appropriate separation techniques to isolate and collect the desired components. This procedure is carried out most effectively in an on-line process wherein blood is removed from a donor, processed through a disposable extracorporeal circuit to obtain the desired components, and thereafter returned to the donor. One blood component collection system which provides for this type of blood component collection procedure is the COBE Spectra™ which is commercially available from the assignee of the present application.

The yield of a particular collection of blood components is an important factor. For instance, presently in the United States a yield must be associated with a collection of blood components in order to be a useful blood component product. COBE Spectra™ presently accommodates for this requirement by processing certain donor biological data such as height, weight, sex, and hematocrit, preconfigured/operator-input data such as the total procedure time, and system-related data such as the type of collection procedure (e.g., single or double needle) and collection efficiency to generate certain process parameters such as the inlet flow to COBE Spectra™ (a combined flow of whole blood from the donor plus typically a flow of anticoagulant) and a predicted blood component yield as well.

An additional consideration presently in the United States relating to blood component yield is that it is determinative of the product classification. With regard to platelets, presently a single platelet product is considered to be a collection of 3×10^{11} platelets and a double platelet product is considered to be a collection of 6×10^{11} platelets. If the collection is between 3×10^{11} and 6×10^{11} platelets it is still considered to be a single platelet product. This classification as a single or double platelet product is relevant to blood component collection facilities (e.g., blood banks/centers) since a double platelet product has a higher selling price associated therewith than a single platelet product and also typically benefits more patients. The yield of a particular collection of blood components may also be a relevant consideration for certain therapeutic treatments.

Other important considerations relating to blood component collection systems relate to the donor. For instance, blood component collection facilities are not only experiencing an increase in the overall demand for blood components, but the demand now typically varies between the blood component types as well. Moreover, not only is the supply of donors unfortunately in many cases inadequate, but donor time constraints are becoming more prevalent. Furthermore, obtainable yields from a given donor may vary from one blood component to another (i.e., one donor may be a better platelet source than a red blood cell source).

Based upon the foregoing, the management of the various aspects of blood component collection systems is becoming increasingly important.

Summary of the Invention

The present invention relates in one application to a blood component collection system which provides management capabilities by incorporating optimization principles. Generally and in this case, the present invention utilizes principles of optimization in terms of the donor, blood component collection system, and/or desired blood component product. For instance, the present invention may be adapted to provide for the collection of a predetermined quantity of at least one predetermined blood component (or more typically the collection of such blood components within a particular range) in a "minimum" amount of time and/or for the collection of a "maximum" quantity of at least one predetermined blood component in a fixed amount of time, all based upon certain process conditions. Moreover, the present invention may be adapted to provide for blood component inventory control by basing donor selection and/or collection procedure selection in terms of the type of blood component to be collected on blood component demand and/or existing inventory. In addition, the present invention may be adapted to provide for further donor management by collecting that blood component type(s) from the donor which provides a maximum yield.

In one aspect, the present invention may be characterized as a blood component collection system having

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blood component product-based optimization-like capabilities. One embodiment comprises a method for collecting at least one predetermined blood component (e.g., a collection of platelets, red blood cells) from a source of whole blood using a blood component collection system which includes a blood component collection device and which utilizes a collection procedure. More particularly, a desired yield of the predetermined blood component(s) is identified (such yield including a single yield or range of yields) and biological data relating to the source is provided to the blood component collection system. Moreover, a value or magnitude is associated with each of the various process parameters used in the collection procedure. A magnitude of at least one of these process parameters is derived from the biological data and the desired yield. These magnitudes, including all magnitudes of process parameters derived from the desired yield, are input to the blood component collection system. Thereafter, the collection procedure is performed with the blood component collection device and with the input process parameters to collect the desired yield of at least one predetermined blood component(s) from the whole blood source.

In another aspect, the present invention may be characterized as a blood component collection system having time-based optimization-like capabilities. One embodiment of such is a method for collecting at least one predetermined blood component from a source of whole blood using a blood component collection system which includes a blood component collection device and which utilizes a collection procedure. A flow of the whole blood from the source, as well as a flow of anticoagulant, is provided to the blood component collection system and collectively constitutes an inlet flow. In the method, a total procedure time for the collection procedure is identified (e.g., based upon donor time availability). One potential inlet flow to the system is derived from at least this identified total procedure time. Another potential inlet flow to the system is derived which provides an "optimum" collection efficiency and is effectively the apex of a bell-shaped yield/inlet flow curve (i.e., the inlet flow which provides the maximum blood component yield). Consequently, if the total procedure time-based inlet flow is greater than the maximum yield-based inlet flow, and thus is an inlet flow on the decreasing slope portion of the yield/inlet flow curve, the maximum yield-based inlet flow magnitude is used in the performance of the collection procedure. However, if the total procedure time-based inlet flow is less than the maximum yield-based inlet flow, and thus is an inlet flow on the increasing slope portion of the yield/inlet flow curve, the total procedure time-based inlet flow magnitude is used in the performance of the collection procedure.

The subject invention provides greater efficiency in blood component collection and management. For example, the present invention can be used to compare blood bank/center component inventories with projected needs, and adjust collection procedures to meet these needs. Further, the present invention provides benefits to donors. In particular, certain information relating to the donor's physical and medical characteristics may be stored in the system and utilized during subsequent visits by the donor to derive magnitudes for the various process control parameters. For example, for a donor with an anticoagulant intolerance, the magnitude of the anticoagulant infusion rate may be set so as to not exceed the donor's tolerance.

Brief Description of the Drawings

Fig. 1 is a schematic representation of a blood component collection system in accordance with principles of the present invention;

Fig. 2 is a schematic representation of one embodiment of a blood component separation assembly which utilizes a dual needle configuration and which may be incorporated into the blood component collection system of Fig. 1;

Fig. 3 is a schematic representation of one embodiment of a blood component separation assembly which utilizes a single needle configuration and which may be incorporated into the blood component collection system of Fig. 1;

Figs. 4a and 4b are perspective and top views, respectively, of one type of a disposable processing channel used in the blood component collection device of Figs. 2 and 3;

Fig. 5 is a flow chart of a blood component collection procedure utilizing principles of the present invention;

Fig. 6 is a flow chart of one optimization model for deriving at least one optimal process parameter from a desired blood component yield or from a total procedure time in accordance with principles of the present invention;

Fig. 7 is a flow chart of one optimization model for deriving at least one optimal process parameter from a desired blood component yield or from a total procedure time in accordance with principles of the present invention; and

Fig. 8 is a yield/inlet flow curve.

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Detailed Description

The present invention will be described with reference to the accompanying drawings which assist in illustrating the pertinent features thereof. One application of the present invention is embodied within a blood component collection system which separates, removes, and collects at least one type of blood component (e.g., platelets, red blood cells, white blood cells, plasma) from a source of whole blood (e.g., a donor) through utilization of a collection procedure derived from a typically site-configured/operator-input goal(s) and the "maximization" of at least one process control parameter. This type of derivation is referred to herein as an "optimization process" and the derived process control parameters are referred to herein as "optimal values."

Referring to Fig. 1, the present invention is embodied within the blood component collection system 2 which would typically be implemented at a blood bank/center (not shown). The system 2 includes an optimization assembly 140 (e.g., appropriate microprocessor(s) such as an IBM compatible PC and software) and at least one blood component collection assembly 10 (three shown) which each includes a blood component collection device 18 as an integral part thereof. As will be discussed below, the optimization assembly 140 (or at least a portion thereof) and associated blood component collection assemblies 10 are preferably appropriately interfaced but may be completely separate as well. That is, optimization procedures in accordance with principles of the present invention are not limited to being performed at any particular location.

Generally, the optimization assembly 140 includes a central input station 148 (e.g., an appropriate microprocessor such as an IBM compatible PC and attendant software) for inputting and maintaining donor-related-data, and also typically for preparing an initial procedure order (the process control parameters derived from the donor-related data and other considerations) for a given donor. These procedures may also be performed at the appropriate operator interface module 16 as well such that a central input station 148 is not required. However, where a central input station 148 is used, this donor-related data and/or initial procedure order is transferred to one of the operator interface modules 16 (e.g., an appropriate microprocessor such as an IBM compatible microprocessor and interfaced with the device 18 via an RS232 or other lab specific interface, including the Digital Equipment Corp. PCP 30, which is also known as the DEC pc 325SL and which utilizes a 386 processor) which are located at each blood component collection device 18 and which as noted preferably interfaces with an optimizer module 144 (part of the optimizing assembly 140) for providing the operator with one or more optimization options. These optimization options provide a different set of process control parameters than the initial procedure order based upon one or more specified conditions/goals (e.g., input blood component yield, input procedure time) and a particular derivation for the process control parameters. If an optimization option is selected the procedure order is modified to reflect the results of the optimization, the collection procedure is initialized/reinitialized (i.e., the collection procedure would be reinitialized in the case of an optimization which is performed after the collection procedure has been initiated and such is referenced to as a downstream optimization) with the results of the optimization, and the collection procedure is thereafter performed with the blood component collection device 18.

Various embodiments of blood component collection assemblies may incorporate principles of the present invention. However, as noted above on-line techniques have been determined to be quite effective and thus the present invention is being described with reference to such techniques. One embodiment of an on-line technique and attendant apparatus which may be incorporated into the blood component collection system 2 of Fig. 1 is illustrated in Fig. 2. The blood component collection assembly 10' utilizes an on-line technique in that a donor 14 (e.g., the whole blood source) is directly integrated with the system 10' by fluid interconnection with the blood component collection device 18. This particular on-line technique is more particularly referred to as a dual needle configuration since there are two fluid interconnections between the donor 14 and the blood component collection device 18.

The donor 14 is fluidly connected to the blood component collection device 18 by an inlet line 22 and appropriate needle assembly (not shown). Whole blood from the donor 14 is thus continuously provided to the blood component collection device 18 through the inlet line 22 for separation of the desired blood component(s) therefrom, utilizing an inlet pump 26 (e.g., a peristaltic pump) to maintain this flow if desired/required. Prior to the blood of the donor 14 entering the blood component collection device 18, anticoagulant from an anticoagulant ("AC") container 30 may be provided to the whole blood, utilizing an AC pump 32 (e.g., a peristaltic pump) to maintain this particular flow if desired/required. Consequently, the inlet flow to the blood component collection device 18 typically includes both a flow of whole blood from the donor 14 and a flow of anticoagulant from the AC container 30.

The blood component collection device 18 separates the whole blood provided on line by the donor 14 into three primary constituents, namely platelets, a combination of red and white blood cells ("RBC/WBC"), and plasma. The platelets collected from the blood component device 18 are directed through a platelet collect line(s) 34 to one or more platelet collect bags 38 via a collect pump 36. The plasma and RBC/WBC are provided

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back to the donor 14 through a plasma line 42 and RBC/WBC line 46, respectively, both of which are interconnected with a second needle assembly (not shown) on the donor 14 via a donor return line 50. The plasma line 42 includes a plasma pump 40 (e.g., a peristaltic pump) to maintain the flow of plasma if desired/required. Although plasma may be provided back to the donor 14 in the above manner, it may be desirable to collect the separated plasma in some cases. In this regard, a plasma collect bag 54 may be provided and interconnected with the plasma line 42 (interconnection shown in phantom). In this case, appropriate valving 56 may be incorporated in the plasma line 42.

The blood component separation assembly 10" of Fig. 3 is similar to that of the dual needle configuration of Fig. 2 except that a single needle assembly (not shown) integrates the donor 14 within the blood component collection assembly 10". Consequently, similar components are similarly identified where appropriate. With regard to the single needle configuration of Fig. 3, whole blood of the donor 14 initially flows through a donor access line 62 and into an inlet line 66 which is fluidly connected with the blood component collection device 18 such that the platelets are separated and collected in the above-described manner. The plasma and RBC from the blood component collection device 18 flow through the plasma and RBC/WBC lines 42, 46, respectively, both of which are fluidly interconnected with a return flow controller 74. As above, however, the plasma may alternatively be directed to a plasma collect bag 54. In the event that plasma is not collected, the RBC/WBC and plasma are provided back to the donor 14 through the return flow controller 74 via a donor return line 70 which is interconnected with the donor access line 62. As can be appreciated, since only a single line is directly connected to the donor 14, namely the donor access line 62, blood is either being removed from or provided back to the donor 14 such that the procedure is effectively two-step versus continuous in relation to the donor 14.

The blood component collection device 18 used in the blood component collection assembly 10 is more particularly illustrated in Figs. 4A-B. This device 18 is the subject of U.S. Patent No. 4,387,848 to Kellog et al., entitled "CENTRIFUGE ASSEMBLY", issued June 14, 1983, and the disclosure of which is incorporated by reference in its entirety herein. This device 18 is also commercially available from the assignee of the present application as such is incorporated in COBE Spectra™.

Referring to Figs. 4A-B, the blood component collection device 18 utilizes a processing channel 80 to provide the desired disposable extracorporeal circuit. The channel 80 is positioned within a groove formed directly or indirectly in a centrifuge rotor (not shown) (e.g., a separate filler may receive the channel 80 and be attached to the centrifuge rotor), and is illustrated in the shape which it assumes during processing (i.e., during flow of blood therethrough). All subsequent references herein to the structural and operational characteristics of the blood component collection device 18 will be to the processing channel 80 in the illustrated condition.

The processing channel 80 generally includes a first stage 84 for collectively separating red blood cells ("RBC") and white blood cells ("WBC") from platelet-rich plasma, a second stage 92 for thereafter separating platelets from the platelet-rich plasma, a transition portion 88 defining a separation between the first stage 84 and second stage 92, and a control chamber 124 for maintaining a proper interface between the first stage 84 and second stage 92, namely the position of the interface between the RBC/WBC and platelet-rich plasma within the transition portion 88.

The first stage 84 extends from one end of the control chamber 124 along an arcuate path generally inwardly, toward the axis 132 about which the processing channel 80 rotates via the centrifuge rotor, until terminating at the transition portion 88. Specifically, the end of the first stage 84 adjacent the control chamber 124 is positioned at a greater radial distance from the axis 132 than the end of the first stage 84 adjacent the transition portion 88. An inlet tube 96 is fluidly connected with the first stage 84 between its two ends to introduce whole blood into the processing channel 80 and a RBC/WBC tube 100 is provided in the control chamber 124 for removing the separated RBC/WBC from the channel 80. Both the inlet tube 96 and RBC/WBC tube 100 extend externally of the rotatable device 18 for interconnection with the donor 14 and/or collection bags 38, 54.

As RBC/WBC sediment against the outer wall in the first stage 84 during rotation of the centrifuge rotor they are directed and counterflow toward the RBC/WBC tube 100 for removal from the channel 80 due to the increased centrifugal forces at the RBC/WBC tube 100 in comparison with the transition portion 88. That is, since the first stage 84 extends along an arcuate path generally outwardly away from the axis 132 proceeding from the transition portion 88 to the control chamber 124, the centrifugal force differential along the first stage 84 establishes the described counterflow of the separated RBC/WBC. Moreover, the transition portion 88 also assists in providing for this counterflow since it extends along an arcuate path generally inwardly toward the axis 132 proceeding from the first stage 84 to the second stage 92.

The platelet-rich plasma, which has a lower density than the RBC and WBC, flows beyond the transition portion 88 from the first stage 84 into the second stage 92 for further processing, while the RBC/WBC are directed back toward the RBC/WBC tube 100 in the above-described manner. The second stage 92 initiates

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at the radially inwardmost part of the transition portion 88 and extends along an arcuate path generally outwardly away from the axis 132 to a platelet collection chamber 104. Platelets are removed from the processing channel 80 at the platelet collection chamber 104 by a platelet tube 108 which interfaces with the outer wall of the processing channel 80 at the platelet collection chamber 104. Thereafter, the second stage 92 extends along an arcuate path generally inwardly toward the axis 132 until terminating at the plasma tube 112. Both the platelet tube 108 and plasma tube 112 extend externally of the rotatable device 18 for interconnection with the platelet collect bag(s) 38 and donor 14/plasma collect bag(s) 54, respectively.

Platelets which do not separate from the plasma in the initial portion of the second stage 92 between the transition portion 88 and platelet collection chamber 104 are separated in the portion of the second stage 92 between the platelet collection chamber 104 and the plasma tube 112. These platelets will flow back towards the platelet collection chamber 104 in the opposite direction of the flow of platelet-rich plasma/platelet-poor plasma through the second stage 92 due to the configuration of this portion of the second stage 92. That is, the platelet collection chamber 104 assumes the radially outwardmost position in the second stage 92 such that all platelets, regardless of where separation occurs in the second stage 92, flow towards the platelet collection chamber 104 for removal from the channel 80.

Platelet-poor plasma exits the second stage 92 and flows out through the plasma tube 112 which interfaces with the inner wall of the processing channel 80 and/or continues to flow through the remaining portion of the processing channel 80 to the control chamber 124. Plasma which flows to the control chamber 124 exits the channel through the control tube 114 which joins with the RBC/WBC tube 100 into a single outlet tube 120. The positionings and diameters of the RBC/WBC tube 100 and control tube 114 and the joinder of such into the common outlet tube 120 regulate the position of the RBC/WBC-platelet-rich plasma interface within the transition portion 88 using conservation of mass principles.

The blood component collection device 18 includes a prediction model 20 (appropriately interfaced with the operator input module 16 as shown in Fig. 1 as noted above and which may be used to configure the prediction model 20 and/or to allow operator input of various parameters to be used by the prediction model 20) for predicting a platelet yield before a collection procedure is initiated using a compilation of algorithms. The prediction model 20 may be used by the optimizer assembly 140 which is associated with principles of the present invention and thus will be briefly described herein. Notwithstanding the following discussion of the specifics of the prediction model 20, those skilled in the art will appreciate that the prediction model 20 is associated with the functional and operational characteristics of the blood component device 18 described herein. Therefore, the algorithms used in the prediction model 20 could and likely would vary in the case of other blood component collection devices which may be used by the present invention. Moreover, different algorithms could of course be used even for the prediction model 20. Furthermore, the algorithms are specific to platelet collection and therefore may and likely would change if used in relation to other blood component types such as red blood cells.

The prediction model 20 is typically configured by the site (e.g., the blood bank/center) for a particular blood component collection procedure (e.g., single or dual needle) used by the site and will be presented with regard to the dual needle procedure of Fig. 2 and in relation to a platelet-collecting procedure. In this regard, an AC infusion rate (i.e., the rate at which anticoagulant is provided to the donor 14 per the blood volume of the donor 14) and the AC ratio (i.e., the collective flow of AC and blood through the inlet line 22 in relation to the flow of AC through the line 22) must be specified (through configuration or modified input as will be discussed below). Moreover, in the event that plasma is to be collected into the plasma collect bag 54 in the collection procedure, the maximum amount of plasma which should be collected considering the medical and physical characteristics of the donor 14 must also be provided.

There are two alternatives for establishing the plasma volume limit. The first alternative relating to the plasma volume limit is to provide a weight cutoff (e.g., 0-500 pounds), associated with the weight of the donor 14 which is input as will be discussed below. In this regard, a plasma volume upper limit (e.g., 10-1500 ml.) may be established for a weight of a donor 14 in excess of this cutoff, and a plasma volume lower limit (e.g., 10-1500 ml.) may be established for a weight of such donor 14 which is less than this cutoff. For instance, if the weight cutoff is 175 pounds, the plasma volume upper limit can be 600 ml. for a donor 14 weight greater than or equal to 175 pounds, and the plasma volume lower limit can be 500 ml. for a donor 14 weight less than 175 pounds.

The second alternative for a plasma volume limit is to configure the prediction model 20 such that the plasma volume limit is expressed as a percentage of the total blood volume of the donor 14 which is calculated pursuant to Eq. 10 below. For instance, the plasma volume limit may be established as 1-15% of the total blood volume of the donor 14, and is preferably established as about 12% of such volume.

Further information is required by the prediction model 20 prior to performing its yield prediction function. For instance, the total procedure time is typically input by the operator or preconfigured by the user (e.g., the

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blood bank/center). When configured the procedure time is typically 100 minutes. Moreover, the total procedure time is affected by whether a stepdown option is utilized for the blood component collection device 18 so as to enhance separation of the various blood components. When this stepdown option is selected, the angular velocity of the blood component collection device 18 is incrementally reduced during the platelet-collection procedure. For instance, the stepdown option could provide for angular velocities for the device 18 of 2400, 2200, and 2000 RPM, each of which would be for a specified duration.

Based upon the foregoing, the configuration of the prediction model 20 in relation to the blood component separation assembly 10' and associated protocol in effect standardizes site protocol for purposes of "normal" operations. However, for a particular donor 14 it may be desirable to alter the "configuration" for one processing run. Consequently, the prediction model 20 utilizes a procedure in which certain parameters utilized in the following equations may be adjusted on a one-at-a-time basis. Such is referred to as modified input data and the associated parameters are procedure time (e.g., 10-999 minutes), inlet flow rate to the device 18 (e.g., 0-150 ml/min. for the Fig. 2 assembly and 0-50 ml/min. for the Fig. 2 assembly), AC ratio option as discussed above (3-50), the desired platelet collect volume (e.g., 10-9999 ml.), the desired platelet collect concentration (e.g., 100-8000 x 10^6/ml.), and the desired source plasma volume to be collected (e.g., 0-9999 ml.). Moreover, other parameters such as AC infusion rate (0.8-1.1), stepdown option (yes or no), needle option (single or double), and high flow option (yes or no) may also be entered as modified input data by an operator.

Having configured the prediction model 20 in the above-described manner, the following additional information is provided and is utilized in the various calculations of Equations 1-22 presented below: (1) needle option, namely whether the procedure is dual needle (Fig. 2) or single needle (Fig. 3); (2) run identification number for purposes of associating the data/output generated by the various equations with a particular donor 14 and processing run; (3) the sex of the donor 14; (4) the height of the donor 14; (5) the weight of the donor 14; (6) the total blood volume as calculated in Eq. 10 below; (7) the hematocrit of the donor 14, either based upon an initial estimation and thereafter updated based upon analysis of the donor's 14 blood sample (e.g., by a cell counter) or input directly from such an analysis; (8) the platelet precount, either based upon an initial estimation and thereafter updated based upon analysis of the donor's 14 blood sample (e.g., cell counter) or input directly from such an analysis; and (9) whether plasma collection is desired in conjunction with the platelet collection.

Based upon the above initial configuration and subsequent data input (except when entered as modified input data), the following output is generated by the prediction model 20: (1) platelet yield; (2) inlet flow rate; (3) AC ratio; (4) procedure time; (5) platelet collect volume; (6) platelet collect concentration; (7) source plasma volume; (8) AC in the platelet and plasma collect bags 38, 54; (9) platelet postcount; (10) AC infusion rate; and (11) output approval. This information is utilized at least in part in the following equations to generate, inter alia, the predicted platelet yield value of the collected platelets for the case of the dual needle procedure of Fig. 2 and also for the case of the single needle procedure of Fig. 3. The differences between those procedures with regard to the prediction model 20 are identified herein. As will be appreciated, some of the equations are utilized in the calculation of the predicted platelet yield, whereas other equations are used to generate additional information for output and informational purposes. The variables or parameters and the units associated therewith of the equations are presented after the equations in the Variables Index.

Platelet Yield:

$$Y = 1 \times 10^6 \, C_{PR} \, V_B \, F_Y \left[1-\exp\left[-E_c \, (f_{BP} - 0.12)\right]\right] \quad \text{(Eq. 1)}$$

where:

$$f_{BP} = (Q_{IN} \, t_E + 50) \, (1 - 1/R)/V_B \quad \text{(Eq. 2)}$$

and where:

$$Q_{IN} = RQ_{AC} = 0.001 \, I \, V_B \, PR \leqq 150 \quad \text{(Eq. 3)}$$

Alternatively, the platelet yield may be expressed as:

$$Y=1x10^6 C_{PR} V_B F_Y\left[1-\exp\left[-E_c(0.001\, I(R-1)\, Pt_E+50\,(1-1/R)/V_B-0.12\right]\right]\geq 0 \quad \text{(Eq. 4)}$$

Platelet Collection Efficiency:

$$E_C = C_1 - C_2 \exp\left[9.91\,(1 - 1/R)H\right] Q_{INA} \geqq 0 \quad \text{(Eq. 5)}$$

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where the constant C_1 is defined as follows:

$C_1 = 0.803$ - dual needle, without stepdown

$C_1 = 0.840$ - dual needle, with stepdown

where the constant C_2 is defined as follows:

$C_2 = 4.08 \times 10^{-5}$ - dual needle, without stepdown

- dual needle, with stepdown

and where:

$$Q_{INA} = Q_{IN}\,(t_E/t_P) \quad \text{(Eq. 6)}$$

In Eq. 6, t_P may be provided as configuration data or modified data as provided above, or alternatively may be derived from the solution of Eq. 4 for t_E.

Effective Procedure Time:

$$t_E = t_P \;,\; Q_{IN} \leq 45$$
$$= t_P - 500\,(1/45 - 1/Q_{IN}) \;,\; Q_{IN} > 45 \quad \text{(Eq. 7)}$$

Only high-flow protocol is used for $Q_{IN} > 45$.

AC Infusion Rate Constant:

$$I = 1000\,Q_{IN}/(PRV_B) \quad \text{(Eq. 8)}$$

Alternatively to the use of Eq. 8 for the derivation of the AC infusion rate constant I, such may be provided as configuration or modified input data pursuant to the above.

AC Ratio:

Initially, the AC ratio may be provided as configuration or modified input data pursuant to the above. In configuration, it is defined as follows:

$$R = 1 + 2.51/H \quad \text{low}$$
$$= 1.33(1 + 2.51/H) \quad \text{medium}$$
$$= 1.67(1 + 2.51/H) \quad \text{high} \quad \text{(Eq. 9)}$$

Total Blood Volume:

$$V_B = 604 + 0.006012\,L^3 + 14.6\,W \text{ ml (male)} \quad \text{(Eq. 10)}$$
$$= 183 + 0.005835\,L^3 + 15.0\,W \text{ ml (female)}$$

Plasma Collect Factor:

AC infusion rate control maintains the AC flow to the donor as:

$$Q_{ACD} = 0.001\,I\,V_B \quad \text{(Eq. 11)}$$

where the inlet flow associated with this is:

$$Q_{INO} = RQ_{ACD} = 0.001\,IRV_B \quad \text{(Eq. 12)}$$

Q_{IN} is proportional to the total AC flow, as given by Eq. 3, which includes the AC that flows to the platelet collect bag 38 and the plasma collect bag 54. P (Eq. 13) is the factor by which Q_{IN} is increased by collecting AC, relative to not collecting AC. That is,

$$P = Q_{IN}/Q_{INO} = (\text{average } Q_{AC})/Q_{ACD} \quad \text{(Eq. 13)}$$

where:

$$P = 1 + (f_{ACP}/Q_{ACD})\,[V_C/\,(t_P - 150/Q_{IN}) + V_{SP}/\,(t_P - 500/Q_{IN})] \quad \text{(Eq. 14)}$$

and where:

$$f_{ACP} = [(R - 1)\,(1 - H)]^{-1} \quad \text{(Eq. 15)}$$

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Platelet Collect Volume:

$$V_C = 1 \times 10^{-6}\, Y / [C_B (1 + f_{ACP})] \quad \text{(Eq. 16)}$$

Source Plasma Volume:

The four choices provided are as follows:

$$\left.\begin{aligned} V_{SP} &= 0 \\ &= V_{CON} - V_C \\ &= f_{SP} V_B - V_C \\ &= \textit{specified as modified input} \end{aligned}\right\} \geq 0 \quad \text{(Eq. 17)}$$

where:

$$\begin{aligned} V_{CON} &= V_{CONL}\ ,\ W < W_C \\ &= V_{CONH}\ ,\ W \geq W_C \end{aligned} \quad \text{(Eq. 18)}$$

and where:

$$0.01 \leqq f_{SP} \leqq 0.15 \quad \text{(Eq. 19)}$$

Donor Postcount:

$$C_{PO} = C_{PR} \exp[-E_C(0.001 / (R - 1)Pt_E + 50(1 - 1/R)/V_B - 0.12)] \leqq C_{PR} \quad \text{(Eq. 20)}$$

A warning is given if $C_{PO} < 100$.

Collect Volumes:

$$V_{CB} = V_C (1 + f_{ACP}) \quad \text{(Eq. 21)}$$

$$V_{SPB} = V_{SP} (1 + f_{ACP}) \quad \text{(Eq. 22)}$$

The primary equation to be solved for purposes of the yield prediction by the prediction model 20 is Eq. 4. Consequently, Eqs. 1-3 and 5-22 are ancillary to Eq. 4 although they may be used to calculate other output data and/or information required by Eq. 4. With regard to the manner in which Eqs. 1-22 are solved, all the iteration loops are based on the technique of successive approximation, in which each iteration is a repeat of the previous one, but using updated parameter values calculated in the previous iteration. This process continues until all the convergence criteria are met. The convergence criteria are that, on successive iterations, the variable difference is $\leqq 1$ for V_C, $\leqq 0.2$ for t_E, and $\leqq 10$ for C_B.

As noted above, the foregoing was based upon a dual needle configuration as illustrated in Fig. 2. In the event that a single needle configuration such as that illustrated in Fig. 3 is utilized, the following Eq. 7' is used in place of Eq. 7 and the constants C_1 and C_2 for Eq. 5 are as follows:

C_1=0.803

C_2=8.54 x 10 -5

$$\begin{aligned} t_E &= t_P\ ,\ Q_{IN} \leq 20 \\ &= t_P - 215\,(1/20 - 1/Q_{IN})\ ,\ Q_{IN} > 20 \end{aligned} \quad \text{(Eq. 7')}$$

Variables Index

Symbols for Equations:

C_1, C_2 = constants in platelet collection efficiency equations

C_B = platelet concentration in collect bag, expressed as 10^3 platelets/microliter

C_{PO} = donor postcount, expressed as 10^3 platelets/microliter

C_{PR} = donor precount, expressed as 10^3 platelets/microliter

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E_C = platelet collection efficiency
f_{ACP} = AC expressed as a fraction of pure plasma volume
f_{BP} = fraction of V_B processed in platelet collection procedure
f_{SP} = V_{CON} expressed as a fraction of V_B
F_Y = user-specific (e.g., blood bank/center) yield calibration factor
H = hematocrit of donor or patient
I = AC infusion rate constant
L = donor or patient height, inches
P = plasma collect factor
Q_{AC} = AC flow, ml/min
Q_{ACD} = AC flow infused into donor for platelet collection procedures, ml/min
Q_{IN} = inlet flow, ml/min
Q_{INA} = average inlet flow for platelet procedures, ml/min
Q_{INO} = RQ_{ACD} = inlet flow associated with Q_{ACD}, ml/min
R = AC ratio
t_E = equivalent procedure time, min
t_P = procedure time, min
V_B = total blood volume of donor or patient, ml
V_C = volume of pure plasma in platelet collect bag, ml
V_{CB} = total volume in platelet collect bag, ml
V_{CON} = volume constraint for total pure plasma collected, ml
V_{CONH} = higher value of V_{CON}, ml
V_{CONL} = lower value of V_{CON}, ml
V_{SP} = volume of pure plasma in source plasma bag, ml
V_{SPB} = total volume in source plasma bag, ml
W = donor or patient weight, lbs
W_C = weight constraint associated with V_{CON}, lb
Y = platelet yield, number of platelets.

As noted above, the optimizer assembly 140 associated with principles of the present invention interfaces with or at least provides information to one or more blood component collection assemblies 10 to provide a blood component collection system 2. That is, although there are definite advantages to having an interface between the optimizer assembly 140, particularly the optimizer module 144, and the blood component collection device 18, the optimization procedure may be performed at any location and input into the blood component collection device 18 in any manner. Since the general principles of the blood component collection assembly 10 were described with relation to the collection assemblies 10, 10" which included the blood component collection device 18 and its various features, the optimizer assembly 140 will be described in relation to such assemblies 10', 10". However, it will be appreciated that the fundamental optimization principles of the present invention are not limited to these collection procedures and/or apparatus.

As noted (Fig. 1), the optimization assembly 140 generally includes a central input station 148, as well as an optimizer module 144 for each blood component collection device 18. Initially, it should be noted that the optimizer module 144 may be separate from the internal control of the blood component collection device 18 which is accessible by the operator interface module 16. However, typically the optimizer module 144 will be integrated with this internal control along with the above-described prediction model 20.

Referring to Fig. 5, the optimizer assembly 140 will be described with regard to a standard procedure. The central input station 148 will typically be used by blood banks/centers as the primary means for donor data input and donor data management. Information relating to a donor such as sex, height, weight, and demographics will be input at the central input station 148. Moreover, information relating to the donor's hematocrit and a blood component precount, both of which may be obtained from a donor blood sample and determined by known techniques such as cell counters, may also be entered at the central station 148. In addition to donor-related data, the particular type of collection procedure to be used for the donor (e.g., single needle or double needle) may be input/confirmed at the central input station 148. Based upon this information and certain site-standardized conditions (e.g., total procedure time, collection efficiency, AC infusion rate), an initial procedure order is thereafter generated which specifies the various process control parameters associated with the selected collection procedure.

The initial procedure order may be transferred/downloaded onto the internal control of a blood component collection device 18 by a computer disk 142 (Fig. 1) or electronically if a network system is implemented (not shown), through use of the operator interface module 16 if required/desired. When this operator interface module 16 exists, it may of course be used for the initial donor data input and/or to generate the initial procedure

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order and thereby alleviate the need for a central input station 148. However, it may be more efficient to use the central input station. Although this initial procedure order may be used in the collection process, the initial procedure order may be optimized in accordance with principles of the present invention to obtain one or more optimal values for the process control parameters. As noted, this optimization process may be utilized before the collection procedure is actually initiated, but may also be initiated during a given collection procedure and such is referred to as downstream optimization.

With regard to the various optimization options, process control parameters may be derived for a product-based optimization. More particularly, the optimizer assembly 140 and specifically the optimizer module 144 derives process control parameters for achieving a predetermined yield of blood components through a maximization of at least one process parameter as will be discussed below in relation to the optimization models 152 (Fig. 6), 172 (Fig. 7). As noted above, in the United States a single platelet product (SPP) is 3×10^{11} platelets and a double platelet product (DPP) is 6×10^{11} platelets. Consequently, the optimizer module 144 may be configured to provide a number of product-based optimizations such as SPP and DPP. Although the exact values for a current U.S. SPP and DPP could be configured into the optimizer module 144, in order to increase the probability that the actual yield will equal or exceed the yield requirements for a current U.S. SPP or a DPP, the site may configure a SPP to be 3.5×10^{11} platelets and a DPP to be 7.0×10^{11} platelets (e.g., to effectively provide a given confidence level that the specified yield will actually be met).

The optimizer module 144 may also be configured to provide a time-based optimization. That is, for a given amount of time which a donor is available, the optimizer module 144 will derive those process parameters which allow for the collection of a "maximum" amount of platelets in this time period in relation to a maximization of at least one of the process control parameters.

Once the optimization is complete, the values for the various process control parameters generated thereby, as well any ancillary/previously specified values, are downloaded to the internal control of the blood collection device 18 such that the collection procedure may be initiated or reinitiated (downstream optimization) as the case may be in accordance with these values. Once the procedure is completed, certain data is transferrable (via the disk 142 or electronically as noted) back to the central input station 148 for further use with regard to the particular donor. In addition, this information as well as the initial input may be used to generate various types of reports which may further assist in the management of the blood bank/center (e.g., individual run, donor/patient, summary reports). That is, this information may be used in the derivation of subsequent procedure orders for the particular donor. For instance, in the event that a certain AC infusion rate was used in the collection procedure which had certain effects on the donor, this may be recorded in the central input station 148 such that a lower AC infusion rate would be suggested/required for subsequent donations by the donor.

One model which may be incorporated into the optimization module 144 is illustrated in Fig. 6 and will be described with regard to platelet collections in accordance with the dual needle configuration of Fig. 2, although the module 144 may be used with a variety of other collection procedures and including the single needle configuration of Fig. 3, as well as with various other blood components. Initially, it should be noted that all references in Fig. 6 to "derivations" are actually provided by the prediction model 20 discussed above such that there is either an appropriate interface between the prediction model 20 and optimizer module 144 or the optimization module 144 actually includes the prediction model 20. Moreover, as noted the prediction model 20 is specific to the blood component collection device 18 and to platelet collections. Therefore, if other devices are used the associated prediction model would also likely change as noted. Moreover, the associated prediction model may also vary in the case where different blood components such as red blood cells are to be collected.

The optimizer model 152 of Fig. 6 may be used for both product-based and time-based optimizations. Initially, the optimizer model 152 will be described with regard to a product-based optimization. That is, the fundamental premise of the optimization is to achieve a predetermined platelet (or other blood component type) yield (or within a yield range), preferably in the minimum amount of time.

The optimizer model 152 of Fig. 6 is comprised of four iterative loops. Generally, the first loop 156 is a derivation of an inlet flow (Q_{IN}) associated with a specified AC infusion rate (I_{SPEC}) which is typically set at a maximum value for purposes of the present invention and which is entered at the input station 154. This derivation is thereafter performed by the processing station 158 and includes the solution of Eqs. 4, 8, 14, and 16 and/or equations ancillary thereto by the prediction model 20 as discussed above.

There are of course various convergence criterion/criteria which may be incorporated into the first loop 156. For instance, convergence may be based upon the current inlet flow (Q_{IN-C}) in the first loop 156 through use of a binary search technique. In this case, in solving the noted equations at the processing station 158 certain parameters remain fixed in the iterative derivation of the inlet flow (Q_{IN}) which achieves the 'specified AC infusion rate (I_{SPEC}) and these parameters are also specified at input station 154. These include the total blood

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volume (V_B) which can be calculated using Eq. 10 since the donor's height, weight, and sex are entered at the central input station 148, and the AC ratio (R), which can be calculated using Eq. 9 since the donor's hematocrit (H) has been determined, or may be specified at some value. Moreover, the total procedure time (t_P) remains fixed in each iterative derivation of the inlet flow (Q_{IN}) associated with the specified AC infusion rate (I_{SPEC}) in the first loop 156. However, since the total procedure time (t_P) is not known in the case of a product-based optimization and thus cannot be specified at the input station 154, a current total procedure time (t_{P-C}) initially will be assumed (e.g., this assumption is configured in the optimizer model 152 and since a range of total procedure times is provided in the prediction model 20 as noted above, the mean total procedure time (t_P) is typically configured into this portion of the optimizer model 152 as the initial current total procedure time (t_{P-C})). The "current" designation is used for the total procedure time in this case since the optimizer model 152 provides for an adjustment of the total procedure time after each iterative determination of the inlet flow (Q_{IN}) which provides the specified AC infusion rate (I_{SPEC}) in the second loop 160 in order to achieve the desired yield (Y) if required in the case of a product-based optimization as will be discussed in more detail below.

Generally, the inlet flow-based binary search technique convergence may be provided by assuming a current value for the inlet flow (Q_{IN-C}), calculating a current plasma collect factor (P_C) using the current total procedure time (t_{P-C}), calculating a current AC infusion rate (I_C) using the current inlet flow (Q_{IN-C}) and current plasma collect factor (P_C), and adjusting the current inlet flow (Q_{IN-C}) (at the parameter update in the first loop 156) in accordance with the selected binary search technique until there is a predetermined convergence between the two most recent values for the current inlet flow (Q_{IN-C}) (i.e., wherein the difference between the two most recent values of Q_{IN-C} is less than some predetermined amount which means that the convergence criterion is met). In the case of a binary search technique, there will always be convergence (i.e., the convergence criterion will always be met) such that the optimizer model 152 will always exit the first loop 156 and enter the second loop 160.

As an alternative to the noted inlet flow-based convergence criterion/criteria and the noted binary search technique, another possibility is to base convergence on the specified AC infusion rate (I_{SPEC}) and use an iterative derivation to determine the desired inlet flow (Q_{IN}). In this case, the first loop 156 is used to once again iteratively derive the inlet flow (Q_{IN}) which provides the specified AC infusion rate (I_{SPEC}) at the processing station 158 from certain specified parameters. That is, the first loop 156 is still a maximization of the inlet flow (Q_{IN}) based upon the specified AC infusion rate (I_{SPEC}) which should be associated with the donor 14. This is again primarily through the solution of Eqs. 4, 8, 14, and 16 and/or equations ancillary thereto by the prediction model 20 discussed above.

For purposes of solving the above-identified equations in relation to the infusion rate-based convergence criterion, certain parameters remain fixed in the iterative derivation of the inlet flow (Q_{IN}) which achieves the specified AC infusion rate (I_{SPEC}) in the first loop 156 and these parameters are also specified at the input station 154. These include the specified AC infusion rate (I_{SPEC}) which is known and which is typically a maximum value for the donor 14, the total blood volume (V_B) which can be calculated using Eq. 10 since the donor's 14 height, weight, and sex are entered in the central input station 148, and the AC ratio (R) which can be calculated using Eq. 9 since the donor's 14 hematocrit (H) has been determined and input in the central input station 148, or may be entered as modified input data. Moreover, the total procedure time (t_P) remains fixed in each iterative derivation of the inlet flow (Q_{IN}) associated with the specified AC infusion rate (I_{SPEC}). However, once again the total procedure time (t_P) is not known in the case of a product-based optimization and thus cannot be specified at the input station 154. Therefore, a current total procedure time (t_{P-C}) initially will be assumed (e.g., this assumption is configured in the optimizer model 152, and since a range of total procedure times is provided in the prediction model 20 as noted above, the mean total procedure time (t_P) is typically configured into the first loop 156 of the optimizer model 152). The "current" designation for the total procedure time is used for the above-identified reasons relating to the adjustment of the total procedure time in the second loop 160 if required to attain the desired yield (Y).

The solution of Eqs. 4, 8, 14, and 16 also requires that certain values be assumed for certain of the remaining parameters with still other parameters being derived from this assumption. In this case, an iterative procedure is used and updated/current values are used in the next iterative calculation(s). All parameters which change on each iteration of the first loop 156 are identified herein with a "c" subscript to designate that the most current value is to be used. Although the derivation of that inlet flow (Q_{IN}) which provides the specified AC infusion rate (I_{SPEC}) may be accomplished in a variety of manners via Eqs. 4, 8, 14, and 16, one way is to assume a current value for the plasma collect factor (P_C), then calculate the current inlet flow (Q_{IN-C}) using the specified AC infusion rate (I_{SPEC}), then calculate the current yield (Y_C), then calculate the current plasma collection factor (P_C) using the current yield (Y_C), and repeat this procedure with the current values until there has been acceptable convergence on the current inlet flow (Q_{IN-C}) in relation to the specified AC infusion rate (I_{SPEC}) (e.g., when the particular convergence criterion/criteria is met/established). When there is acceptable

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infusion rate-based convergence, the optimizer model 152 exits the first loop 156 and enters the second loop 160. In order to offer protection for cases when there is no such convergence, a maximum number of iterations for the first loop 156 may be specified (not shown).

The second loop 160 of the optimizer model 152 is a total procedure time (t_P) iteration. That is, the second loop 160 is an iterative adjustment of the current total procedure time (t_{P-C}). Initially, in the second loop 160 and in the case of a product-based optimization the model 152 will never exit at the first comparator 162 since a total procedure time (t_P) is not specified at the input station 154. Consequently, the optimizer model 152 proceeds to the second comparator 166 where convergence criteria (i.e., more than one check) is made. One convergence criterion which is checked at the second comparator 166 is whether the current yield (Y_C) is greater than or equal to the desired and specified yield (Y). In this case, the current yield (Y_C) may be calculated based upon the values specified at the input station 158, values derived at the processing station 158, and the current total procedure time (t_{P-C}) for comparison with the desired and specified yield (Y) (in some cases, this current yield calculation (Y_C) may have been performed in the first loop 156 and need not be repeated in the second loop 160). If the yield convergence criterion is met, the model 152 exits the second loop 160 and actually exits all the way through to the exit 151, as will be discussed below. In this case, the specified/derived values are "optimal" and the collection procedure could be performed on the device 18 using the noted values for the various control parameters.

In the event that the yield-based criterion is not met at second comparator 166, the second comparator 166 looks to a total procedure time-based convergence criterion which may be similar to that discussed above with regard to the inlet flow-based criterion (e.g., using a binary search technique with the convergence criterion then being a predetermined difference between the two most current values of the total procedure time (t_{P-C})). On the first time through the second loop 160 after the noted yield-based convergence criterion has failed and the total procedure time convergence criterion has failed, the current total procedure time (t_{P-C}) is adjusted and the model 152 returns to the first loop 156. That is, each time that the current total procedure time (t_{P-C}) is adjusted in the second loop 160, the entirety of the first loop 152 is repeated (i.e., a new inlet flow (Q_{IN}) associated with the specified AC infusion rate (I_{SPEC}) is derived using the current total procedure time (t_{P-C}) provided by the adjustment in the second loop 160). Other convergence criterion/criteria could be used in the second loop 160, such as specifying a maximum number of iterations to be performed by the second loop 160.

In the event that the yield-based convergence criterion is not met on the second loop 160 and the total procedure time-based convergence criterion is met at the second comparator 166 in the second loop 160, the optimizer model 152 exits the second loop 160 and enters the third loop 164. The third loop 164 is an iterative adjustment of the AC ratio (R). However, the model 152 initially enters the third comparator 169 where convergence criteria (i.e., more than one) are checked. One convergence criterion is again the above-noted yield-based convergence criterion. If this yield-based convergence criterion is again not met, an AC ratio-based convergence criterion is checked at the third comparator 169. This may be similar to the inlet flow-based criterion discussed above (e.g., using a binary search technique with the convergence criterion being the two most current values of the AC ratio). On the first time through the third loop 164 after the yield-based criterion has failed and the AC ratio-based convergence criterion has failed, the AC ratio is adjusted and the optimizer model 152 returns to the first loop 152. That is, each time that the AC ratio (R) is adjusted in the third loop 164, the entirety of the first and second loops 156, 160, respectively, is repeated. Other convergence criterion/criteria could be used in the third loop 164, such as specifying a maximum number of iterations of the third loop 164.

In the event that the yield-based convergence criterion is not met in the second or third loops 160, 164, respectively, and the second and third comparator 166, 169, respectively, and the AC ratio-based convergence criterion is met at the third comparator 169 in the third loop 164, the optimizer model 152 exits the third loop 164 and enters the fourth loop 168. The fourth loop 168 is an iterative adjustment of the specified AC infusion rate (I_{SPEC}). However, the optimizer model 152 initially enters the fourth comparator 170 where convergence criteria (i.e., more than one) are checked. One convergence criterion is the noted yield-based convergence criterion. If the noted yield-based convergence criterion is not met at the fourth comparator 170, an AC infusion rate-based criterion is checked at the fourth comparator 170. This may be similar to the inlet-flow based criterion discussed above (e.g., using a binary search technique with the convergence criterion being the two most current values of the AC infusion rate). On the first time through the fourth loop 168 after the yield-based criterion has failed and the AC infusion rate-based convergence criterion has failed, the AC infusion rate is adjusted and the model 152 returns to the first loop 152. That is, each time that the specified AC infusion rate (I_{SPEC}) is adjusted, the entirety of the first, second and third loops 156, 160, 164, respectively, is repeated (with the AC ratio set back to its initial value as entered at the input station 154 on each iteration of the fourth loop 168). Other convergence criterion/criteria could be used in the fourth loop 168, such as specifying a maximum number of iterations of the fourth loop 168. In cases where the specified AC infusion rate (I_{SPEC}) is actually the maximum AC infusion rate, typically the fourth loop 168 will execute only a single time with a one-time

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increase in the AC infusion rate of, for instance, 20% (e.g., may be site-configured).

In the foregoing loops where a yield-based convergence criteria are identified, when the criteria are met the optimizer model 152 exits to exit 151 and the specified/derived (i.e., current) values for the various process control parameters may be provided to the device 18 for performing the collection procedure. However, there may be cases where no optimization occurs, such as when the optimizer model 152 exits to the exit 151 based upon the AC infusion rate based convergence criterion being met.

The optimizer model 152 may also be used for a time optimization. That is, the optimizer model will derive optimal process parameters for a predetermined total procedure time (t_P) through maximization of at least one of the process parameters in order to maximize the platelet collection (or for other blood component types). In this case, the optimizer model 152 only executes the first loop 156 to derive the inlet flow (Q_{IN}) associated with a specified AC infusion rate (I_{SPEC}) (typically a maximum value) using the input total procedure time (t_P) in this iterative derivation instead of the assumed total procedure time (t_P) referenced above. Once there is acceptable convergence as defined above in the product-based optimization such that model 152 exits the first loop 156, the current yield (Y_C) may be calculated in the first loop 156 (but again may already have been calculated in the first loop 156 at the processing station 158 such that no further calculation is required) and the convergence criterion will be met at the first comparator 162 when entering the second loop 160 (i.e., in a time-based optimization when a total procedure time is specified at the input station 154, the model 152 will exit when entering the second loop 158). As a result, the inlet flow (Q_{IN}) and AC infusion rate (I) will be optimal and the collection procedure may be performed with such values.

Another optimization model is presented in Fig. 7 and may be used for both product-based and time-based optimizations. As in the case of the optimizer model 152, the optimizer model 172 may interface with the prediction model 20 or actually integrally incorporate the prediction model 20, and thus reference to Eqs. 1-22 will be further made herein. Generally, the optimizer model 172 is based upon the principle that optimization occurs when an optimal inlet flow (Q_L) associated with an optimum system collection efficiency is used in the derivation of various process control parameters. Referring to Fig. 8, a representative inlet flow (Q_{IN})/yield (Y) curve is presented to show the optimal inlet flow (Q_L) associated with the maximum yield (Y_{MAX}). This optimal inlet flow (Q_L) is mathematically expressed by Eq. 23 presented below which results from differentiating Eq. 4 of the prediction model 20 with regard to the inlet flow (Q_{IN}). As can be appreciated, where different algorithms are used in the associated prediction model (whether based upon collection of blood components other than platelets, different collection apparatus, or alternative derivations of the various parameters with the same collection procedure and apparatus), the optimal inlet flow may be mathematically expressed in a different manner.

$$Q_L = \left(\frac{C_1}{2C_2}\right) e^{-9.91(1-1/R)H} - C_3 \qquad \text{(Eq. 23)}$$

$$C_3 = \frac{1}{2(t_P/K_7 - 1/K_9)}, \quad \begin{matrix} Q_o \geq 45 \text{ for Dual Needle ("DN")} \\ \geq 20 \text{ for Single Needle ("SN")} \end{matrix} \qquad \text{(Eq. 24)}$$

$$= 0, \quad \begin{matrix} Q_o < 45 \text{ for DN} \\ < 20 \text{ for SN} \end{matrix} \qquad \text{(Eq. 25)}$$

$$K_7 = \begin{matrix} 500 \ (DN) \\ 215 \ (SN) \end{matrix} \qquad K_9 = \begin{matrix} 45 \ (DN) \\ 20 \ (SN) \end{matrix} \qquad \text{(Eq. 26)}$$

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$$C_1 = 0.803 \ (SN, \ DN \ without \ stepdown) \\ = 0.840 \ (DN \ with \ stepdown) \qquad \text{(Eq. 27)}$$

$$C_2 = 4.08 \ x \ 10^{-5} \ (DN) \\ = 8.54 \ x \ 10^{-5} \ (SN) \qquad \text{(Eq. 28)}$$

Based upon the foregoing, the optimal inlet flow (Q_L) is really "optimal" in terms of the collection apparatus.

Referring again to Fig. 7, the optimizer model 172 will initially be described with regard to a product-based optimization wherein the desired yield (Y) is specified at input station 184. Generally, the inlet flow (Q_{IN}) associated with a specified AC infusion rate (I_{SPEC}) (typically the maximum AC infusion rate and also specified at input station 184) is iteratively derived from certain other specified parameters. This inlet flow calculation, particularly when the maximum AC infusion rate (I_{MAX}) and maximum AC ratio (R_{MAX}) are specified, the inlet flow (Q_{IN}) is optimal based on the physiological considerations of the donor 14. This is primarily through the solution of Eqs. 4, 8, 14, and 16 and/or equations ancillary thereto by the prediction model 20 discussed above. For purposes of solving these equations certain parameters remain fixed in the iterative derivation of the inlet flow (Q_{IN}) which achieves the specified AC infusion rate (I_{SPEC}) and these parameters are also specified at input station 184. These include the total blood volume (V_B) which can be calculated using Eq. 10 since the donor's height, weight, and sex are entered in the central input station 148, and the AC ratio (R), which can be calculated using Eq. 9 since the donor's hematocrit (H) has been determined, or may be specified at some maximum value. Moreover, the total procedure time (t_P) remains fixed in each iterative derivation of the inlet flow (Q_{IN}) associated with the specified AC infusion rate (I_{SPEC}). However, since the total procedure time (tP) is not known in the case of a product-based optimization and thus cannot be specified at the input station 184, a current total procedure time (t_{P-C}) initially will be assumed (e.g., this assumption is configured in the optimizer model 172 and since a range of total procedure times is provided in the prediction model 20 as noted above, the mean total procedure time (t_P) is typically configured into this portion of the optimizer model 172 as the initial current total procedure time (t_{P-C})). The "current" designation is used for the total procedure time in this case since the optimizer model 172 provides for an adjustment of the total procedure time after each iterative determination of the inlet flow (Q_{IN}) which provides the specified AC infusion rate (I_{SPEC}) in order to achieve the desired yield (Y) if required in the case of a product-based optimization as will be discussed in more detail below.

The solution of Eqs. 4, 8, 14, and 16 also requires that certain values initially be assumed for certain of the remaining parameters. In this case, an iterative procedure is used in the solution of the yield equation (Eq. 4) (and including equations ancillary thereto as noted above) and updated values are used in the next iterative calculation(s) at the processing station 188. Although the derivation of that inlet flow (Q_{IN}) which provides the specified (typically maximum) AC infusion rate (I_{SPEC}) may be accomplished in a variety of manners via Eqs. 4, 8, 14, and 16, one way is to assume a current value for the plasma collect factor (P), then calculate the current inlet flow (Q_{IN-C}) using the specified AC infusion rate (I_{SPEC}), then calculate the current yield (Y_C), then calculate the current plasma collection factor (P_C) using the current yield (Y_C), and repeat the foregoing with the updated parameters, all within the processing station 188, until there has been acceptable convergence on the current inlet flow (Q_{IN-C}) in relation to the specified AC infusion rate (I_{SPEC}).

In addition to the calculation of the current inlet flow (Q_{IN-C}) associated with the specified AC infusion rate (I_{SPEC}), the above-discussed optimal inlet flow (Q_L) is calculated at processing station 192. Consequently, a comparison can be made between the current inlet flow (Q_{IN-C}) which was derived in the above-described manner and the optimal inlet flow (Q_L) at the first comparator 176. If the current inlet flow (Q_{IN-C}) is less than the optimal inlet flow (Q_L) at the first comparator 176, the specified values for the various parameters associated with the inlet flow Q_{IN} are "optimum", namely the AC ratio (R) and the AC infusion rate (I) specified at the input station 184. Thereafter, the current yield (Y_C) (which was calculated in the derivation of the current inlet flow (Q_{IN-C}) associated with the specified AC infusion rate (I_{SPEC}) at the processing station 188) is compared with the input yield (Y) at second comparator 180. In the event that there has been acceptable convergence between these yield values, the current total procedure time (t_{P-C}) is also "optimal". However, in the event that there has not been acceptable convergence between these yield values, the current total procedure time (t_{P-C}) is adjusted at adjusting station 196 and the foregoing iterative derivation of the current inlet flow (Q_{IN-C}) associated with the specified AC infusion rate (I_{SPEC}) is repeated until such convergence is achieved (i.e., using the initially specified AC infusion rate (I_{SPEC}) and the now adjusted current total procedure time (t_{P-C}, a new current inlet flow (Q_{IN-C}) is iteratively derived in the above-described manner).

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Referring back to the first comparator 176, if the current inlet flow (Q_{IN-C}) associated with the specified AC infusion rate (I_{SPEC}) derived at processing station 188 is greater than the optimal inlet flow (Q_L), a current AC infusion rate (I_C) associated with this particular inlet flow (Q_L) is iteratively derived at the processing station 188 generally in the above-described manner (i.e., the initially specified AC infusion rate (I_{SPEC}) is disregarded in this derivation and a current AC infusion rate (I_C) is iteratively derived to coincide with the inlet flow (Q_L)). In this case, the current inlet flow (Q_{IN-C}) will always be equal to the optimal inlet flow (Q_L) at the first comparator 176 and the optimizer model 172 thereafter proceeds to the second comparator 180 for the yield comparison in accordance with the above-described procedure.

The optimizer model 176 may also be used for a time-based optimization. In this case, the total procedure time (t_P) is specified at the input station 184 as a specified total procedure time (t_{P-SPEC}) and thus is not assumed as in the product-based optimization. The optimizer model 172 thereafter proceeds in the same manner discussed above with regard to the product-based optimization except at the second comparator 180. Since no yield was input there is no yield comparison made at the second comparator 180. Instead a total procedure time comparison is made at the second comparator 180. Since the current total procedure time (t_{P-C}) was set equal to the specified total procedure time (t_{P-SPEC}) prior to the model 172 proceeding to the processing station 188 in this time-based optimization, the model 172 will exit each time at the second comparator for a time-based optimization.

In addition to the above-described product-based and time-based optimizations, the principles of the present invention may be extended to other applications relating to enhancing blood component system management. For instance, an optimization in accordance with principles of the present invention may be extended to encompass donor management issues. In one such case, another "optimization" associated with the blood component collection process would be to collect blood components as dictated by existing inventory (i.e., use optimization as dictated by existing inventory (i.e., use optimization as an inventory control). That is, information relating to the inventory of the various types of blood components in the blood bank/center and/or the demand for one or more blood component types could be maintained such that specific collection procedures could be selected to accommodate for a low supply of a given blood component type and/or a high demand for such blood component type. More specifically, in the event that the supply of red blood cells was low and/or the demand for red blood cells was high, or anticipated to be so in the near future, prompts could be provided to operators that red blood cells should be selected for collection if possible from donors during a given time period. Relatedly, the optimization principles of the present invention would be applicable to maintaining data on blood component collections from a given donor such that a determination could be made as to what type or types of blood components from the particular donor provided the maximum yield in the collection procedure. That is, information could be collected and maintained from prior blood component donations such that a determination could be made for a specific donor as to which type or types of blood components the donor has had a propensity to produce maximum yields therefor.

Notwithstanding the foregoing description of the present invention in relation to an on-line blood component collection process, those skilled in the art will appreciate that the source of blood may be provided to the blood component collection device from an appropriate blood container (not shown) interconnected with the blood component collection device 18 versus receiving such directly from the donor. Moreover, the blood of course may be provided from alternative sources such as animals. Furthermore, as illustrated in Fig. 3 the described platelet harvesting procedure may be performed utilizing a single needle configuration. In addition, the present invention is applicable to the collection of other types of blood components such as red blood cells, white blood cells, and/or plasma, and is further applicable to the simultaneous collection of more than one blood component type. In the case of red blood cell collection and optimization in accordance with principles of the present invention, the donor's blood type should be known and used in various algorithms. Moreover, the present invention is not limited to the source being whole blood. That is, the principles of the present invention may be applicable to removal of a component from any liquid.

The foregoing description of the present invention has been presented for purposes of illustration and description. Furthermore, the description is not intended to limit the invention to the form disclosed herein. Consequently, variations and modifications commensurate with the above teachings, and skill and knowledge of the relevant art, are within the scope of the present invention. The embodiments described hereinabove are further intended to explain best modes known of practicing the invention and to enable others skilled in the art to utilize the invention, and such other embodiments, and with various modifications required by the particular applications or uses of the present invention. It is intended that the appended claims be construed to include alternative embodiments to the extent permitted by the prior art.

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Claims

1. A method for collecting at least one predetermined type of blood component from a source of whole blood using a blood component collection system comprising a blood component collection device and collection procedure, said collection procedure having a plurality of parameters associated therewith, **characterized in that** said method comprises the steps of:

providing biological data relating to said source;

identifying a desired yield of said at least one predetermined blood component;

associating a magnitude with each of said parameters, said associating step comprising performing a first deriving step comprising deriving a magnitude for at least one of said parameters from said providing and identifying steps;

inputting said magnitude of each said parameter into said blood component collection system after said associating step; and

performing said collection procedure on said blood component collection device using said inputting step to collect said desired yield of said at least one predetermined blood component from said source of whole blood.

2. A method as claimed in Claim 1, **characterized in that:**

said source is a human donor and said biological data comprises said donor's hematocrit, height, weight, and sex.

3. A method as claimed in Claim 1 or 2 **characterized in that:**

one of said parameters is an inlet flow to said blood collection device and another of said parameters is a flow of anticoagulant into said blood component collection system, wherein said inlet flow comprises a flow of whole blood from said source and said flow of anticoagulant, wherein said source of said blood has a volume, wherein at least part of said flow of anticoagulant is provided to said source, wherein an AC ratio is a ratio of said inlet flow to said flow of anticoagulant, and wherein an AC infusion rate is said at least part of said flow of anticoagulant per said volume.

4. A method as claimed in any one of Claims 1-3 **characterized in that** said performing a first deriving step further comprises:

deriving said magnitude of said inlet flow associated with a predetermined magnitude of said AC infusion rate.

5. A method as claimed in Claim 4, **characterized in that** said deriving said magnitude of said inlet flow step comprises:

using said predetermined magnitude of said AC infusion rate and a current magnitude for a total procedure time, said total procedure time being another of said parameters.

6. A method as claimed in Claim 5, **characterized in that** said deriving said magnitude of said inlet flow step further comprises:

assuming a current magnitude for said inlet flow and performing a first iteration procedure comprising calculating a current magnitude for said AC infusion rate from at least said current magnitude of said inlet flow, evaluating convergence criteria relating to said current magnitude of said inlet flow, and adjusting said current magnitude of said inlet flow and repeating said first iteration procedure until said convergence criteria is established.

7. A method as claimed in Claim 5 or 6 **characterized in that:**

said deriving said magnitude of said inlet flow step comprises:

deriving a current magnitude for said AC infusion rate, said performing a first deriving step further comprising iteratively calculating a current blood component yield using at least said current magnitude of said inlet flow and said current magnitude of said AC infusion rate and by using said providing step and by iteratively adjusting said magnitude of said current total procedure time until achieving said desired yield of blood components.

8. A method as claimed in any one of Claims 5-7 **characterized in that:**

said deriving said magnitude of said inlet flow step comprises:

deriving a current magnitude for said AC infusion rate, said performing a first deriving step further comprising performing a second iteration procedure after said deriving said magnitude of said inlet flow

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step, said second iteration procedure step comprising calculating a current yield from said current magnitude of said inlet flow, said current magnitude of said AC infusion rate, and said current magnitude of said procedure time, comparing said current yield with said desired yield, performing said inputting step after said comparing step when said current yield is within a predetermined amount of said desired yield, adjusting said current magnitude of said total procedure time when said current yield differs from desired yield by more than said predetermined amount, repeating said deriving a magnitude of said inlet flow step after said adjusting said current magnitude of said total procedure time step, and repeating said second iteration procedure step after said repeating said second iteration procedure step until predetermined convergence criteria relating to said current total procedure time is established.

9. A method as claimed in any one of Claims 5-9, **characterized in that:**

said performing a first deriving step further comprises deriving a total procedure time after said deriving said magnitude of said inlet flow step which provides a current yield within a predetermined amount of said desired yield, said total procedure time being another of said parameters.

10. A method as claimed in Claim 8 or 9 **characterized in that:**

said performing a first deriving step further comprises:

performing a third iteration procedure after said second iteration procedure step and when said convergence criteria associated with said second iteration procedure is established, said third iteration procedure step comprising adjusting said magnitude of said AC ratio, repeating said first and second iteration procedure steps, and repeating said third iteration procedure step until predetermined convergence criteria relating to said magnitude of said AC ratio is established.

11. A method as claimed in Claim 10, **characterized in that:**

said maximum AC infusion rate is increased by a predetermined amount when said convergence criteria associated with said third iteration procedure step is established, wherein said performing a first deriving step further comprises repeating said first, second, and third iteration procedure steps using said increased AC infusion rate.

12. A method as claimed an any one of Claims 3-11 **characterized in that:**

said associating step comprises selecting a maximum magnitude for said AC infusion rate, and wherein said associating step further comprises generating a calculated magnitude of said inlet flow using at least said maximum magnitude of said AC infusion rate.

13. A method as claimed in Claim 12, **characterzied in that:**

said performing a first deriving step further comprises:

calculating a theoretical magnitude of said inlet flow which provides a maximum yield of said at least one predetermined blood component and comparing said theoretical and calculated magnitudes of said inlet flow, and wherein said inputting step comprises inputting the lesser of said theoretical magnitude and said calculated magnitude of said inlet flow.

14. A method as claimed in Claim 13, **characterized in that:**

another of said parameters is a total procedure time, wherein a current magnitude for said total procedure time is assumed, and wherein said performing a first deriving step further comprises performing a first iteration procedure, said performing a first iteration procedure step comprising calculating a current blood component yield using the lesser of said calculated and theoretical magnitudes of said inlet flow of whole blood, said current magnitude of said total procedure time, and said maximum AC infusion rate, comparing said current blood component yield with said desired blood component yield, and repeating said first iteration procedure using an adjusting current total procedure times until said current magnitude of said blood component yield is within a predetermined amount of said desired blood component yield.

15. A method as claimed in Claim 13, **characterized in that:**

another of said parameters is a total procedure time and said performing a first deriving step further comprises assuming a current magnitude for said total procedure time and performing a first iteration procedure, said performing a first iteration procedure step comprising calculating a current yield from the lesser of said actual and theoretical magnitudes of said inlet flows, said maximum AC ratio, and said maximum AC infusion rate, and said current magnitude of said procedure time, comparing said current yield with said desired yield, incrementally adjusting said current magnitude of said total procedure time when

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said current yield differs from desired yield by more than a predetermined amount, and repeating said first iteration procedure step until at least one of a first and second condition is satisfied, said first condition being that said current yield is within said first predetermined amount of said desired yield and said second condition being that said second iteration procedure step has been performed a predetermined number of times.

16. A method, as claimed in any one of Claims 3-15 **characterized in that:**
said at least one of said parameters is a total procedure time, said performing a first deriving step comprising maximizing said inlet flow and minimizing said total procedure time.

17. A method, as claimed in any one of Claims 1-16, **characterized in that:**
providing a magnitude for each of said parameters before said identifying step;
performing said collection procedure on said blood component collection device before said identifying step, using said providing a magnitude step, and for a first time period, wherein said associating step is performed after expiration of said first time period.

18. A method, as claimed in any one of Claims 1-17 **characterized in that:**
one of said parameters is a total procedure time, and wherein said performing a first deriving step comprises minimizing said magnitude of said total procedure time based upon said magnitude of at least one of said parameters other than said total procedure time.

19. A method, as claimed in Claim 18, **characterized in that:**
one of said parameters is an inlet flow to said blood collection device and another of said parameters is a flow of anticoagulant into said blood component collection system, wherein said inlet flow comprises a flow of whole blood from said source and said flow of anticoagulant, wherein said blood within from said source has a volume, wherein at least part of said flow of anticoagulant is provided to said source, wherein an AC ratio is a ratio of said inlet flow to said flow of anticoagulant, wherein an AC infusion rate is said at least part of said flow of anticoagulant per said volume, and wherein said at least one of said parameters associated with said minimizing step comprises said magnitude of said AC infusion rate and said magnitude of said inlet flow.

20. A method, as claimed in any one of Claims 1-19, **characterized in that:**
said associating step comprises optimizing said magnitude of at least one of said parameters.

21. A method for collecting a blood component from a source of whole blood using a blood component collection system comprising a blood component collection device and collection procedure, wherein an inlet flow to said blood component collection system comprises a flow of whole blood from said source and a flow of anticoagulant, said method **characterized in that** it comprises the steps of:
identifying a total procedure time for said collection procedure;
deriving a first inlet flow to said collection system which provides a maximum yield of said blood components;
deriving a second inlet flow to said collection system using at least said identifying a total procedure time step;
identifying a smallest magnitude of said first and second inlet flows as an actual inlet flow to said blood component collection system; and
performing said collection procedure with said blood component collection device, using said actual inlet flow, and for said total procedure time to collect said blood components from said source of whole blood.

22. A method, as claimed in Claim 21, **characterized in that:**
said blood within said source has a volume, wherein at least part of said flow of anticoagulant is provided to said volume, wherein an AC ratio is a ratio of said inlet flow to said flow of anticoagulant, wherein an AC infusion rate is said at least part of said flow of anticoagulant per said volume, and wherein said deriving a second inlet flow step further uses a maximum AC ratio and a maximum AC infusion rate.

23. A method for collecting a blood component from a donor using a blood component collection system comprising a blood component collection device and a collection procedure, said collection procedure comprising a plurality of parameters, **characterized in that** said method comprises the steps of:
providing biological data relating to said donor;

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associating a magnitude with each said control parameter based upon at least said providing step;

optimizing said magnitude of at least one of said control parameters in relation to both donor constraints and system constraints, said optimizing step allowing for achieving at least one of first and second conditions, said first condition being collecting a predetermined quantity of said blood components in a minimum amount of time and said second condition being collecting a maximum quantity of said blood components in a predetermined amount of time;

inputting said magnitudes of said parameters into said blood component collection device after said optimizing step; and

performing said collection procedure on said blood component collection device using said parameters to collect said blood components from said donor to achieve at least one of said first and second conditions.

24. A blood component collection control and information communication system used in conjunction with a blood component collection device in a procedure performed on a donor to separate, remove and collect components from blood received from the donor, comprising:

an information communication medium;

a first station interactive with the communication medium to transmit and receive information on the medium describing biological data of the donor, describing process parameters for controlling the collection device during the procedure performed on the donor, describing physical and medical characteristics of the donor observed during performance of a prior procedure on the donor, and describing the yield of at least one component obtained from the donor during performance of the procedure; the first station including an information input device by which to supply donor data, process parameters, prior procedure characteristics and component yield information to communication medium; the first station further including a computer responsive to the donor data, prior procedure characteristics and component yield information received from the communication medium to determine at least one process parameter to be used for controlling the blood component collection device during performance of a subsequent procedure on the donor; and the first station also including a display by which to display the donor data, process parameters, prior procedure characteristics and component yield information;

a second station interactive with the communication medium to transmit and receive information on the medium describing biological data of the donor, describing process parameters for controlling the collection device during the procedure performed on the donor, describing physical and medical characteristics of the donor observed during performance of a prior procedure on the donor, and describing the yield of at least one component obtained from the donor during performance of a procedure; the second station including an information input device by which to supply donor data, process parameters, prior procedure characteristics and component yield information to communication medium; the second station further including a computer responsive to the donor data, prior procedure characteristics and component yield information received from the communication medium to determine at least one process parameter to be used for controlling the blood component collection device during performance of a subsequent procedure on the donor; and the second station also including a display by which to display the donor data, process parameters, prior procedure characteristics and component yield information; and

an interface of at least one of the first or second stations which connects to the blood component collection device to the one station, the interface adaptable for controlling the blood collection device to perform the procedure in response to the process parameter information transmitted to the one station by the communication medium; the interface further supplying information to the medium at the one station describing the yield of at least one component obtained from the donor during performance of the procedure performed.

25. A method of controlling a blood component collection device in a procedure performed on a donor to separate, remove and collect components from blood received from the donor and for communicating information describing the procedure, comprising the steps of:

establishing first and second stations, each of which includes a computer, an information input device and a display;

connecting one of the first and second stations to the blood component collection device;

communicating information between the first and second stations which describes biological data of the donor, process parameters for controlling the collection device during the procedure performed on the donor, physical and medical characteristics of the donor observed during performance of a prior procedure on the donor, and the yield of at least one component obtained from the donor during performance of the procedure;

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using the information input device at either the first or the second station to create at least some of one of the donor data information, the process parameter information, the prior procedure characteristics information and the component yield information;

deriving at least some of the process parameter information by processing the donor data, prior procedure characteristics and component yield information with the computer at one of the first or second stations; and

controlling the operation of the blood component collection device in response to the process parameter information which was communicated, created by using the information input device and derived from the computer.

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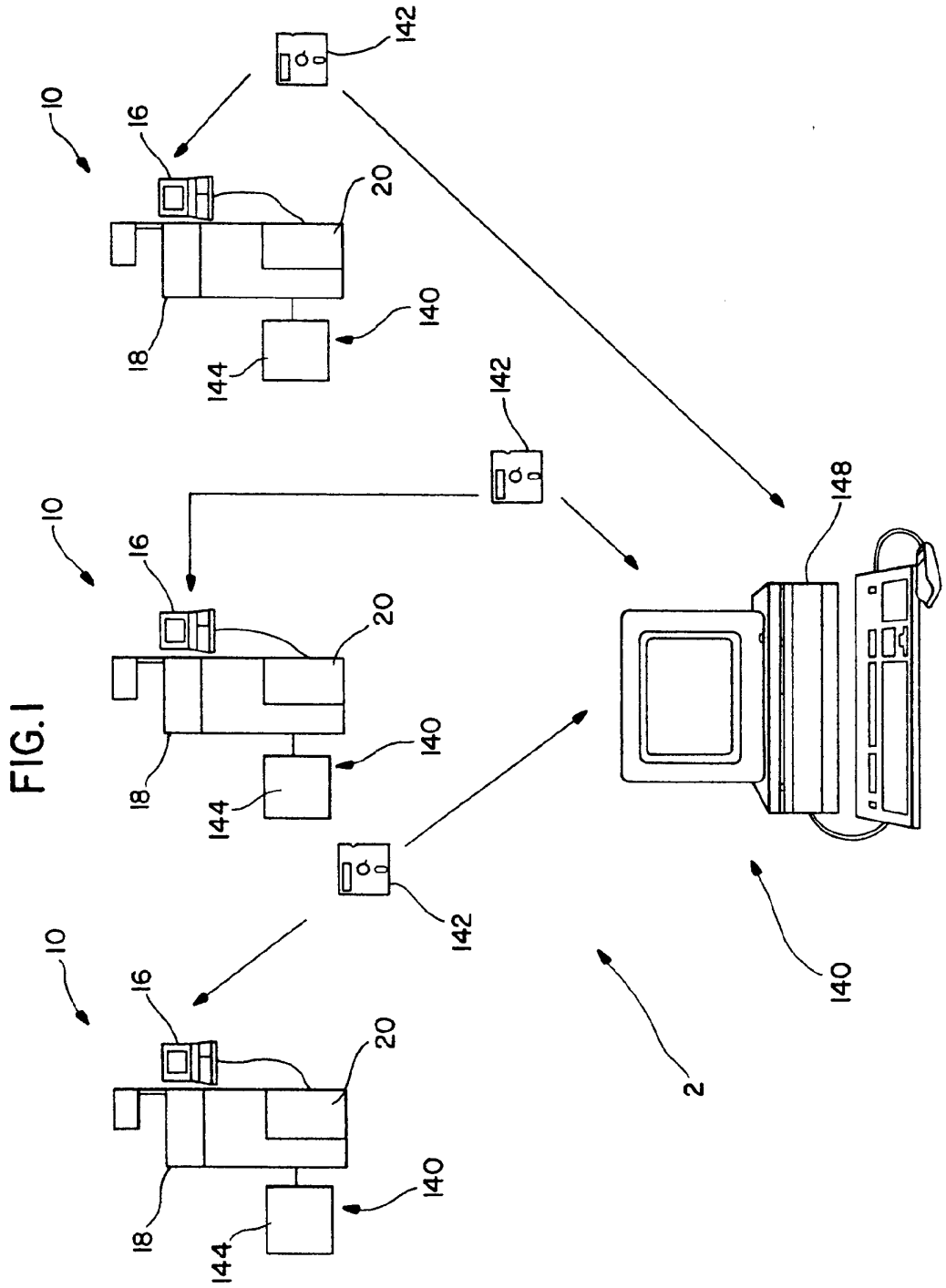


FIG. 1

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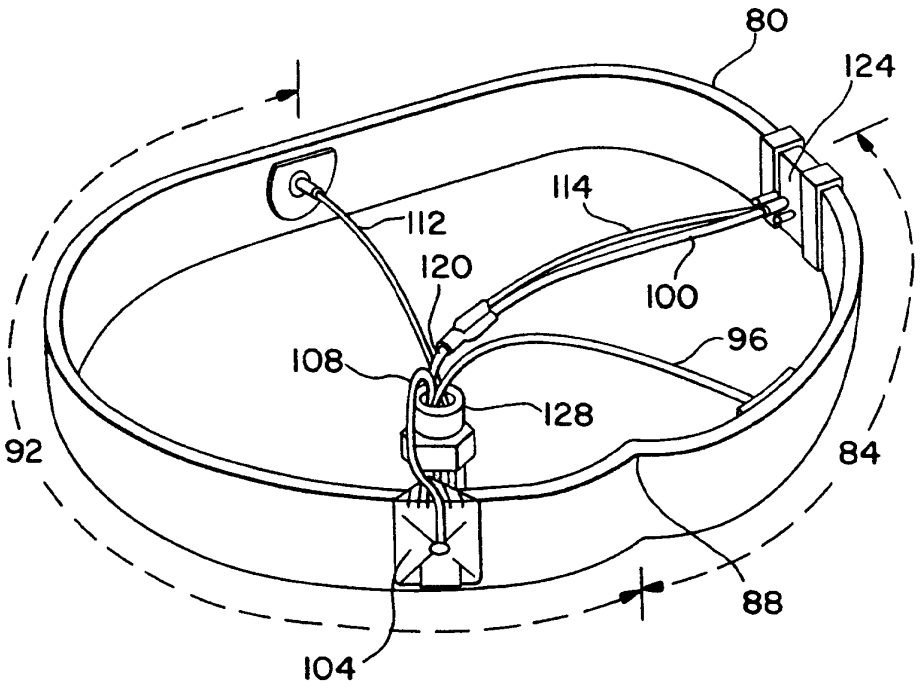
FIG.2

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FIG.3

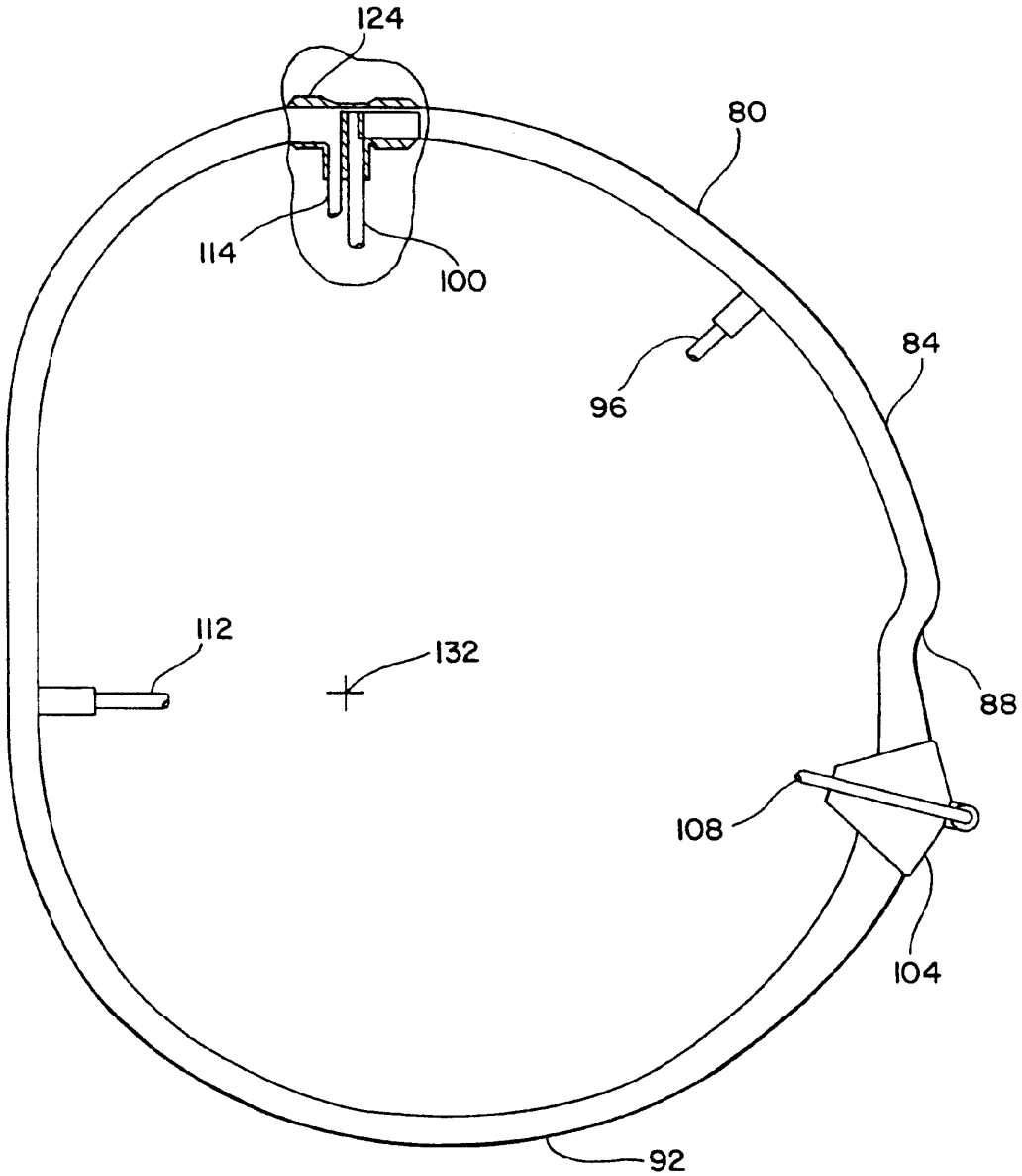
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FIG. 4A



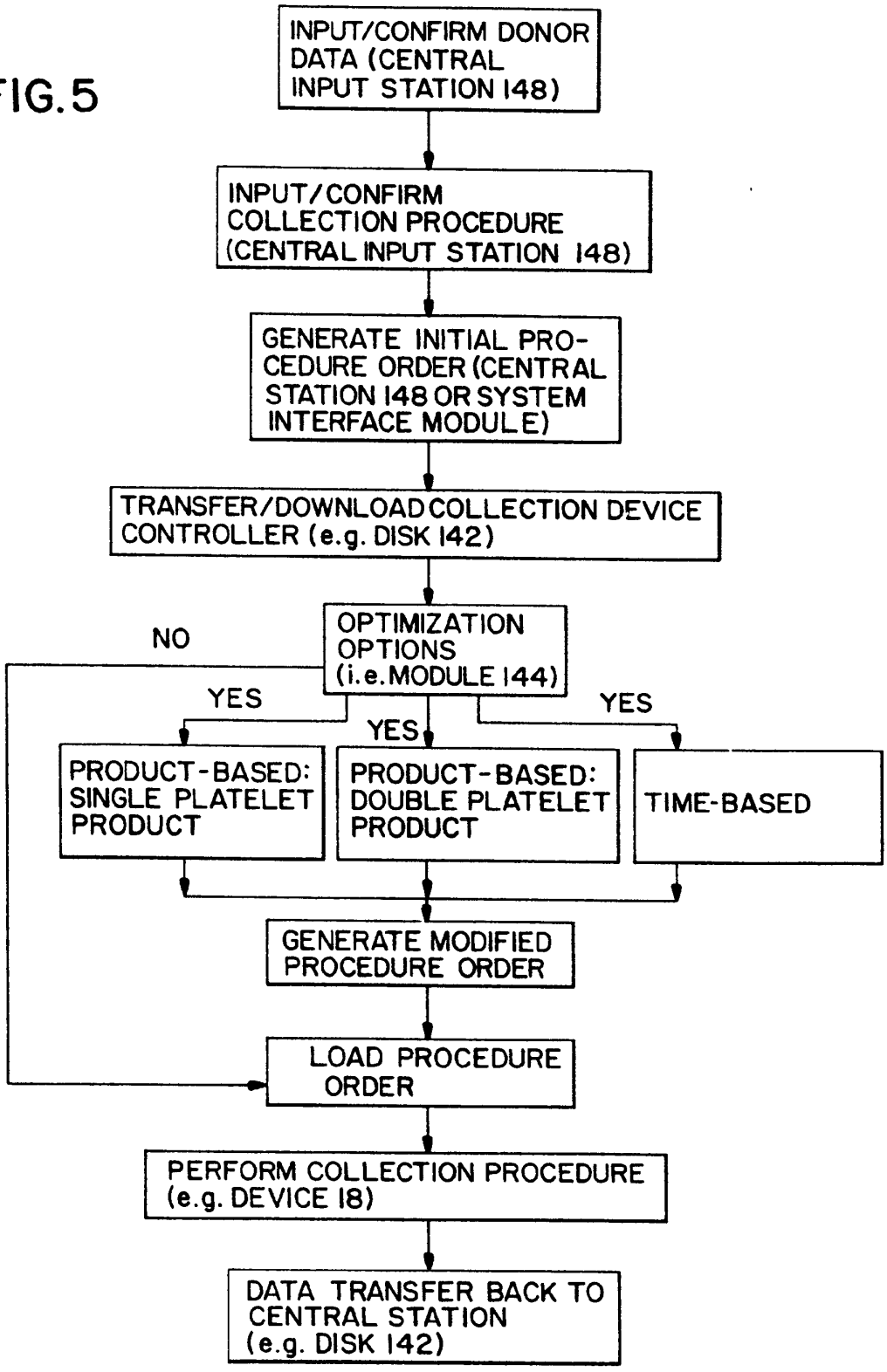
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FIG. 4B



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FIG.5

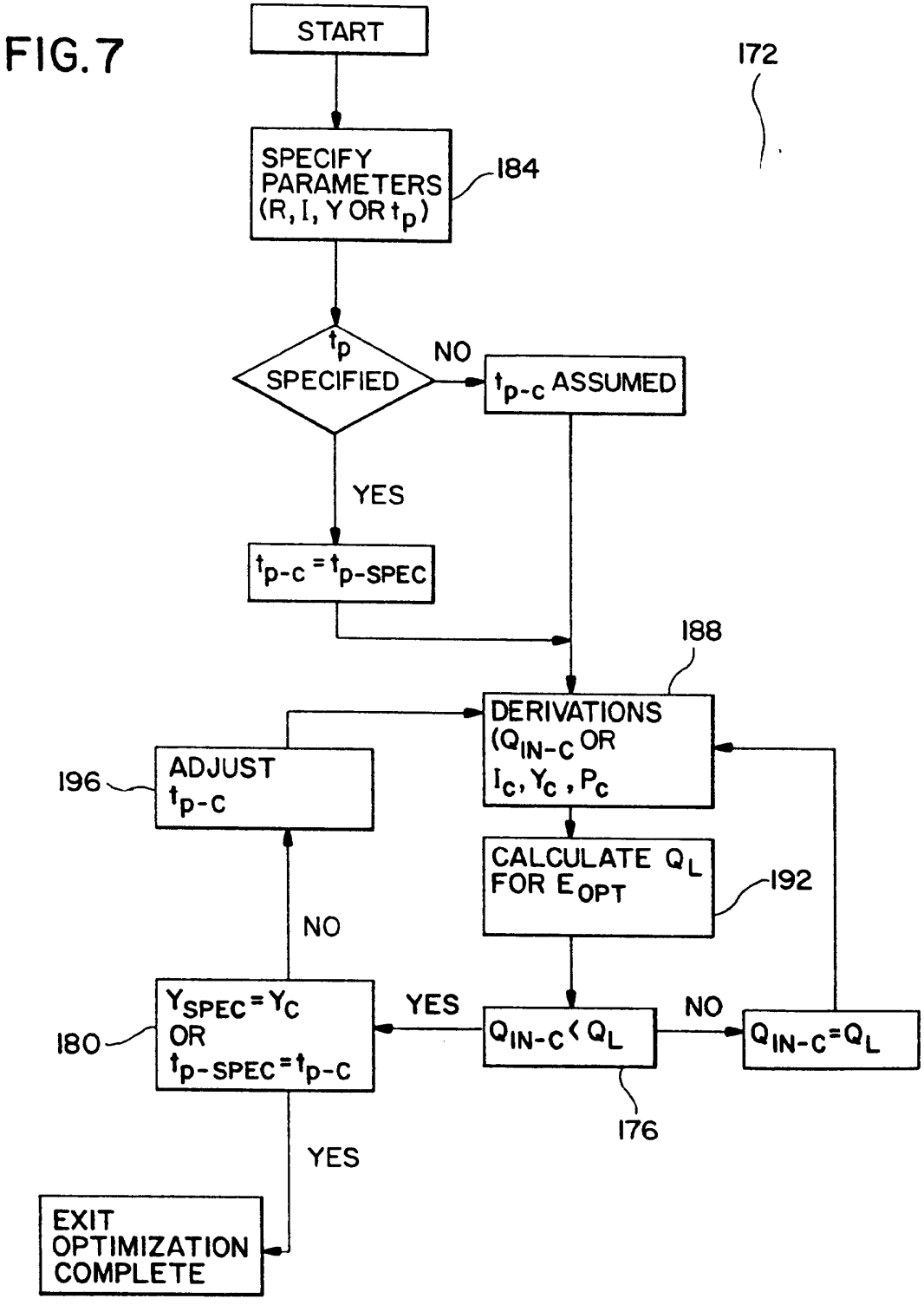


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FIG.6

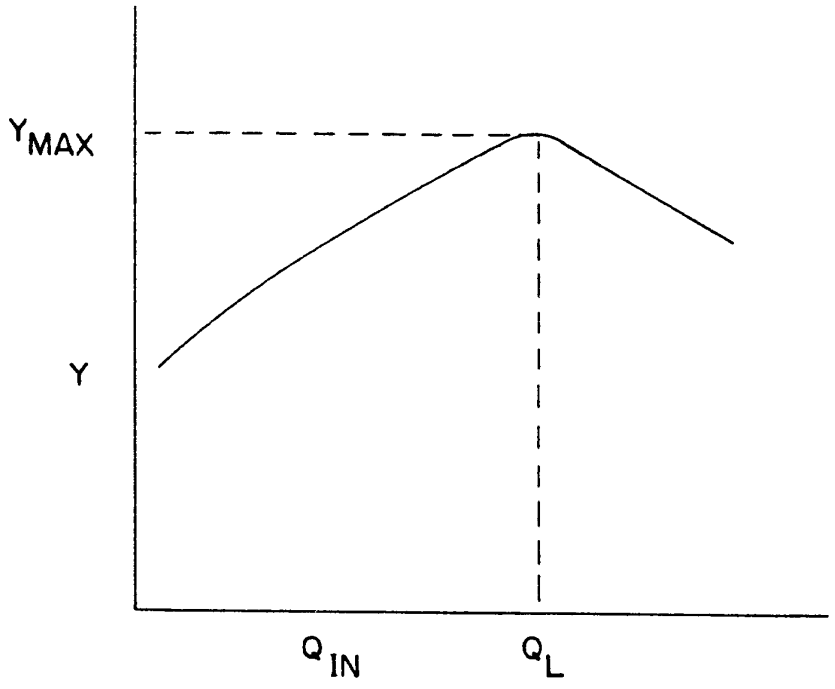
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FIG. 7



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FIG. 8



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European Patent Office

EUROPEAN SEARCH REPORT

Application Number EP 94307735.4

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 6)
X,P, A	EP - A - 0 580 299 (COBE LAB.) * Totality, especially page 2, lines 34-50; page 4, lines 18-26; page 5, line 47 - page 6, line 27; page 7, lines 7-20; page 10, lines 22-37 * --	1-4, 12,16, 18,21, 23-25	A 61 M 1/36
A	US - A - 4 968 295 (H.J. NEUMANN) * Totality * ----	1-4	

TECHNICAL FIELDS SEARCHED (Int. Cl. 6)

A 61 M

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	10-02-1995	LUDWIG

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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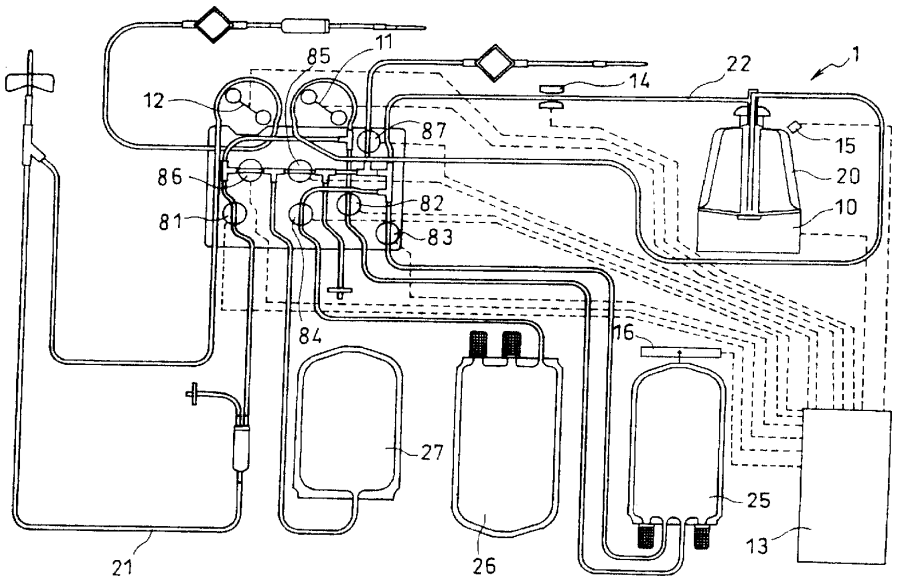
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(54) Blood component collecting apparatus

(57) A blood component collecting apparatus 1 is provided with a controller 13 for controlling a centrifugal separator drive unit 10, a pump 11, a pump 12 and a plurality of flow path shutters so as to execute plasma collecting-circulation steps including a plasma collecting step for collecting the blood containing added anticoagulant by starting the first and the second pumps 11, 12 and collecting a predetermined amount of plasma obtained from the blood in a plasma collecting bag 25 by activating the centrifugal separator drive unit 10; and a plasma circulation step for temporarily suspending blood collection subsequent to the plasma collecting step and circulating the plasma contained in the plasma collecting bag 25 to the centrifugal separator 20, which is followed by a platelet collecting step and a blood returning step.

Fig. 4



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Description

BACKGROUND OF THE INVENTION

The present invention relates to a blood component collecting apparatus and a blood component collecting circuit for separating predetermined blood components from the blood.

For effectively utilizing the blood and reducing the burden on the blood donor in the blood-collection, the collected blood is separated into various blood components centrifugally to extract only the components required for the donee, and the remaining components are returned to the donor.

In the case where a platelet product is produced from this blood component collection process, the blood donated from the donor is introduced to a blood component collecting circuit, separated into four components of plasma, white cells, platelets and red cells by a centrifugal separator called the centrifugal bowl installed in the blood component collecting circuit. Among these blood components, the platelets are recovered in a container to produce a platelet product. Meanwhile the remaining components including the plasma, white cells and red cells are returned to the donor.

Methods of collecting the platelets, first and second methods, are disclosed in WO 94/25086. In the first method, a liquid is sent to the centrifugal bowl and added to the whole blood while being diluted at a predetermined flow rate. According to the second method, the whole blood is sent to the centrifugal bowl and centrifugally separated into a low-density component, a middle-density component and a high-density component. The low-density component is retrieved in a first container, and the circuit is switched to circulate the low-density component at a first flow rate (fixed rate) to expand the middle-density component area in the centrifugal bowl, and the middle-density component, while being recirculated at a second flow rate (acceleration), is retrieved.

The first method, however, requires three pumps including an ACD pump, a blood collecting-returning pump and a circulation pump, and thus enlarges the apparatus size. In the second method, on the other hand, the platelets can be collected by two pumps, thus reducing the apparatus size. Nevertheless, the collected platelets are likely to be mixed with white cells, which fails to meet the requirement of the liquid containing platelets for a platetet product demanded to contain as few white cells as possible.

Accordingly, the object of the present invention is to provide a compact blood component collecting apparatus and a blood component collecting circuit used therein which is capable of producing a high-concentration platelets-contained liquid with low content of white cells at a high platelet collecting efficiency.

SUMMARY OF THE INVENTION

The aforementioned object of the invention can be achieved by a blood component collecting apparatus which comprises a blood component collecting circuit including: a centrifugal separator having a rotor having an internal blood storage space, an inlet and an outlet communicating with said blood storage space for centrifugally separating the blood introduced therein through said inlet by rotation of said rotor; a first line for connection between a blood-collection needle or a blood-collection unit connector and said inlet of said centrifugal separator; a second line connected to said outlet of said centrifugal separator; a third line connected to said first line for injecting an anticoagulant; a plasma collecting bag having a first tube connected to a middle point of said first line and a second tube connected to said second line; and a platelet collecting bag connected to said second line; said blood component collecting apparatus further comprising a centrifugal separator drive unit for rotating said rotor of said centrifugal separator, a first liquid supply pump for said first line arranged at a position of said first line between said centrifugal separator and a connecting portion for connecting said first tube to said first line, a second liquid supply pump for said third line, a plurality of flow path shutter means for opening/ closing the flow paths of said blood component collecting circuit; and a controller for controlling said centrifugal separator drive unit, said first liquid supply pump, said second liquid supply pump and said plurality of flow path shutter means; wherein said controller controls said centrifugal separator drive unit, said first liquid supply pump, said second liquid supply pump and said plurality of flow path shutter means so as to execute a platelet collecting operation which includes at least twice of plasma collecting-circulation steps including a plasma collecting step for collecting blood added anticoagulant by starting said first and second liquid supply pumps and collecting said plasma obtained from said blood in said plasma collecting bag by activating said centrifugal separator drive unit and a plasma circulation step for temporarily suspending blood-collection subsequent to said plasma collecting step and circulating said plasma contained in said plasma collecting bag to said centrifugal separator by activating said centrifugal separator drive unit, subsequent to said plasma collecting-circulation steps, a platelet collecting step for collecting platelet released from said centrifugal separator into said platelet collecting bag by accelerating a plasma circulation rate by said first liquid supply pump; and to execute a blood returning step, subsequent to said platelet collecting step, for returning said blood contained in said centrifugal separator.

Further, the aforementioned object of the invention can be achieved by a blood component collecting circuit which comprises a centrifugal separator having an inlet and an outlet; a blood-collection needle or a blood-collection unit

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connector; a first line having a first pump tube for connection between said blood-collection needle or said blood-collection unit connector and the inlet of said centrifugal separator; a second line connected to the outlet of said centrifugal separator; a third line having a second pump tube connected to a portion near said blood-collection needle or said blood-collection unit connector of said first line; a plasma collecting bag having a first tube connected to a portion of said first line between said blood-collection needle or said blood-collection unit connector and said first pump tube and a second tube connected to said second line; a platelet collecting bag having a third tube connected to said second line; and a cassette housing for partially containing and partially holding said first line, said second line, said third line, said first tube, said second tube and said third tube; wherein said first pump tube and said second pump tube are fixed on said cassette housing so as to extend therefrom; wherein said cassette housing includes a first opening for exposing the portion of said, first line between said blood-collection needle or said blood-collection unit connector and said first pump tube and capable of being intruded by a flow path shutter means, a second opening for exposing said first pump tube and capable of being intruded by a flow path shutter means, a third opening for exposing said second tube and capable of being intruded by a flow path shutter means, a fourth opening for exposing said third tube and capable of being intruded by a flow path shutter means, a fifth opening for exposing the portion of said second line between said centrifugal separator and a connecting portion for connecting said fourth tube to said second line and capable of being intruded by a flow path shutter means.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic drawing of an example configuration of a blood component collecting circuit used in a blood component collecting apparatus according to the present invention.

Fig. 2 is a plan view showing a cassette housing portion of the blood component collecting circuit shown in Fig. 1.

Fig. 3 is a partially cutaway sectional view showing the state in which a drive unit is mounted on a centrifugal separator used in a blood component collecting circuit.

Fig. 4 is a schematic drawing of a blood component collecting apparatus according to an embodiment of the invention having a blood component collecting circuit mounted thereon.

Fig. 5 is a flowchart representing the operation of a blood component collecting apparatus according to the invention.

Fig. 6 is a flowchart for explaining the operation of a blood component collecting apparatus according to the invention.

Fig. 7 is a flowchart representing the operation of a blood component collecting apparatus according to the invention.

Fig. 8 is a flowchart representing the operation of a blood component collecting apparatus according to the invention.

Fig. 9 is a flowchart representing the operation of a blood component collecting apparatus according to the invention.

Fig. 10 is a flowchart representing the operation of a blood component collecting apparatus according to the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

A blood component collecting apparatus according to the present invention will be described with reference to an embodiment shown in the accompanying drawings.

A blood component collecting apparatus 1 according to the invention is provided with a blood component collecting circuit 2 including a centrifugal separator 20 having a rotor 142 having an internal blood storage space, an inlet and an outlet communicating with the blood storage space for centrifugally separating, in the blood storage space, the blood introduced therein through the inlet by the rotation of the rotor 142, a first line 21 for connection between a connector of a blood-collection needle 29 or a blood pool and the inlet of the centrifugal separator 20, a second line 22 connected to the outlet of the centrifugal separator 20, a third line 23 connected to the first line 21 for injecting an anticoagulant, a plasma collecting bag 25 having a first tube 25a connected to the first line 21 and a second tube 25b connected to the second line 22, and a platelet collecting bag 26 connected to the second line 22.

The blood component collecting apparatus 1 has a centrifugal separator drive unit 10 for rotating the rotor 142 of the centrifugal separator 20, a first liquid supply pump 11 for the first line 21, a second liquid supply pump 12 for the third line 23, a plurality of flow path shutter means 81, 82, 83, 84, 85, 86, 87 for opening/closing the flow paths of the blood component collecting circuit 2, and a controller 13 for controlling the centrifugal separator drive unit 10, the first liquid supply pump 11, the second liquid supply pump 12 and a plurality of the flow path shutter means 81, 82, 83, 84, 85, 86, 87.

First, the blood component collecting circuit 2 will be explained.

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The blood component collecting circuit 2 is used for collecting the blood components, more specifically, the platelets. The blood component collecting circuit 2 is provided with a blood collector such as a blood-collection needle 29 or a connector (blood collector connector) for connecting a blood collector such as a blood-collection needle 29 or a blood pool connector, a first line 21 (blood-collection/ returning line) having a first pump tube 21g for connection between the blood-collection needle 29 or the blood collector connector and the inlet of the centrifugal separator 20, a second line 22 for connection between the outlet of the centrifugal separator 20 and the first line 21, a third line (anticoagulant injection line) 23 having a second pump tube 23a connected to a portion of the first line 21 near the blood-collection needle 29 or the blood collector connector, a plasma collecting bag 25 having a first tube 25a connected to the portion of the first line 21 between the blood-collection needle 29 or the blood collector connector and the pump tube 21g and a second tube 25b connected to the second line 22, a platelet collecting bag 26 having a third tube 26a connected to the second line 22, a buffy coat collecting bag 27 having a fourth tube 27a connected to the second line 22, and a fourth line 24 for injecting liquid (physiological salt solution) connected to the second line 22. The blood component collecting circuit 2 may employ a connector (such as a metal or plastic needle) for connecting a blood pool such as a blood bag rather than the blood-collection needle.

The first liquid supply pump 11 for said first line is arranged at a position (first pump tube 21g) of the first line between said centrifugal separator and a connecting portion for connecting the first tube to said first line. The second liquid supply pump 12 for said third line is arranged at second pump tube 23a.

Conventionally a known metal needle is used as the blood-collection needle 29. The first line 21 includes a portion 21a to which the blood-collection needle 29 is connected and a portion 21b to which the inlet of the centrifugal separator 20 is connected. The first line portion 21a closer to the blood-collection needle is formed by a plurality of soft plastic tubes connected thereto. The portion 21a of the first line 21 closer to the blood-collection needle has such elements arranged as viewed from the blood-collection needle side, a branching connector 21c for connecting the third line 23, a chamber 21d for removing bubbles and micro-aggregates, a branching connector 21e for connecting the second line 22, and a branching connector 21f for connecting the first tube 25a communicated with the plasma collecting bag 25. The chamber 21d is connected to an air-permeable, germ-blocking filter 21i. The first line portion 21b closer to the centrifugal separator 20 is connected to a branching connector 21f for connecting the first tube 25a and has a pump tube 21g formed in the vicinity thereof.

The second line 22 for connection between the outlet of the centrifugal separator 20 and the first line 21 has an end thereof connected to the outlet of the centrifugal separator 20 and the other end thereof connected to the branching connector 21e for connecting the first line 21. The second line 22 has such elements arranged as viewed from the centrifugal separator side, a branching connector 22a for connecting the second tube 25b communicated with the plasma collecting bag 25 and the third tube 26a communicated with the platelet collecting bag 26, a branching connector 22b for connecting the fourth line 24, a branching connector 22c for connecting a tube having a bubble-removing filter 22f, and a branching connector 22d for connecting the fourth tube 27a communicated with the buffy coat collecting bag 27.

The third line 23 is connected to the branching connector 21c having an end thereof connected to the first line 21. The third line 23 has such elements as a pump tube 23a, a foreign matter removing filter 23b, a bubble removing chamber 23c and an anticoagulant container connecting needle 23d arranged as viewed from the connector 21c.

One end of the fourth line 24 is connected to the branching connector 22b for connecting the second line 22. The fourth line 24 has such elements as a foreign matter removing filter 24a and a physiological salt solution container connecting needle 24b arranged as viewed from the connector 22b.

The plasma collecting bag 25 includes a first tube 25a connected to the branching connector 21f located between the blood-collection needle 29 and the pump tube 21g of the first line 21, and a second tube 25b connected to the branching connector 22a of the second line 22. The platelet collecting bag 26 includes a third tube 26a connected to the branching connector 22a of the second line 22. The buffy coat collecting bag 27 includes a fourth tube 27a connected to the branching connector 22d of the second line 22.

The tubes and the pump tubes used for forming the first to fourth lines and the tubes connected to the bags as described above are composed of such materials as polyvinyl chloride, polyethylene, polypropylene, polyester such as PET or PBT, ethylene-vinyl acetate copolymer, polyurethane, polyester elastomer, thermoplastic elastomer such as styrene-butadiene-styrene copolymer. Of all these component materials, polyvinyl chloride is the most preferable. If all the tubes are made of polyvinyl chloride, sufficient flexibility and plasticity can be obtained for easy handling. Also, this material is suitably used to cope with clogging caused by a clamp and the like. Component materials similar to these tube materials can also be used for forming the branching connectors. The pump tubes are required to have a sufficient strength to bear the pressure applied by the roller pump.

Each of the plasma collecting bag 25, the platelet collecting bag 26 and the buffy coat collecting bag 27 is composed of layers of flexible plastic sheets having the peripheral edges thereof fusion bonded (thermally or with high frequencies) or adhered. Soft polyvinyl chloride is the most preferable material for forming the bags 25, 26, 27. Plasticizers used for the soft polyvinyl chloride include, for example, di-(ethylhexyl) phthalate (DEHP), di-(n-decyl) phthalate (DnDP) and

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the like. The content of these plasticizers preferably ranges from approximately 30 to 70 wt.% to 100 wt.% of the polyvinyl chloride.

Other sheet materials that can be used for forming the bags 25, 26, 27 may be polyolefin, that is, a polymer formed by polymerizing or copolymerizing an olefin or di-olefin of ethylene, propylene, butadiene, isoprene or the like. More specifically, polyethylene, polypropylene, ethylene-vinyl acetate copolymer (EVA), polymer blend of EVA and various thermoplastic elastomers, etc. or an arbitrary combination thereof can be used. Still other applicable materials include polyester such as polyethylene terephthalate (PET), polybutylene terephthalate (PBT), poly-1, 4-cyclohexanedimethyl terephthalate (PCHT) and polyvinylidene chloride.

The sheet material used for the platelet collecting bag 26 is preferably superior in gas permeability for assuring an improved platelet shelf life. Such sheet materials preferably include, for example, the above-mentioned polyolefin or DnDP plasticized polyvinyl chloride, etc. Alternatively, using comparatively thin (say, about 0.1 to 0.5 mm thick, or especially, about 0.1 to 0.3 mm thick) materials is further preferable. The platelet collecting bag can be preliminarily filled with a platelet retainer such as physiological salt solution, GAC, PAS, PSM-1.

The essential portions of the blood component collecting circuit 2 are housed in a cassette as shown in Fig. 2. The blood component collecting circuit 2 includes a cassette housing 28 for partially containing or partially holding all the lines (first, second, third and fourth lines) and all the tubes (first, second, third and fourth tubes), that is, for partially fixing them. The cassette housing 28 has both ends of the first pump tube 21g and the second pump tube 23a fixed thereto. The pump tubes 21g, 23a extend from the cassette housing 28 in a loop to correspond to the shape of the roller pump. As a result, the first and the second pump tubes 21g, 23a can be readily mounted on the roller pump 11, 12.

Further, the cassette housing 28 includes a plurality of openings located therein. Specifically, located in the cassette housing 28 are a first opening 91 that exposes the portion of the first line 21 between the blood-collection needle and the pump tube 21g and can be intruded by the first flow path shutter means 81 of the blood component collecting apparatus 1, a second opening 92 that exposes the first tube 25a of the plasma collecting bag 25 and can be intruded by the second flow path shutter means 82 of the blood component collecting apparatus 1, a third opening 93 that exposes the second tube 25b of the plasma collecting bag 25 and can be intruded by the third flow path shutter means 83 of the blood component collecting apparatus 1, a fourth opening 94 that exposes the third tube of the platelet collecting bag 26 and can be intruded by the fourth flow path shutter means 84 of the blood component collecting apparatus 1, a fifth opening 95 that exposes the portion of the second line 22 between the centrifugal separator (connector 22c) and the connector 22d for connecting the fourth tube 27a of the buffy coat collecting bag 27 to the second line 22 and can be intruded by the fifth flow path shutter means 85 of the blood component collecting apparatus 1, a sixth opening 96 that exposes the portion of the second line 22 between the connector of the first line 21 and the connector of the fourth tube 27a of the buffy coat collecting bag 27 (downstream of the connector of the second line 22 and the fourth tube 27a) and can be intruded by the sixth flow path shutter means 86 of the blood component collecting apparatus 1 and a seventh opening 97 that exposes the fourth line 24 and can be intruded by the seventh flow path shutter means 87 of the blood component collecting apparatus 1.

Also, the above-mentioned branching connectors are fixed to the inner surface of the cassette housing 28. Further, at least a reinforcing tube for holding the lines and tubes extended from the side of the housing and preventing the portions thereof in contact with the housing from being bent is arranged in the vicinity of the side of the cassette housing 28. The cassette housing 28 is box-shaped and contains the parts indicated by dashed lines. The cassette housing 28 is formed of a synthetic resin having a rigidity to a certain degree.

The blood component collecting apparatus 1 includes a mount (not shown) of the cassette housing. When the cassette housing 28 is mounted on the cassette housing mount of the blood component collecting apparatus 1, the lines and tubes exposed from the openings of the cassette housing 28 are automatically mounted on the corresponding flow path shutter means, respectively. As a result, the circuit can be easily mounted while performing rapid preparations for collecting the blood components. Also, the blood component collecting apparatus 1 has two pumps adjacent to the cassette housing mount. The pump tubes exposed from the cassette housing 28 can thus be easily mounted on the pump.

The centrifugal separator 20 mounted in the blood component collecting circuit 2, which is usually called the centrifugal bowl, separates the blood into components by centrifugal force. The centrifugal separator 20, as shown in Fig. 3, includes a tubular member 141 extending vertically and having an inlet 143 formed at the upper end thereof, and a hollow rotor 142 sealed in fluid-tight at the upper portion 145 thereof and adapted to rotate around the tubular member 141. The rotor 142 has a flow path (blood storage space) along the bottom and the inner peripheral wall surface thereof. An outlet 144 is formed to communicate with the upper portion of the flow path. In this case, for example, the volume of the rotor 142 ranges from approximately 100 to 350 ml.

The rotor 142 is rotated under predetermined centrifugal conditions (rotational speed and rotation time) by the rotor drive unit 10 of the blood component collecting apparatus 1. These centrifugal conditions are used to set a pattern of the blood separated (the number of blood components to be separated, for example) in the rotor 142. According to this embodiment, as shown in Fig. 3, the centrifugal conditions are set such that the blood is separated into a plasma

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layer 131, a buffy coat layer 132 and a red cell layer 133 laminated from the inside within the flow path of the rotor 142.

Referring to Fig. 4, the blood component collecting apparatus 1 according to this invention will be described.

The blood component collecting apparatus 1 is provided with the centrifugal separator drive unit 10 for rotating the rotor 142 of the centrifugal separator 20, the first liquid supply pump 11 for the first line 21, the second liquid supply pump 12 for the third line 23, a plurality of the flow path shutter means 81, 82, 83, 84, 85, 86, 87 for opening closing the flow paths of the blood component collecting circuit 2, and the controller 13 for controlling the centrifugal separator drive unit 10, the first liquid supply pump 11, the second liquid supply pump 12 and the flow path shutter means. Further, the blood component collecting apparatus 1 comprises a turbidity sensor 14 mounted on the portion of the second line 22 between the centrifugal separator and the connector 22a for connecting the second tube 25b to the second line 22, an optical sensor 15 mounted above the centrifugal separator 20 and a weight sensor 16 for detecting the weight of the plasma collecting bag 25.

The controller 13 includes two pump controllers (not shown) for the first liquid supply pump 11 and the second liquid supply pump 12 respectively. The control mechanism of the controller 13 is electrically complected to the first liquid supply pump 11 and the second liquid supply pump 12 through a pump controller. The drive controller of the centrifugal separator drive unit 10 is electrically connected to the controller 13. The flow path shutter means 81, 82, 83, 84, 85, 86, 87 are all connected to the controller 13 for controlling the respective opening/closing operations. Also, the turbidity sensor 14, the optical sensor 15 arranged above the centrifugal separator 20 and the weight sensor 16 for detecting the weight of the plasma collecting bag 25 are electrically connected to the controller 13 to which the signals output from these components are applied. The control mechanism of the controller 13 is configured of, for example, a microcomputer and the detection signals from the weight sensor 16, the optical sensor 15 and the turbidity sensor 14 are applied to the controller 13 from time to time. The controller 13 controls the start and stop of the rotation and rotational direction (forward/backward) of each pump based on the signals from the turbidity sensor 14, the optical sensor 15 and the weight sensor 16 while controlling the opening/ closing operation of the flow path shutter means and the centrifugal separator drive unit 10.

The first flow path shutter means 81 is provided for opening/closing the portion of the first line 21 between the blood-collection needle and the pump tube 21g. The second flow path shutter means 82 is provided for opening/closing the first tube 25a communicated with the plasma collecting bag 25. The third flow path shutter means 83 is provided for opening/closing the second tube 25b communicated with the plasma collecting bag 25. The fourth flow path shutter means 84 is provided for opening/closing the third tube communicated with the platelet collecting bag 26. The fifth flow path shutter means 85 is provided for opening/closing the portion of the second line 22 between the centrifugal separator and the connector 22d for connection between the second line 22 and the fourth tube 27a communicated with the buffy coat collecting bag 27. The sixth flow path shutter means 86 is provided for opening/closing the portion of the second line 22 between the connector 21e of the fist line 21 and the connector 22d of the fourth tube 27a (downstream of the connector of the second line 22 and the fourth tube 27a). The seventh flow path shutter means 87 is provided for opening/closing the fourth line 24. Each of these how path shutter means includes a line or tube insertion member having a clamp adapted to be energized by, for example, a solenoid, an electric motor, a (hydraulic or pneumatic) cylinder or other drive source. Specifically, an electromagnetic clamp operated by the solenoid is preferable. The clamp provided with the flow path shutter means is operated based on the signal from the controller 13.

The drive unit 10, as shown in Fig. 3, includes a rotor drive unit housing 151 for containing the centrifugal separator 20, a pedestal 152, a motor 153 constituting a drive source and a circular rest 155 for holding the centrifugal separator 20. The housing 151 is mounted and fixed on the pedestal 152. Also, a motor 153 is fixed to the lower surface of the housing 151 with a bolt 156 via a spacer 157. The forward end of the rotary shaft 154 of the motor 153 is fitted such that the rest 155 rotates coaxially and integrally with the rotational shaft 154. The upper portion of the rest 155 has a recess formed therein to which the bottom of the rotor 142 is fitted. Also, the upper portion 145 of the centrifugal separator 20 is fixed to the housing 151 with a fixing member not shown. Once the motor 153 for the rotor drive unit 10 is started, the rest 155 and the rotor 142 fixed thereto are rotated at a rotational speed, for example, ranging from 3000 to 6000 rpm.

The inner wall of the rotor drive unit housing 151 has an optical sensor 15 that is fixedly mounted thereon with a mounting member 158 for optically detecting the boundaries of the separated blood components (for example, the boundary B between the plasma layer 131 and the buffy coat layer 132, and the boundary between the buffy coat layer 132 and the red cell layer 133) in the rotor 142. The above optical sensor 15 is adapted to scan the outer peripheral surface of the rotor 142 in vertical direction. This sensor 15 includes a light source for emitting a light beam toward the shoulder of the centrifugal separator 20 and a photo-detector for receiving the light reflected and returned from the centrifugal bowl. Specifically, a light emitting element like LED and a light receiving element are linearly arranged. The light emitted from the light emitting element and reflected from a blood component is received by the light receiving element, such that the amount of the received light is subjected to photoelectric conversion. The intensity of the reflected light varies depending on the separated blood component (for example, the boundary B between the plasma layer 131 and the buffy coat layer 132). The position on the light receiving element that has changed in the received light amount,

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therefore, is detected as a corresponding position of the boundary B. More specifically, arrival of the buffy coat layer at a light passage is detected based on the difference in the received light amount between the time when the centrifugal separator 20 is filled with a transparent liquid (plasma or water) at a point of the light passage and the time when it is filled with the buffy coat layer at the particular point of the light passage. The point where the buffy coat layer is detected is adjusted by changing the point of light passage in the bowl. The point of light passage, once determined, is usually fixed there.

The turbidity sensor 14 is used for detecting the turbidity of the fluid flowing through the second line 22 and outputs a voltage value corresponding to the detected turbidity. Specifically, a low voltage value is output when the turbidity is high, while a high voltage value is output when the turbidity is low.

Each of the first liquid supply pump 11 mounted the pump tube 21g of the first line 21 and the second liquid supply pump 12 mounted the pump tube 23a of the third lure 23 are preferably formed as a pump kept out of contact with the blood such as a roller pump or peristaltic pump. Also, a pump that can supply the blood in either direction is used as the first liquid supply pump 11 (blood pump). Specifically, a roller pump capable of rotating forward/ backward is used.

The controller 13 controls the centrifugal separator drive unit 10, the first liquid supply pump 11, the second liquid supply pump 12 and a plurality of the flow path shutter means in order to execute a platelet collecting operation. The platelet collecting operation includes a plurality (at least two times, preferably, twice to seventh times, more preferably, three times to sixth times) of plasma collecting-circulation steps including a plasma collecting step for collecting blood added anticoagulant by starting the first and the second liquid supply pumps 11, 12 and collecting a predetermined amount of plasma in the plasma collecting bag 25 by activating the centrifugal separator drive unit, and a plasma circulation step for temporarily suspending blood-collection subsequent to the plasma collecting step and circulating the plasma contained in the plasma collecting bag to the centrifugal separator 20 by activating the centrifugal separator drive unit 10; and, subsequent to a plurality of plasma collecting-circulation steps, to execute a platelet collecting step for collecting platelets released from the centrifugal separator 20 in the platelet collecting bag 26 by accelerating the plasma circulation rate by the first liquid supply pump 11, which is followed by a blood returning step for returning the blood contained in the centrifugal separator 20.

Further, the controller 13 of the blood component collecting apparatus 1 according to this embodiment controls the centrifugal separator drive unit 10, the first liquid supply pump 11, the second liquid supply pump 12 and a plurality of the flow path shutter means such that the platelet collecting operation is executed at least twice, or specifically, twice to fifth times, more preferably, three times.

Specifically, the first plasma collecting-circulation step including the first plasma collecting step and the first plasma circulation step is executed. In the first plasma collecting step, the blood containing the added anticoagulant is collected by starting the first and the second liquid supply pumps 11, 12 and the centrifugal separator drive unit 10 is activated to collect a first predetermined amount of plasma in the plasma collecting bag 25. This step is followed by the first plasma circulation step in which the blood-collection is temporarily suspended and the centrifugal separator drive unit 10 is activated to circulate the plasma contained in the plasma collecting bag to the centrifugal separator 20. Then a second plasma collecting-circulation step including the second plasma collecting step and the second plasma circulation step is executed. In the second plasma collecting step, the first and the second liquid supply pumps 11, 12 are started to collect the blood added anticoagulant and the centrifugal separator drive unit 10 is activated to collect the plasma until the amount of plasma contained in the plasma collecting bag 25 reaches a second predetermined amount (total amount) that is larger than the first predetermined amount. The second plasma collecting step is followed by the second plasma circulation step in which the blood-collection is temporarily suspended and the centrifugal separator drive unit 10 is activated to circulate the plasma contained in the plasma collecting bag 25 to the centrifugal separator 20.

The controller 13 of the blood component collecting apparatus 1 according to this embodiment executes a third plasma collecting-circulation step subsequent to the second plasma circulation step. The third plasma collecting-circulation step includes a third plasma collecting step and a third plasma circulation step. In the third plasma collecting step, the first and second liquid supply pumps 11, 12 are started to collect the blood added anticoagulant, and the centrifugal separator drive unit 10 is activated to collect the plasma until the amount thereof contained in the plasma collecting bag 25 reaches a third predetermined amount (total amount) that is larger than the second predetermined amount. The above third plasma collecting step is followed by the third plasma circulation step in which the blood-collection is temporarily suspended and the centrifugal separator drive unit 10 is activated to circulate the plasma contained in the plasma collecting bag to the centrifugal separator 20.

Further, the controller 13 of the blood component collecting apparatus 1 executes a fourth plasma collecting-circulation step upon completion of the third plasma circulation step. The fourth plasma collecting-circulation step includes a fourth plasma collecting step and a fourth plasma circulation step. In the fourth plasma collecting step, the first and the second liquid supply pumps 11, 12 are started to collect the blood added anticoagulant, and the centrifugal separator drive unit 10 is activated to collect the plasma until the amount thereof contained in the plasma collecting bag 25 reaches a fourth predetermined amount (total amount) that is larger than the third predetermined amount. The fourth plasma collecting step is followed by the fourth plasma circulation step, in which the blood-collection is temporarily

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suspended and the centrifugal separator drive unit 10 is activated to circulate the plasma contained in the plasma collecting bag 25 to the centrifugal separator 20.

The second predetermined amount is larger than the first predetermined amount because the total amount of plasma contained in the plasma collecting bag 25 is increased. Therefore, the amount of the plasma collected in the second plasma collecting step is not necessarily larger than the that of the plasma collected in the first plasma collecting step. Therefore, the amount of the plasma collected in the third plasma collecting step is not necessarily larger than the that of the plasma collected in the second plasma collecting step. Therefore, the amount of the plasma collected in the fourth plasma collecting step is not necessarily larger than the that of the plasma collected in the third plasma collecting step. In other words, an arbitrary amount of the plasma can be collected in each plasma collecting step. For the controlling purpose, the first, second, third and fourth predetermined amounts are stored in the controller, each of which is compared with the weight signal detected by the weight sensor. When it is detected that the weight of the plasma contained in the plasma collecting bag has reached a particular predetermined value, each plasma collecting step is terminated.

Further, the controller 13 of the blood component collecting apparatus 1 according to this embodiment executes a fifth plasma collecting-circulation step subsequent to the fourth plasma circulation step. The fifth plasma collecting-circulation step similarly includes a fifth plasma collecting step and a fifth plasma circulation step. In the fifth plasma collecting step, the first and the second liquid supply pumps 11, 12 are started to collect the blood added anticoagulant, and the centrifugal separator drive unit 10 is activated to collect the plasma contained in the plasma collecting bag 25. The fifth plasma collecting step is followed by the fifth plasma circulation step in which the blood-collection is temporarily suspended and the centrifugal separator drive unit 10 is activated to circulate the plasma contained in the plasma collecting bag 25 to the centrifugal separator 20. In the fifth plasma collecting step using a boundary sensor, the weight of the plasma bag is not detected.

Subsequent to the platelet collecting step and prior to the start of the blood returning step, the controller 13 of the blood component collecting apparatus 1 according to this embodiment executes a buffy coat collecting step in which the plasma circulation rate by means of the first liquid supply pump 11 is increased to exceed the final rate in the platelet collecting step such that the buffy coat is released from the centrifugal separator 20 into a buffy coat collecting bag 27. The buffy coat coflecting step is not limited to the above-mentioned method. Alternatively it can be executed such that the plasma circulation rate by means of the first liquid supply pump 11 is maintained at the final rate in the platelet collecting step while decreasing the rotational speed of the rotor of the centrifugal separator 20. Further, the buffy coat collecting step can be executed by increasing the plasma circulation rate by means of the first liquid supply pump to exceed the final rate in the platelet collecting step while decreasing the rotational speed. of the rotor of the centrifugal separator.

After completing the buffy coat collecting step, the first liquid supply pump 11 and a plurality of the flow path shutter means are controlled such that the buffy coat returning step for returning the collected, buffy coat into the centrifugal separator 20 is executed prior to the subsequent blood-collection step.

Specifically, an anticoagulant is added to the whole blood by a predetermined ratio (1/6 to 1/ 20, or specifically, 1/10 of the whole blood), and the resultant blood is fed to the centrifugal separator 20 through the first line 21 at a predetermined rate (250 ml/min or less, preferably, 150 to 40 ml/min or less, or specifically, 60 ml/min or less). The centrifugal separator 20 is rotated at a predetermined rotational speed (3000 to 6000 rpm, or preferably, 4700 to 4800 rpm) to separate the blood into components including plasma, buffy coat and red cells. The plasma that has overflowed the centrifugal separator 20 is collected in the plasma collecting bag. At a time point when a predetermined amount (10 to 150 ml, or preferably 20 to 30 ml) of plasma is collected, the blood supply is stopped. Then, the plasma is returned to the centrifugal separator 20 through the first and second lines 21, 22 under predetermined conditions (at a rate higher than that for blood-collection, i.e. 60 to 250 ml/min for 10 to 90 sec, or specifically, 200 ml/min for 30 sec. for the first circulation, and 120 ml/min for 30 sec. for the second and subsequent circulation). Each time when the plasma reaches a predetermined amount (not more than 150 ml collected as measured from the final circulation) before the end of blood-collection, the plasma circulation is repeated. When the buffy coat in the centrifugal separator 20 reaches a predetermined radius (specifically, 30 to 40 mm), the blood-collection is suspended and the plasma is returned to the centrifugal separator 20 through the first and second lines 21, 22 under predetermined conditions (60 to 250 ml/min for 10 to 90 sec, specifically, 120 to 140 ml/min for 30 sec.). Then, the whole blood added anticoagulant is fed again under predetermined conditions (the amount of the collected blood : 0 to 2500/Hct% [ml], or specifically, 1200 to 1400/Hct% [ml]), after which the plasma is returned to the centrifugal separator 20 through the first and second lines 21, 22 under the predetermined conditions. The acceleration rate is increased stepwise under predetermined conditions (stepwise acceleration ranging from 0.1 to 99 ml/min/sec, or specifically, 10 ml/min/sec) until the platelet collecting rate reaches (60 to 250 ml/min, or actually, 200 ml/min). The platelets released from the centrifugal separator 20 are then collected in the platelet collecting bag 26. Further, after collecting the platelets, the blood circulation rate (at 60 to 250 ml/min., or specifically, 200 ml/min) is maintained while reducing the rotation of the centrifugal separator 20 (by about 100 to 300 rpm, or preferably down to 4500 to 4600 rpm). In this way, the released buffy coat is collected and supplied

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to the centrifugal separator 20 prior to the next blood-collection cycle. The buffy coat can alternatively be collected by increasing the blood circulation rate to a predetermined level (not less than the platelet collecting rate, or preferably 60 to 250 ml/min., specifically, 205 ml/min.).

The blood coniponent collecting process (first platelet collecting operation) by the blood component collecting apparatus 1 according to this embodiment will be explained with reference to Figs. 4, 5 to 10. In this embodiment, the platelet collecting operation is repeated three times, and prior to the blood returning step, the buffy coat collecting step is executed after each platelet collecting step other than the last one. Also, prior to the next blood-collection step, the buffy coat returning step is performed to return the buffy coat to the centrifugal separator 20.

First, the third line 23 and the blood-collection needle 29 are primed with an anticoagulant and the needle is inserted into the donor.

As shown in Fig. 5, a first plasma collecting step is executed in which the blood added anticoagulant is collected by starting the first and second liquid supply pumps 11, 12 and a first predetermined amount of plasma obtained from the blood is collected into the plasma collecting bag 25 by working the centrifugal separator drive unit 1.0 .

When the first blood-collection starts, the blood pump 11 starts collecting the blood at a predetermined rate (for example, 60 ml/min). At the same time, the second pump constituting an anticoagulant pump supplies the anticoagulant (for example, ACD-A solution) at a predetermined rate (for example, 1/10 of the blood pump rate). The blood drawn from the donor is mixed with the ACD solution, flows through the first line 21, the chamber and the first flow path shutter means 81, and enters the centrifugal separator 20. At the above time point, the sixth flow path shutter means 86, the fifth flow path shutter means 85, the second flow path shutter means 82, the third flow path shutter means 83 and the seventh flow path shutter means 87 are closed. Meanwhile the first flow path shutter means 81 and the fourth flow path shutter means 84 are open. When the blood added ACD is fed to the centrifugal separator 20, the sterilized air that has stayed in the centrifugal separator 20 flows through the second line 22 and the flow path shutter means 84 into the platelet collecting bag 26. Simultaneously with the start of the blood-collection, the centrifugal separator 20 starts rotating at a predetermined speed (say, 4800 rpm) while being supplied with the blood added ACD. In the centrifugal separator 20, therefore, the blood is centrifugally separated into a plasma layer, a buffy coat layer (BC layer) and a red cell layer formed from the inside. When the blood added ACD is supplied in excess of (about 270 ml) the capacity of the separator, the centrifugal separator 20 is completely filled with the blood, by which the plasma overflows through the outlet of the centrifugal separator 20. The turbidity sensor 14 mounted on the second line 22 connected to the outlet of the centrifugal separator 20 detects the change in the fluid flowing through the line from air to plasma. The controller 13 thus closes the fourth flow path shutter means 84 in response to the detection signal of the turbidity sensor 14 and opens the third flow path shutter means 83 to collect the plasma in the plasma collecting bag 25. The weight of the plasma collecting bag 25 is preliminarily measured by the weight sensor 16, and the measurement value has been applied to the controller 13. When the weight of the plasma collected in the plasma collecting bag 25 is increased to a predetermined amount (for example, 10 to 150 g, or 20 g), the controller 13 closes the first flow path shutter means 81 and opens the second flow path shutter means 82. Then the process proceeds to the first plasma circulation step.

In the first plasma circulation step, the blood-collection is temporarily suspended and the centrifugal separator drive unit 10 is activated, such that the plasma contained in the plasma collecting bag 25 is circulated to the centrifugal separator 20.

Upon start of the first plasma circulation step, the controller 13 keeps the first flow path shutter means 81 closed and the second flow path shutter means 82 opened, stops the ACD pump 12 and starts the blood pump 11 at a predetermined rate (60 to 250 ml/min, for example, 200 ml/min). The plasma collected in the plasma collecting bag 25 thus is fed through the second flow path shutter means 82 to the centrifugal separator 20 rotating at 4800 rpm. At the same time, the plasma flowing from the centrifugal separator 20 enters the plasma collecting bag 25 through the turbidity sensor 14 and the third flow path shutter means 83. With the lapse of a predetermined length of time (10 to 90 sec, for example, 30 sec) from the start of the first plasma circulation step, the controller 13 closes the second flow path shutter means 82, opens the first flow path shutter means 81, and proceeds to the second plasma collecting step. The first plasma circulation step is executed preferably at the flow rate of 60 ml/min or more for at least 10 seconds.

In the second plasma collecting step, the first and second liquid supply pumps 11, 12 are started to collect the blood added anticoagulant, and the centrifugal separator drive unit 10 is activated to collect the plasma until the collected amount in the plasma collecting bag 25 reaches a second predetermined amount that is larger than the first predetermined amount (by 10 to 150 g).

Specifically, the blood pump 11 is activated to collect the blood at a predetermined rate (for example, 60 ml/min). At the same time, the second pump constituting an anticoagulant pump supplies the coagulant (for example, ACD-A solution) at a predetermined rate (say, 1/10 of the rate of the blood pump). The blood drawn from the donor is mixed with the ACD solution, and flows into the centrifugal separator 20 rotating at a predetermined speed (say, 4800 rpm) for collecting the plasma in the plasma collecting bag 25. The weight of the plasma collecting bag 25 is measured by the weight sensor 16 and applied to the controller 13. When the weight of the plasma collected in the plasma collecting

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bag 25 reaches the second predetermined amount (10 to 150 g larger than the first predetermined amount, or specifically, the second predetermined amount may be set to 50 g), the controller 13 closes the first flow path shutter means 81, opens the second flow path shutter means 82, and proceeds to the second plasma circulation step.

In the second plasma circulation step, the blood-collection is temporarily suspended and the centrifugal separator drive unit 10 is activated to circulate the plasma in the plasma collecting bag 25 to the centrifugal separator 20. In the process, the blood pump operates at a predetermined rate lower than that in the first plasma circulation step, for example, at 120 ml/min for about 30 sec. The second plasma circulation is preferably conducted at a rate ranging from 60 to 250 ml/min for 10 to 90 seconds. In other words, the second plasma circulation is conducted preferably at the rate of at least 60 ml/min for not shorter than ten seconds.

Subsequent to the second plasma circulation step, the third plasma collecting step is executed for collecting the blood added anticoagulant. At the same time, the centrifugal separator drive unit 10 is activated to collect the plasma until the collected amount of the plasma in the plasma collecting bag 25 reaches a third predetermined amount that is larger than the second predetermined amount (by 10 to 150 g, or specifically, the third predetermined amount may be set to 80 g).

In the third plasma collecting step, the first liquid supply pump 11 starts blood-collecting at a predetermined rate (say, 60 ml/min). In the process, the second pump constituting an anticoagulant pump supplies an anticoagulant (such as the ACD-A solution) at a predetermined rate (say, 1/10 of the rate of the blood pump). The blood drawn from the donor is mixed with the ACD solution, and flows into the centrifugal separator 20 rotating at a predetermined speed (say, 4800 rpm) for collecting the plasma in the plasma collecting bag 25. The weight of the plasma collecting bag 25 is measured by the weight sensor 16, and the weight signal representing the measurement is applied to the controller 13. Therefore, when the weight of the plasma collected in the plasma collecting bag 25 reaches the third predetermined amount, the controller 13 closes the first flow path shutter means 81, opens the second flow path shutter means 82, and proceeds to the third plasma circulation step.

In the third plasma circulation step, the blood-collection is temporarily suspended and the centrifugal separator drive unit 10 is activated to circulate the plasma in the plasma collecting bag 25 to the centrifugal separator 20. The blood pump is operated at a predetermined rate lower than that in the first plasma circulation step, say, at 120 ml/min for about 30 sec. The third plasma circulation is preferably performed at a rate ranging from 60 to 250 ml/min for 10 to 90 seconds. In other words, the third plasma circulation is preferably executed at the rate of at least 60 ml/min for not shorter than 10 seconds.

Upon completion of the third plasma circulation step, a fourth plasma collecting step is executed. In this step, the blood added anticoagulant is collected and the centrifugal separator drive unit 10 is activated to collect the plasma until the collected amount of the plasma in the plasma collecting bag 25 reaches a fourth predetermined amount (10 to 150 g larger than the third predetermined amount, or specifically the fourth predetermined amount may be set to 120 g) larger than the third predetermined amount.

Specifically, the first liquid supply pump 11 is activated to start blood-collection at a predetermined rate (say, 60 ml/min). At the same time, the second pump constituting an anticoagulant pump supplies an anticoagulant (such as the ACD-A solution) at a predetermined rate (for example, 1/10 of the blood pump rate, for example). The blood supplied from the donor is mixed with the ACD solution and flows into the centrifugal separator 20 rotating at a predetermined speed (say, 4800 rpm), by which the plasma is collected in the plasma collecting bag 25. The weight of the plasma collecting bag 25 is measured by the weight sensor 16, and the weight signal representing the weight measurement is applied to the controller 13. As a result, when the weight of the plasma collected in the plasma collecting bag 25 reaches the fourth predetermined amount, the controller 13 closes the first flow path shutter means 81, opens the second flow path shutter means 82, and proceeds to the fourth plasma circulation step.

In the fourth plasma circulation step, the blood-collection is temporarily suspended and the centrifugal separator drive unit 10 is activated to circulate the plasma in the plasma collecting bag 25 to the centrifugal separator 20. In the process, the blood pump is activated at a predetermined rate lower than that in the first plasma circulation step, say, at 120 ml/min for about 30 sec. The fourth plasma circulation is preferably conducted at a rate of 60 to 250 ml/min for about 10 to 90 seconds. In other words, the fourth plasma circulation is preferably performed at a rate of at least 60 ml/min for at least ten seconds.

Upon completion of the fourth plasma circulation step, a fifth plasma collecting step is executed to collect the blood added anticoagulant. The centrifugal separator drive unit 10 is activated to collect the plasma in the plasma collecting bag 25. Specifically, the first liquid supply pump 11 starts blood-collection at a predetermined rate (say, 60 ml/min). At the same time, the second pump constituting the anticoagulant pump supplies an anticoagulant (such as the ACD-A solution) at a predetermined rate (say, 1/10 of the blood pump rate). The blood drawn from the donor is mixed with the ACD solution and flows into the centrifugal separator 20 rotating at a predetermined speed (say, 4800 rpm), by which the plasma is collected in the plasma collecting bag 25. Normally, when the optical sensor 15 detects the buffy coat layer in the separator accompanied with the increase in the amount of the plasma in the bag, the detection signal is applied to the controller 13, which in turn closes the first flow path shutter means 81 and opens the second flow path

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shutter means 82. Then the process proceeds to a fifth plasma circulation step. In the fifth plasma collecting step, the plasma continues to be collected until the buffy coat (BC boundary : the boundary between the plasma layer and the buffy coat layer) is detected by the sensor. In the apparatus according to this embodiment, as shown in the flowcharts of Figs. 5, 7, 9, the BC boundary is detected in the first to fourth plasma collecting steps. Upon detection of the BC boundary in the first to fourth plasma collecting steps, the plasma collecting operation is suspended, and the process proceeds to what apparently is assumed to be a fifth plasma circulation step (not actually the fifth circulation step but the final circulation step).

In the fifth plasma circulation step (final plasma circulation step), the blood-collection is temporarily suspended and the centrifugal separator drive unit 10 is activated to circulate the plasma in the plasma collecting bag to the centrifugal separator 20. The blood pump operates at a predetermined rate of, for example, 120 ml/min for 30 sec. The fifth plasma circulation is performed at a rate of 60 to 250 ml/min for 10 to 90 seconds, and preferably at a rate of at least 60 ml/min for not less than 10 seconds. Subsequent to this circulation step, the process proceeds to the program referred to as ① in Fig. 6 to perform the blood-collection for boundary adjustment.

As shown in Fig. 6, the blood-collection step for boundary adjustment can be regarded as a step of collecting a small amount of plasma. In this step, in order to keep the position of the buffy coat layer constant irrespective of the donor in the subsequent platelet collecting step, the blood is collected such that only a predetermined amount of red cells is obtained. The amount of supplied red cells is defined as the value derived from dividing the collected amount of blood by the hematocrit value of the donor. Practically about 12 ml of the blood is collected. This blood-collection is also started at a predetermined rate (say, 60 ml/min) by the first liquid supply pump 11. In the process, the second pump constituting the anticoagulant pump also supplies an anticoagulant (such as the ACD-A solution) at a predetermined rate (for example, 1/10 of the blood pump rate, for example). The blood collected from the donor is mixed with the ACD solution and flows into the centrifugal separator 20 rotating at a predetermined speed (say, 4800 rpm) to collect a small amount of plasma. The controller 13 calculates the blood collecting time based on the set collection amount and the pump rate, and terminales the blood-collection when the blood collecting time expires. Then the controller 13 closes the first flow path shutter means 81, opens the second flow path shutter means 82, and proceeds to a platelet collecting step.

Upon completion of the above-mentioned steps, the platelet collecting step is executed to accelerate the plasma circulation rate by the first liquid suppled pump 11. Then platelets are released from the centrifugal separator 20 and collected in the platelet collecting bag 26. The platelet collecting step is also known as the acceleration step. In this step, the controller 13 activates the blood pump so as to accelerate the blood pump from the same rate as that in the fourth circulation step to 200 ml/min stepwise by 10 ml/min at a predetermined time interval (say, every one second). When the rate reaches 200 ml/min, it is maintained until completion of the platelet collecting step.

Upon start of the platelet collecting step, the turbidity of the liquid passing through the turbidity sensor 14 is detected and output as a voltage value by the sensor. The output signal is applied to the controller 13. When the blood pump rate increases to reach a rate ranging from about 160 to 200 ml/min, the platelets contained in the buffy coat layer that have stayed in the centrifugal separator 20 is released. Accompanied with the release of the platelets, the turbidity value of the liquid passing through the turbidity sensor 14 becomes high. At a time point when the voltage output of the sensor drops by 0.2 V, the third flow path shutter means 83 is closed and the fourth flow path shutter means 84 is opened. Thus the platelet-rich plasma released from the centrifugal separator 20 is collected in the platelet collecting bag 26. The voltage output from the turbidity sensor 14 is converted into the platelet concentration by the controller 13 to calculate the platelet concentration in the platelet collecting bag 26 during the platelet collecting operation. The platelet concentration in the platelet collecting bag 26 drops after reaching a maximum value. At a time point when it is detected that the maximum concentration is reached, the platelet collecting step is completed and the process proceeds to the buffy coat collecting step.

Upon completion of the platelet collecting step, the buffy coat collecting step is executed. In this step, the controller 13 closes the fourth flow path shutter means 84 and opens the fifth flow path shutter means 85. The plasma in the plasma collecting bag 25 is fed to the centrifugal separator 20 by the blood pump 11. At the same time, the liquid that has been released from the centrifugal separator 20 (the buffy coat layer portion that has flowed out) flows into the buffy coat collecting bag 27. In the buffy coat collecting step, the final rate of the blood pump in the platelet collecting step is maintained and the rotational speed of the centrifugal separator is decreased to 4600 rpm. As a result, the buffy coat is released from the centrifugal separator 20 and collected in the buffy coat collecting bag 27. At a time point when the amount of the collected buffy coat reaches the value calculated based on the hematocrit value of the donor and the amount of platelet supplied from the donor, the blood pump 11 is stopped and all the valves are closed. Thus the centrifugal separator 20 stops rotating to complete the buffy coat collecting step.

Then, the blood returning step is executed for returning the blood in the centrifugal separator 20. The controller 13 rotates the blood pump 11 in reverse direction, opens the first flow path shutter means 81, and returns the red cell layer remaining in the centrifugal separator 20 to the donor through the first line 21.

Thus, the first (initial) platelet collecting operation is completed.

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Then, the process proceeds to the second platelet collecting operation as shown in Fig. 7.

First, referring to Fig. 7, the buffy coat returning step is executed, in which the buffy coat collected in the first platelet collecting step is returned to tire centrifugal separator 20 prior to the next blood-collection step. Once the process proceeds to the buffy coat returning step, the controller 13 rotates the centrifugal separator 20 at a predetermined rotational speed (say, 4800 rpm), opens the fifth flow path shutter means 85 and the fourth flow path shutter means 84, and starts the blood pump 11 at a predetermined rate (default value : 100 ml/min). The buffy coat contained in the buffy coat collecting bag 27 is fed through the fifth flow path shutter means 85 to the centrifugal separator 20. The air in the centrifugal separator 20 is sent through the second line 22 and the fourth flow path shutter means 84 to the platelet collecting bag 26. After rotating the blood pump 11 to collect the set amount of the buffy coat, the buffy coat returning step is completed.

The process proceeds to the program referred to as ② shown in Fig. 8 after completion of the first plasma collecting step, the first plasma circulation step, the second plasma collecting step, the second plasma circulation step, the third plasma collecting step, the third plasma circulation step, the fourth plasma collecting step, the fourth plasma circulation step, the fifth plasma collecting step and the fifth plasma circulation step, followed by the blood-collection step for boundary adjustment, the platelet collecting step, the buffy coat collecting step and the blood returning step to complete the second platelet collecting operation.

Now, explanation will be given with respect to the last platelet collecting operation as shown in Fig. 9. In this embodiment, the third operation is assumed to be the last one. However, the fourth or subsequent platelet collecting operation may be the last one as far as the equal effects can be obtained. Each of these platelet collecting operations except the last one is identical to the second platelet collecting operation (Figs. 7 and 8).

First, as shown in Fig. 9, the buffy coat returning step is executed. In this step, the buffy coat collected by the second platelet collecting operation is returned into the centrifugal separator 20 prior to the next blood-collection step.

When the process proceeds to the buffy coat returning step, the controller 13 rotates the centrifugal separator 20 at a predetermined rotational speed (say, 4800 rpm), opens the fifth flow path shutter means 85 and the fourth flow path shutter means 84, and activates the blood pump 11 at a predetermined rate (default value : 100 ml/min). The buffy coat contained in the buffy coat collecting bag 27 is passed through the fifth flow path shutter means 85 and supplied to the centrifugal separator 20. The air in the centrifugal separator 20 is sent to the platelet collecting bag 26 through the second line 22 and the fourth flow path shutter means 84. After rotation of the blood pump 11 to collect the set amount of buffy coat, the buffy coat returning step is completed.

Then, the first plasma collecting step is executed in which the first and second liquid supply pumps 11, 12 are started to collect the blood added anticoagulant, and the centrifugal separator drive unit 10 is activated to collect a first predetermined amount of plasma obtained from the blood into the plasma collecting bag 25.

Upon start of the first blood-collection, the first liquid supply pump 11 starts blood-collection at a predetermined rate (say, 60 ml/min). At the same time, the second pump constituting an anticoagulant pump supplies an anticoagulant (such as the ACD-A solution) at a predetermined rate (say, 1/10 of the blood pump rate). The blood supplied from the donor is mixed with the ACD solution, flows through the first line 21, the chamber and the first flow path shutter means 81 and into the centrifugal separator 20. In this process, the sixth flow path shutter means 86, the fifth flow path shutter means 85, the second flow path shutter means 82, the third flow path shutter means 83 and the seventh flow path shutter means 87 are closed. Meanwhile the first flow path shutter means 81 and the fifth flow path shutter means 85 are opened. When the blood added ACD is supplied to the centrifugal separator 20, the sterilized air that has already been admitted into the centrifugal separator 20 flows through a line sensor and the fifth flow path shutter means 85 into the buffy coat collecting bag 27. Simultaneously with the start of the blood-collection step, the centrifugal separator 20 starts rotating at a predetermined speed (say, 4800 rpm). The centrifugal separator 20 is supplied with the ACD-added blood during the rotation, such that the blood is centrifugally separated in the separator into, from the inside thereof, a plasma layer, a buffy coat layer (BC layer) and a red cell layer. When (about 270 ml of) the ACD-added blood exceeding the capacity of the centrifugal separator is supplied, the centrifugal separator 20 is filled with the blood, and the plasma overflows through the outlet of the centrifugal separator 20. The turbidity sensor 14 mounted on the second line 22 connected to the outlet of the centrifugal separator 20 detects that the fluid flowing through the line has changed from air to plasma. In response to the detection signal of the turbidity sensor 14, the controller 13 closes the fifth flow path shutter means 85 and opens the third flow path shutter means 83 to collect the plasma in the plasma collecting bag 25. The weight of the plasma collecting bag 25 is preliminarily measured by the weight sensor 16 and the weight measurement signal is applied to the controller 13. As a result, when the weight of the plasma collected in the plasma collecting bag 25 increases to a predetermined amount (say, 20 g), the controller 13 closes the first flow path shutter means 81, opens the second flow path shutter means 82, and proceeds to the first plasma circulation step.

The process then proceeds to the program referred to as ③ in Fig. 10 after the above-mentioned first plasma circulation step, the second plasma collecting step, the second plasma circulation step, the third plasma collecting step, the third plasma circulation step, the fourth plasma collecting step, the fourth plasma circulation step, the fifth plasma collecting step and the fifth plasma circulation step, followed by the blood-collection step for boundary adjust-

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ment, the platelet collecting step and the blood returning step, thus completing the last platelet collecting operation. The difference between the last and the second platelet collecting operations is that different bags are used for admitting the air in the first plasma circulation step, and the blood is returned without executing the buffy coat collecting step in the last platelet collecting operation.

It is known that in a particle suspension, the apparent viscosity of a particle suspension increases accompanied with the increase in the particle concentration. The increased viscosity reduces the difference in sedimentation velocity between particles having different specific gravity or specific size. When this fact is applied to the platelet collecting step, it follows that an increased viscosity of the particle suspension in the centrifugal separator 20 increases the probability that the white cells having higher specific gravity or specific size than that of the platelets flow out together with the platelets. During the blood-collection, the centrifugal separator 20 is rotating and the centrifugal force is constantly applied to the blood components in the centrifugal separator 20. Each blood component in the centrifugal separator 20, therefore, is progressively concentrated by the centrifugal force. As viewed from outside of the separator, therefore, as shown in Fig. 3, the blood is separated into a red cell layer, a buffy coat layer and a plasma layer. The size of particles in each layer is sequentially reduced along the direction from the outside to inside.

A plurality of what is called cake layers are formed in the centrifugal separator 20. These cake layers are steadily compressed. The newly incoming whole blood flows from the cake layer formed by the outermost cells, which are trapped in the cake layer. Meanwhile the other components are passed to the buffy coat layer and the plasma layer. In the case where the cell cake layers and the buffy coat cake layer are excessively compressed, however, the gap between fine particles in each layer is reduced. This often leads to the phenomenon where platelets are trapped in the cell cake layer of the buffy coat cake layer. The collecting efficiency of the platelets is, thus, expected to be deteriorated.

According to this invention, however, the plasma collecting step is divided into a plurality of steps and therefore the time length of each plasma collecting step can be shortened. The cake layers, therefore, are compressed more slowly. In addition, since a plurality of plasma circulation steps are provided, only the plasma components free of cells enter the centrifugal separator 20 and pass through the cell cake layer and the buffy coat, cake layer within a short time. The cell cake layer and the buffy coat cake layer are thus expanded, and it is expected that the compression, if any, of the cake layers is eliminated. Consequently, the excessive compression of the cell cake layer and the buffy coat cake layer is suppressed, so that less platelets are considered to be trapped in the cell cake layer or the buffy coat cake layer.

EXAMPLES

An apparatus having a circuit configuration as shown in Fig. 4 provided with two pumps including an ACD pump and a blood pump 11 was fabricated, and the platelet collecting performance was compared between the two pumps. A comparison test was conducted on the same donor at an interval of two weeks or longer. An evaluated operation flow was compared as below (n = 2 examples). The number of platelets and the number of white cells of the concentrated plasma containing platelets thus obtained was measured by Sysmex (R)NE-6000. The lower limit of WBC measurement for Sysmex is 0.1 x 10^2 [cells/muL]. For the samples with WBC lower than the lower limit of measurement, therefore, the Nageotte [1:9] method was used for the measurement. In this example, 40 ml of the platelet was collected.

(Example)

The platelet collecting operation was conducted three times using the aforementioned method. The blood-collection rate was 60 ml/min, a first circulation after the total amount of plasma has reached 20 g was conducted under the conditions of 200 ml/min for 30 seconds, a second circulation after the total amount of plasma has reached 50 g was conducted at the rate of 120 ml/min for 30 seconds, a third circulation after tire total amount of plasma has reached 80 g was conducted at the rate of 120 ml/min for 30 seconds, a fourth circulation after detection of a buffy coat layer by an optical sensor was conducted at the rate of 120 ml/min for 30 seconds. The platelets were collected under conditions of the acceleration rate of 10 ml/min/sec and the rate of 200 ml/min up to a predetermined concentration, and the buffy coat was collected at the rate of 205 ml/min up to 40 ml. In the second and third platelet collecting operations, the buffy coat was returned to the centrifugal separator prior to the blood-collection. In the third platelet collecting operation, no buffy coat was collected.

(Comparative Example)

The same apparatus as that used in the above-mentioned embodiment was employed. The platelet collecting operation was performed three times, each of which was conducted under the following conditions. Specifically, the blood-collection rate was set to 60 ml/min, and after detection of the buffy coat layer by the optical sensor, the first circulation was conducted at the rate of 120 ml/min for 3 seconds and the second circulation was conducted at the

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rate of 75 ml/min for 27 seconds. The platelets were collected at the acceleration rate of 8 ml/min/sec up to 50 % of the maximum platelet concentration.

The platelet concentration and the white cell concentration of the plasma with concentrated platelets thus collected in the embodiment and the reference are as follows:

Table 1

	Platelet concentration [cells/muL]	
	Ex. 1	Ex. 2
Example	160.1×10^4	128.0×10^4
Comparative Example	130.1×10^4	123.0×10^4

Table 2

	White cell concentration [cells/muL]	
	Ex. 1	Ex. 2
Embodiment	0.4×10^1	0.4×10^2
Comparative Example	0.6×10^2	0.9×10^2

The blood component collecting apparatus according to this invention is provided with only two pumps, which can be reduced in size. The blood-collection is temporarily suspended in a given platelet collecting operation and the plasma recirculation step for recirculating the collected plasma in the centrifugal separator is executed at least twice. Therefore, the cell layer and the buffy coat layer are prevented from being excessively compressed in the centrifugal separator. It is therefore possible to produce a platelet-contained liquid (the plasma containing concentrated platelets) with a lesser amount of white cells mixed in and exhibiting high platelet collecting efficiency.

Further, the blood component collecting circuit including a cassette housing according to the invention can be readily mounted on a blood component collecting apparatus, leading to quick preparatory work. Also, the blood component collecting circuit can be effectively used for tire blood component collecting apparatus which executes the above-mentioned plasma recirculation step.

Claims

1. A blood component collecting apparatus comprising

a blood component collecting circuit including:
a centrifugal separator having a rotor having an internal blood storage space, an inlet and an outlet communicating with said blood storage space for centrifugally separating the blood introduced therein through said inlet by rotation of said rotor;
a first line for connection between a blood-collection needle or a blood-collection unit connector and said inlet of said centrifugal separator;
a second line connected to said outlet of said centrifugal separator;
a third line connected to said first line for injecting an anticoagulant;
a plasma collecting bag having a first tube connected to a middle point of said first line and a second tube connected to said second line; and
a platelet collecting bag connected to said second line;
said blood component collecting apparatus further comprising a centrifugal separator drive unit for rotating said rotor of said centrifugal separator, a first liquid supply pump for said first line arranged at a position of said first line between said centrifugal separator and a connecting portion for connecting said first tube to said first line, a second liquid supply pump for said third line, a plurality of flow path shutter means for opening/closing the flow paths of said blood component collecting circuit; and a controller for controlling said centrifugal separator drive unit, said first liquid supply pump, said second liquid supply pump and said plurality of flow path shutter means;
wherein said controller controls said centrifugal separator drive unit, said first liquid supply pump, said second liquid supply pump and said plurality of flow path shutter means so as to execute a platelet collecting operation which includes at least twice of plasma collecting-circulation steps including a plasma collecting step for col-

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lecting blood added anticoagulant by starting said first and second liquid supply pumps and collecting said plasma obtained from said blood in said plasma collecting bag by activating said centrifugal separator drive unit and a plasma circulation step for temporarily suspending blood-collection subsequent to said plasma collecting step and circulating said plasma contained in said plasma collecting bag to said centrifugal separator by activating said centrifugal separator drive unit, subsequent to said plasma collecting-circulation steps, a platelet collecting step for collecting platelet released from said centrifugal separator into said platelet collecting bag by accelerating a plasma circulation rate by said first liquid supply pump; and to execute a blood returning step, subsequent to said platelet collecting step, for returning said blood contained in said centrifugal separator.

2. The blood component collecting apparatus according to claim 1, wherein said controller executes said plasma collecting-circulation step at least three times.

3. The blood component collecting apparatus according to claim 1 or 2, wherein said a platelet collecting operation which includes a small plasma collecting step for boundary adjustment, subsequent to said plasma collecting-circulation steps and prior to said platelet collecting step, wherein said controller executes said small plasma collecting step for collecting the blood added anticoagulant by starting said first and second liquid supply pumps and collecting a predetermined amount of plasma obtained from the blood in said plasma collecting bag by activating said centrifugal separator drive unit.

4. The blood component collecting apparatus according to any one of claims 1 to 3, wherein said controller executes a first plasma collecting-circulation step including a first plasma collecting step for collecting blood containing added anticoagulant by starting said first and second liquid supply pumps and collecting a first predetermined amount of plasma obtained from said blood in said plasma collecting bag by activating said centrifugal separator drive unit and a first plasma circulation step, subsequent to said first plasma collecting step, for temporarily suspending blood-collection and circulating said plasma contained in said plasma collecting bag to said centrifugal separator by activating said centrifugal separator drive unit; and a second plasma collecting-circulation step including a second plasma collecting step for collecting blood containing added anticoagulant by starting said first and second liquid supply pumps and collecting plasma by activating said centrifugal separator drive unit until an total amount of plasma contained in said plasma collecting bag reaches a second predetermined amount and a second plasma circulation step, subsequent to said second plasma collecting step, for temporarily suspending blood-collection and circulating said plasma contained in said plasma collecting bag to said centrifugal separator by activating said centrifugal separator drive unit.

5. The blood component collecting apparatus according to claim 4, wherein said controller executes a third plasma collecting-circulation step including a third plasma collecting step, subsequent to said second plasma collecting-circulation step, for collecting blood containing added anticoagulant by starting said first and second liquid supply pumps and collecting said plasma by activating said centrifugal separator drive unit until an total amount of said plasma contained in said plasma collecting bag reaches a third predetermined amount, and a third plasma circulation step, subsequent to said third plasma collecting step, for temporarily suspending blood-collection and circulating said plasma contained in said plasma collecting bag to said centrifugal separator by activating said centrifugal separator drive unit.

6. The blood component collecting apparatus according to claim 5, wherein said controller executes a fourth plasma collecting-circulation step including a fourth plasma collecting step, subsequent to said third plasma collecting-circulation step, for collecting blood containing added anticoagulant by starting said first and second liquid supply pumps and collecting said plasma by activating said centrifugal separator drive unit until an total amount of said plasma contained in said plasma collecting bag reaches a fourth predetermined amount, and a fourth plasma circulation step, subsequent to said fourth plasma collecting step, for temporarily suspending blood-collection and circulating said plasma contained in said plasma collecting bag to said centrifugal separator by activating said centrifugal separator drive unit.

7. The blood component collecting apparatus according to claim 6, wherein said controller executes a fifth plasma collecting-circulation step including a fifth plasma collecting step, subsequent to said fourth plasma collecting-circulation step, for collecting blood containing added anticoagulant by starting said first and second liquid supply pumps and collecting said plasma in said plasma collecting bag by activating said centrifugal separator drive unit, and a fifth plasma circulation step, subsequent to said fifth plasma collecting step for temporarily suspending blood-collection and circulating said plasma contained in said plasma collecting bag to said centrifugal separator by activating said centrifugal separator drive unit.

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8. The blood component collecting apparatus according to any one of claims 1 to 7, further comprising a weight sensor for measuring the weight of said plasma collecting bag.

9. The blood component collecting apparatus according to any one of claims 1 to 8, wherein said controller controls said centrifugal separator drive unit, said first liquid supply pump, said second liquid supply pump and a plurality of said flow path shutter means such that said platelet collecting operation is performed at least twice.

10. The blood component collecting apparatus according to any one of claims 1 to 9, wherein said blood component collecting circuit includes a buffy coat collecting bag connected to said second line, wherein subsequent to said platelet collecting step and prior to said blood returning step, said controller executes a buffy coat collecting step for increasing the plasma circulation rate by said first liquid supply pump to a level higher than the final rate in said platelet collecting step and releasing the buffy coat from said centrifugal separator into said buffy coat collecting bag.

11. The blood component collecting apparatus according to any one of claims 1 to 9, wherein said blood component collecting circuit includes a buffy coat collecting bag connected to said second line, wherein subsequent to said platelet collecting step and prior to said blood returning step, said controller executes a buffy coat collecting step for increasing the plasma circulation rate by said first liquid supply pump to a level equal to or higher than the final rate in said platelet collecting step while reducing the rotational speed of the rotor of said centrifugal separator to release the buffy coat from said centrifugal separator into said buffy coat collecting bag.

12. The blood component collecting apparatus according to claim 10 or 11, wherein said controller controls said first liquid supply pump and a plurality of said flow path shutter means to execute a buffy coat returning step for returning the collected buffy coat into said centrifugal separator prior to the next blood-collection step in the case where the platelet collecting operation is further executed subsequent to said buffy coat collecting step.

13. A blood component collecting circuit comprising:

a centrifugal separator having an inlet and an outlet;
a blood-collection needle or a blood-collection unit connector;
a first line having a first pump tube for connection between said blood-collection needle or said blood-collection unit connector and the inlet of said centrifugal separator;
a second line connected to the outlet of said centrifugal separator;
a third line having a second pump tube connected to a portion near said blood-collection needle or said blood-collection unit connector of said first line;
a plasma collecting bag having a first tube connected to a portion of said first line between said blood-collection needle or said blood-collection unit connector and said first pump tube and a second tube connected to said second line;
a platelet collecting bag having a third tube connected to said second line; and
a cassette housing for partially containing and partially holding said first line, said second line, said third line, said first tube, said second tube and said third tube;
wherein said first pump tube and said second pump tube are fixed on said cassette housing so as to extend therefrom;
wherein said cassette housing includes a first opening for exposing the portion of said first line between said blood-collection needle or said blood-collection unit connector and said first pump tube and capable of being intruded by a flow path shutter means, a second opening for exposing said first pump tube and capable of being intruded by a flow path shutter means, a third opening for exposing said second tube and capable of being intruded by a flow path shutter means, a fourth opening for exposing said third tube and capable of being intruded by a flow path shutter means, a fifth opening for exposing the portion of said second line between said centrifugal separator and a connecting portion for connecting said fourth tube to said second line and capable of being intruded by a flow path shutter means.

14. The blood component collecting circuit according to claim 13, wherein said second line is connected to said first line, and said cassette housing includes a sixth opening for exposing a portion of said second line between a connecting portion to said first line and said connecting portion of said fourth tube and capable of being intruded by a flow path shutter means.

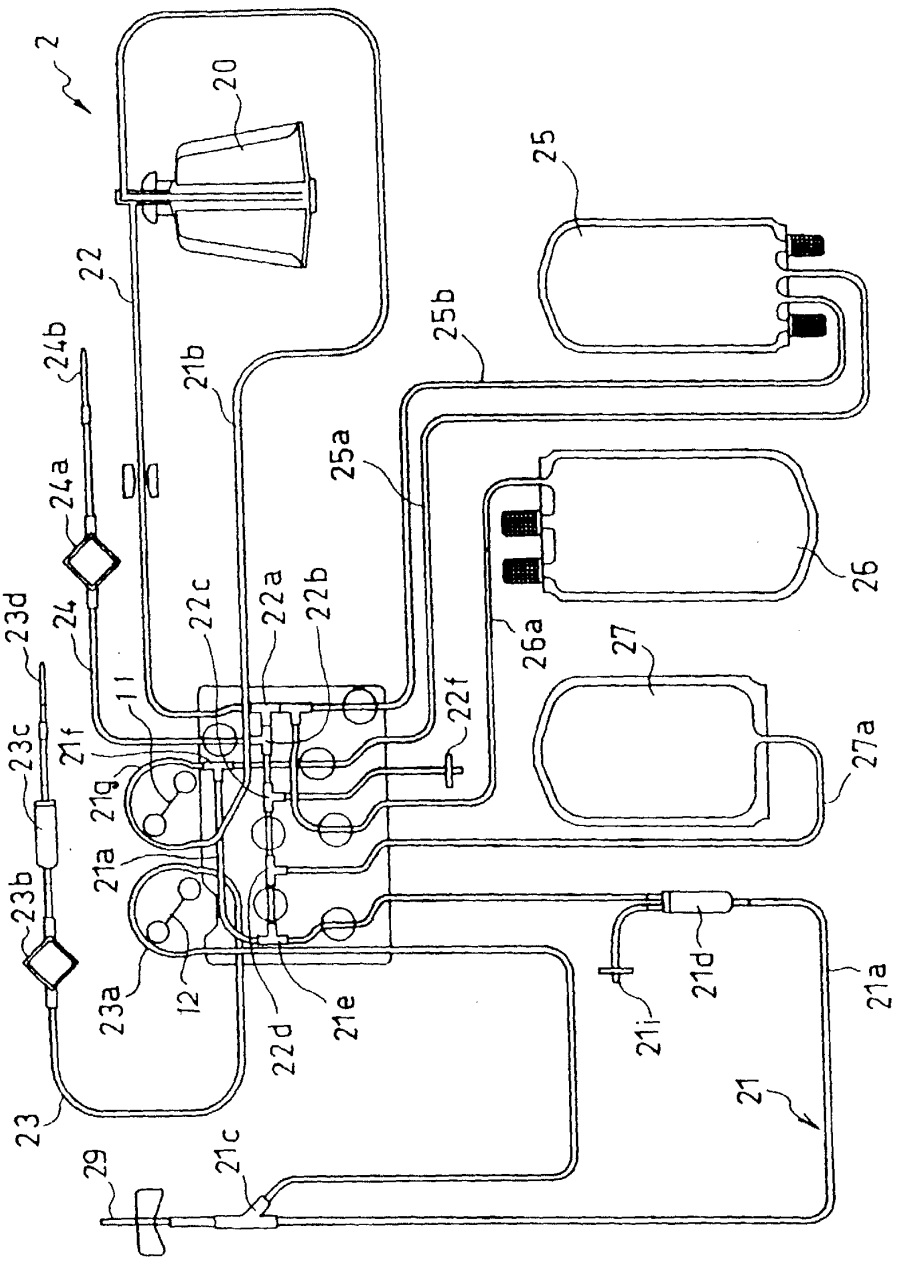
15. The blood component collecting circuit according to claim 14, further comprising a fourth line connected to said

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second line, wherein said cassette housing partially contains and partially holds said fourth line and includes a seventh opening for exposing said fourth line and capable of being intruded by a flow path shutter means.

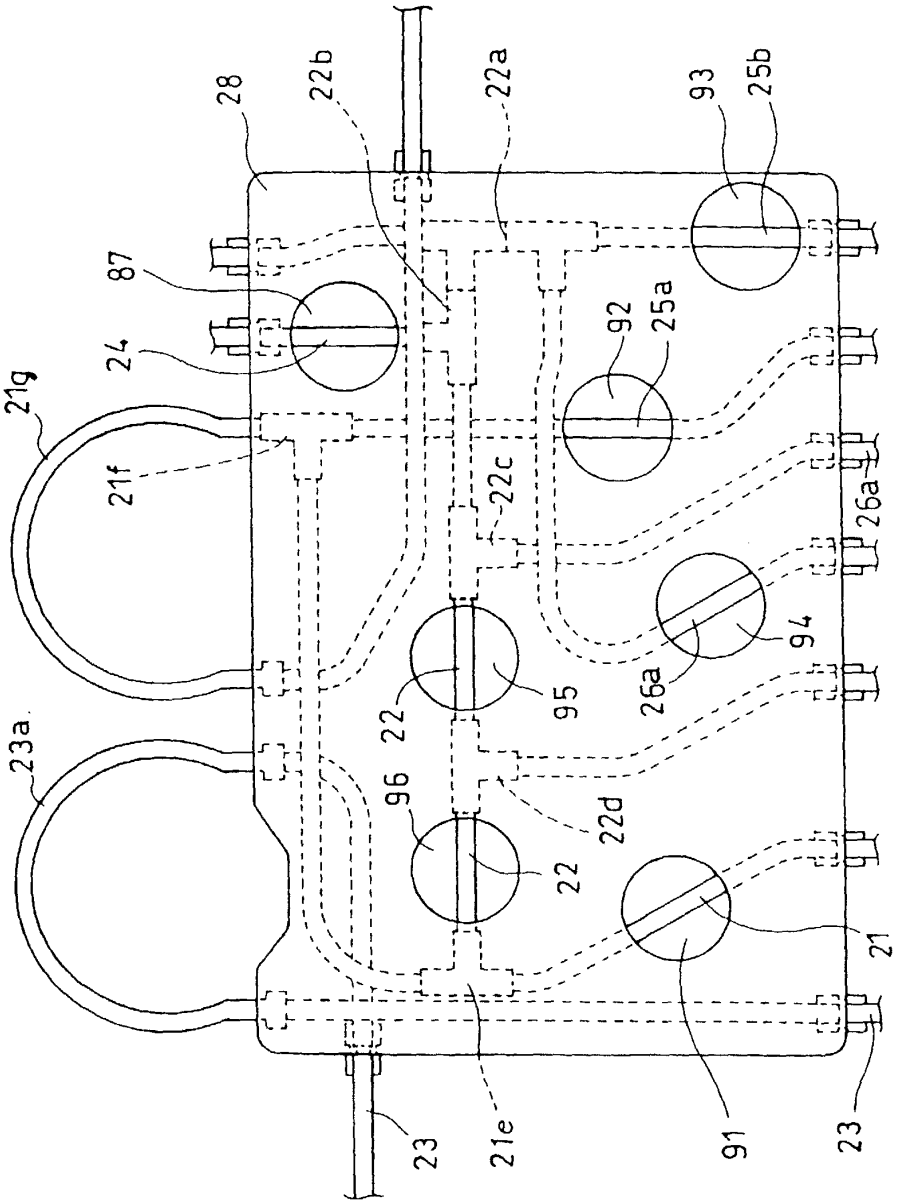
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Fig. 1



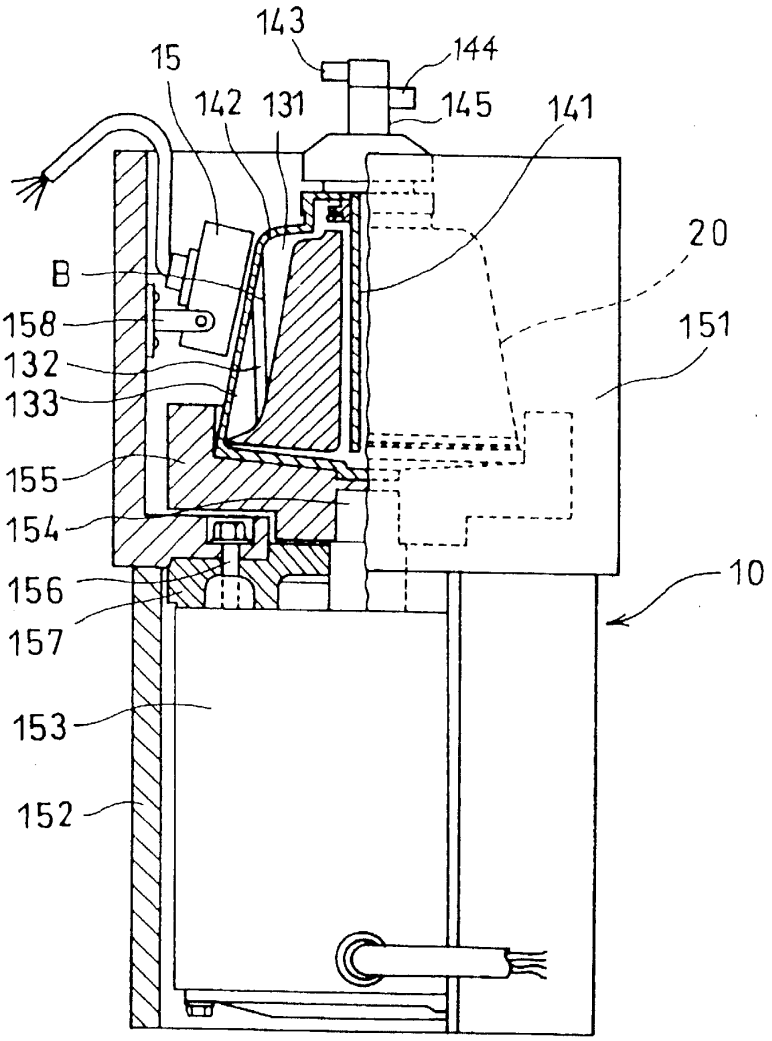
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Fig. 2



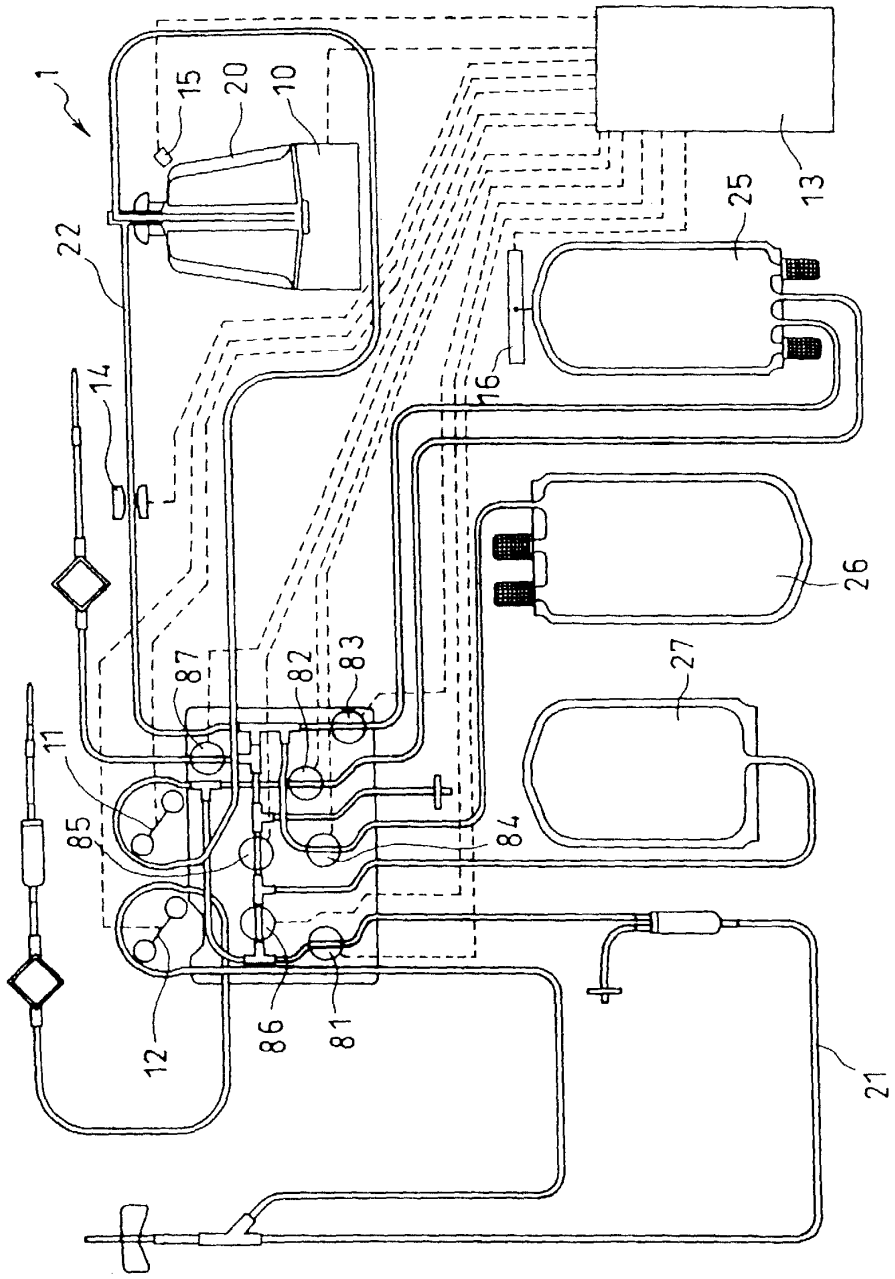
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Fig. 3



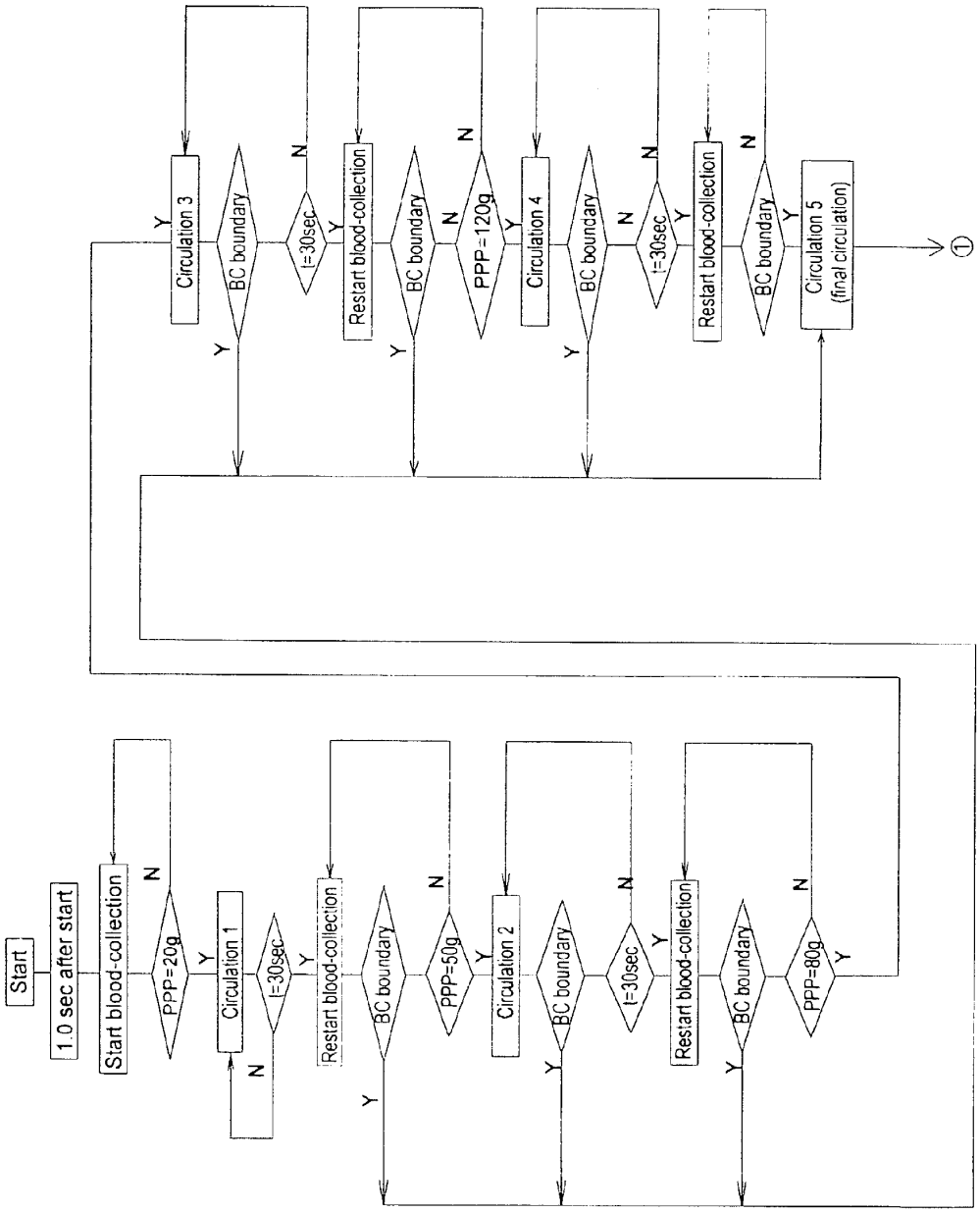
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Fig. 4



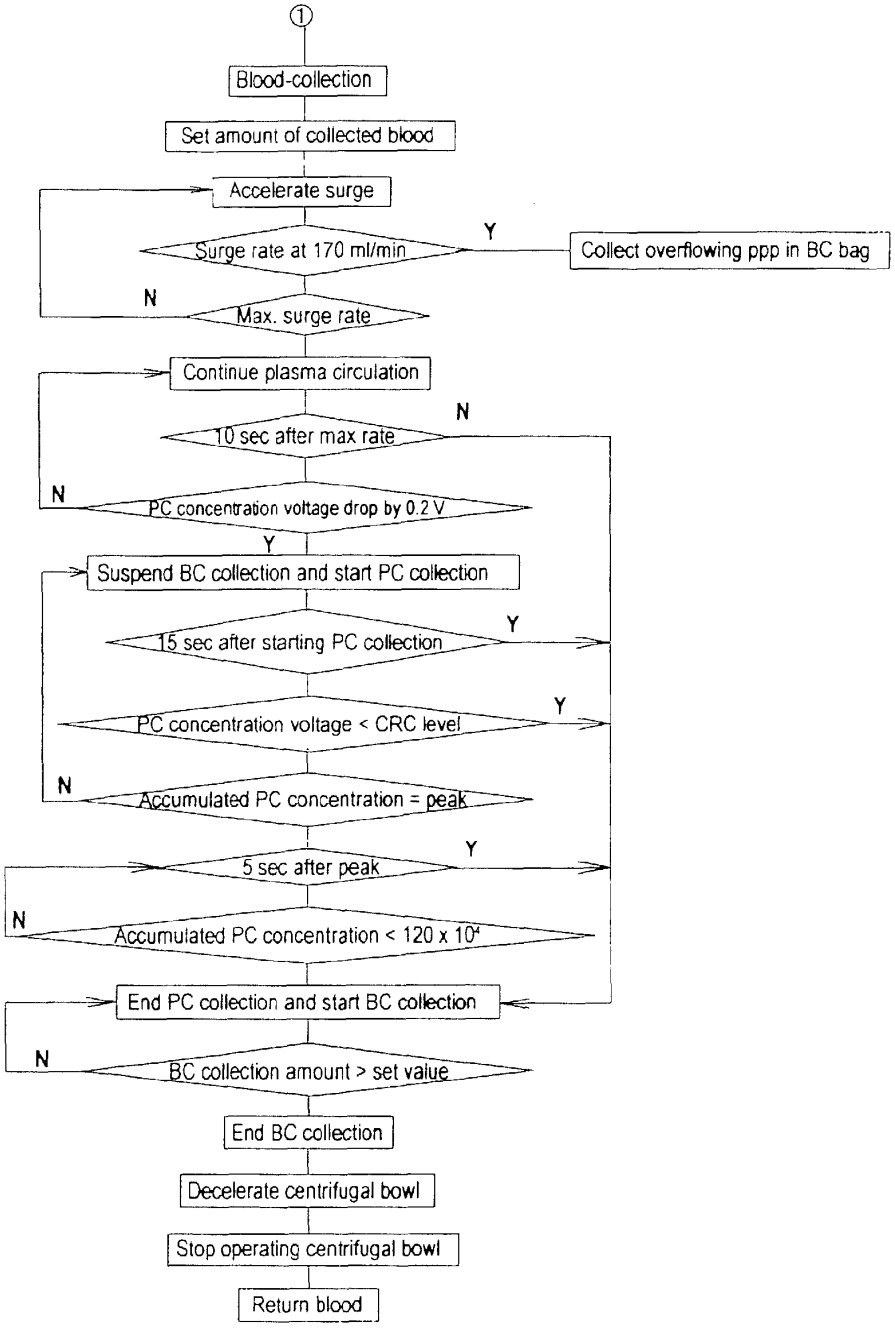
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Fig. 5



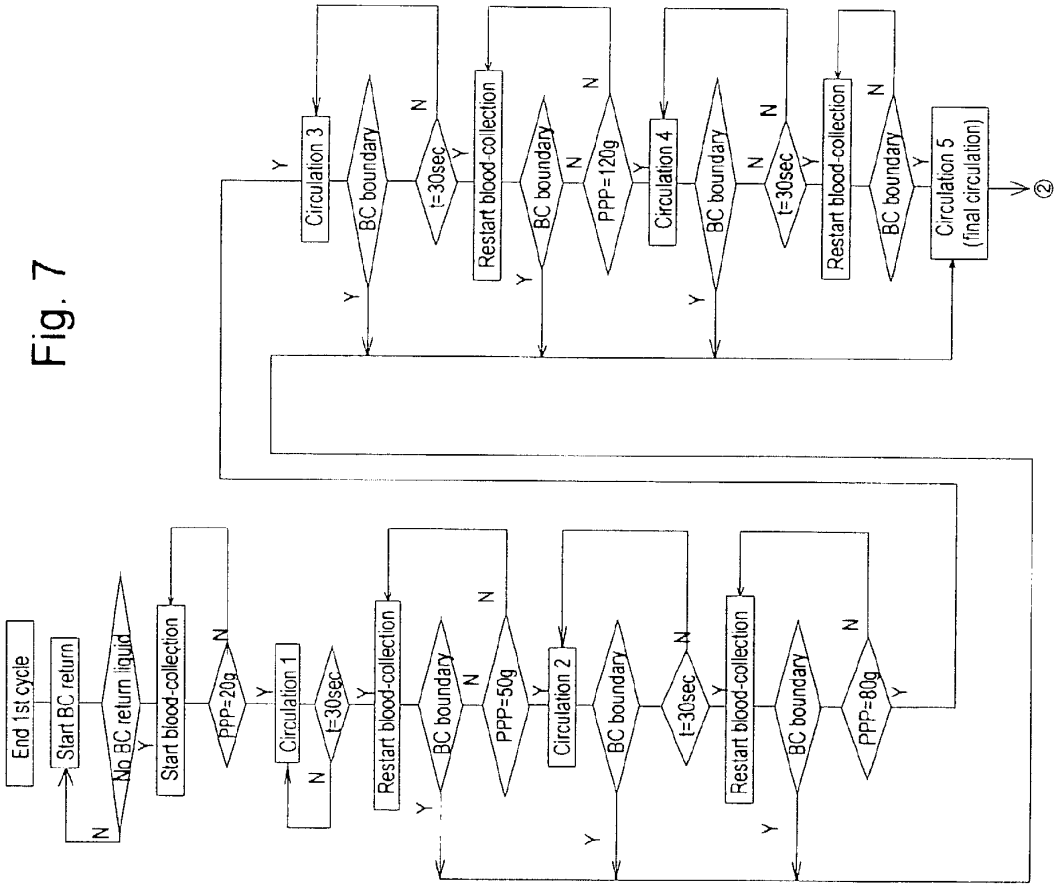
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Fig. 6



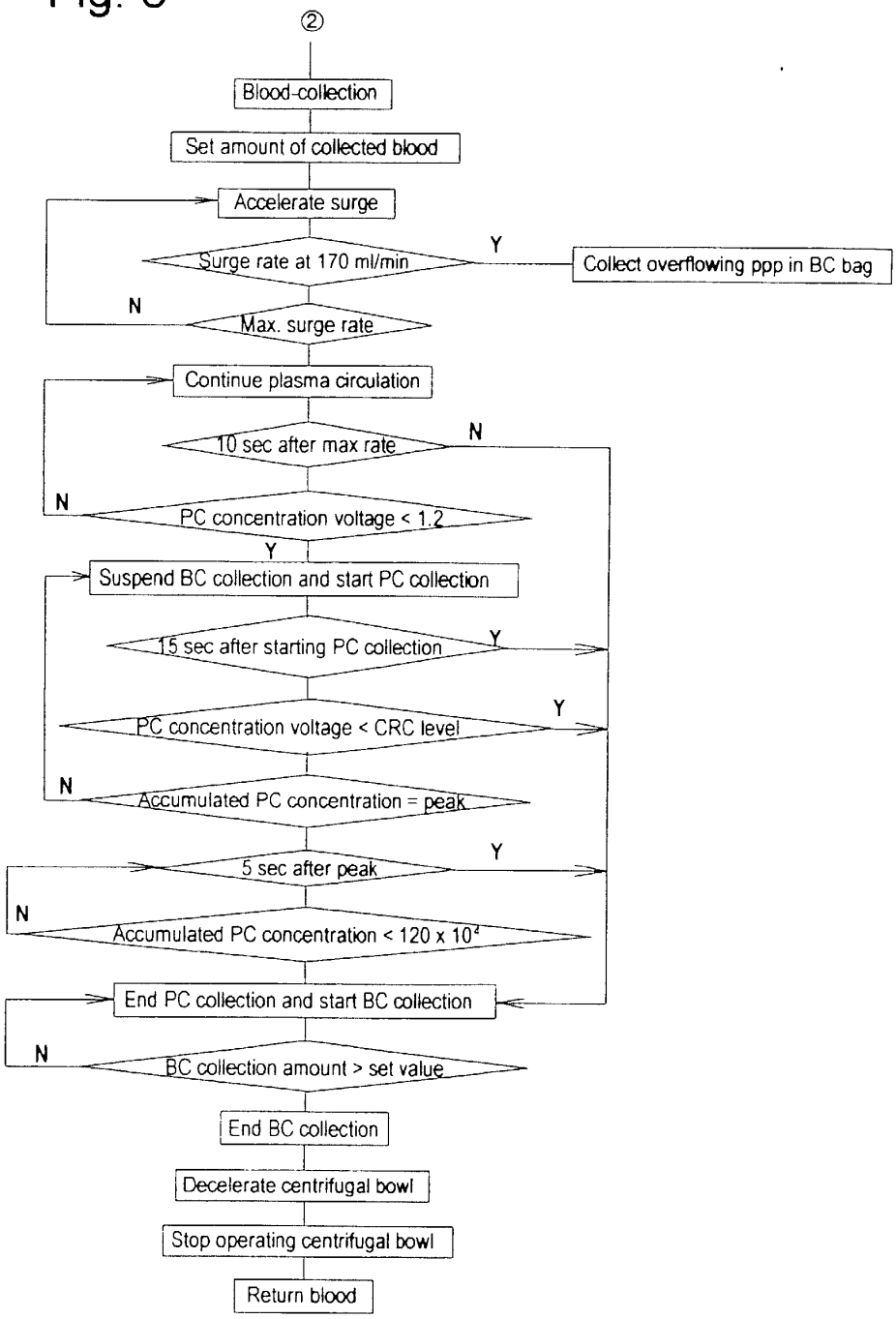
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Fig. 7



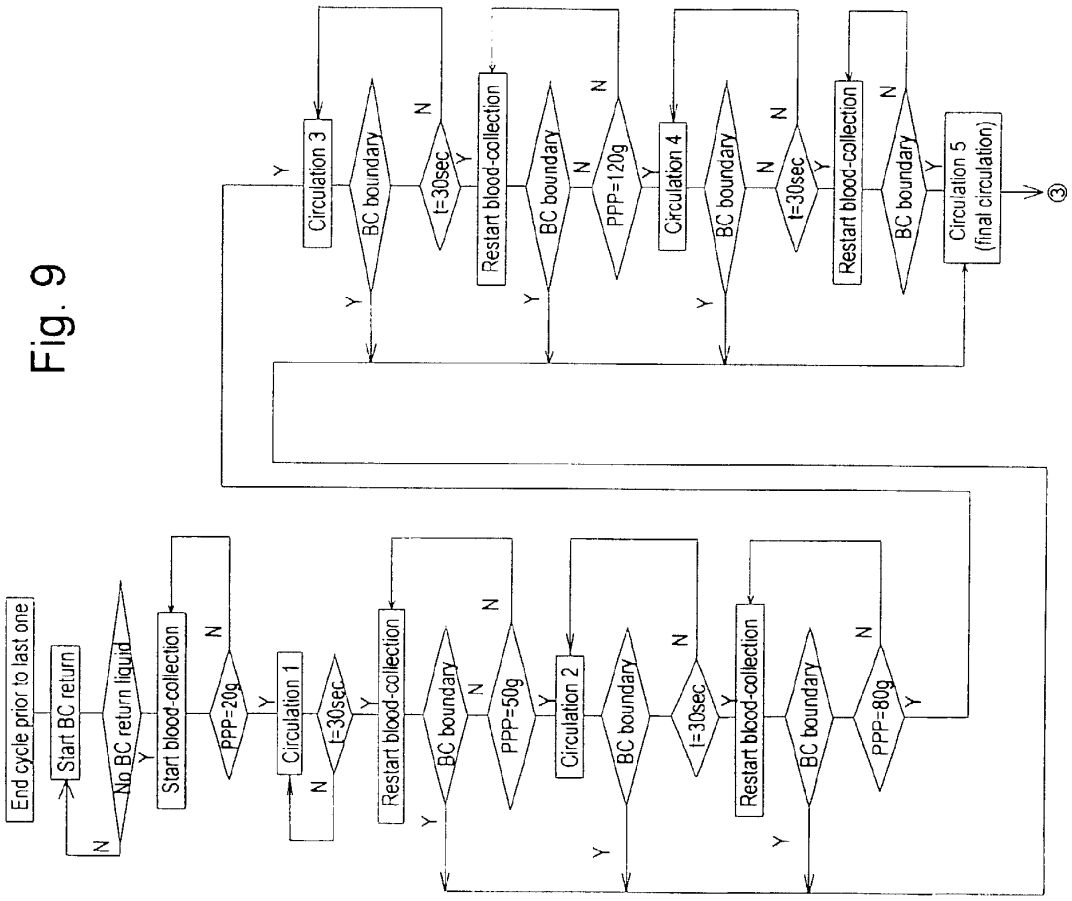
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Fig. 8



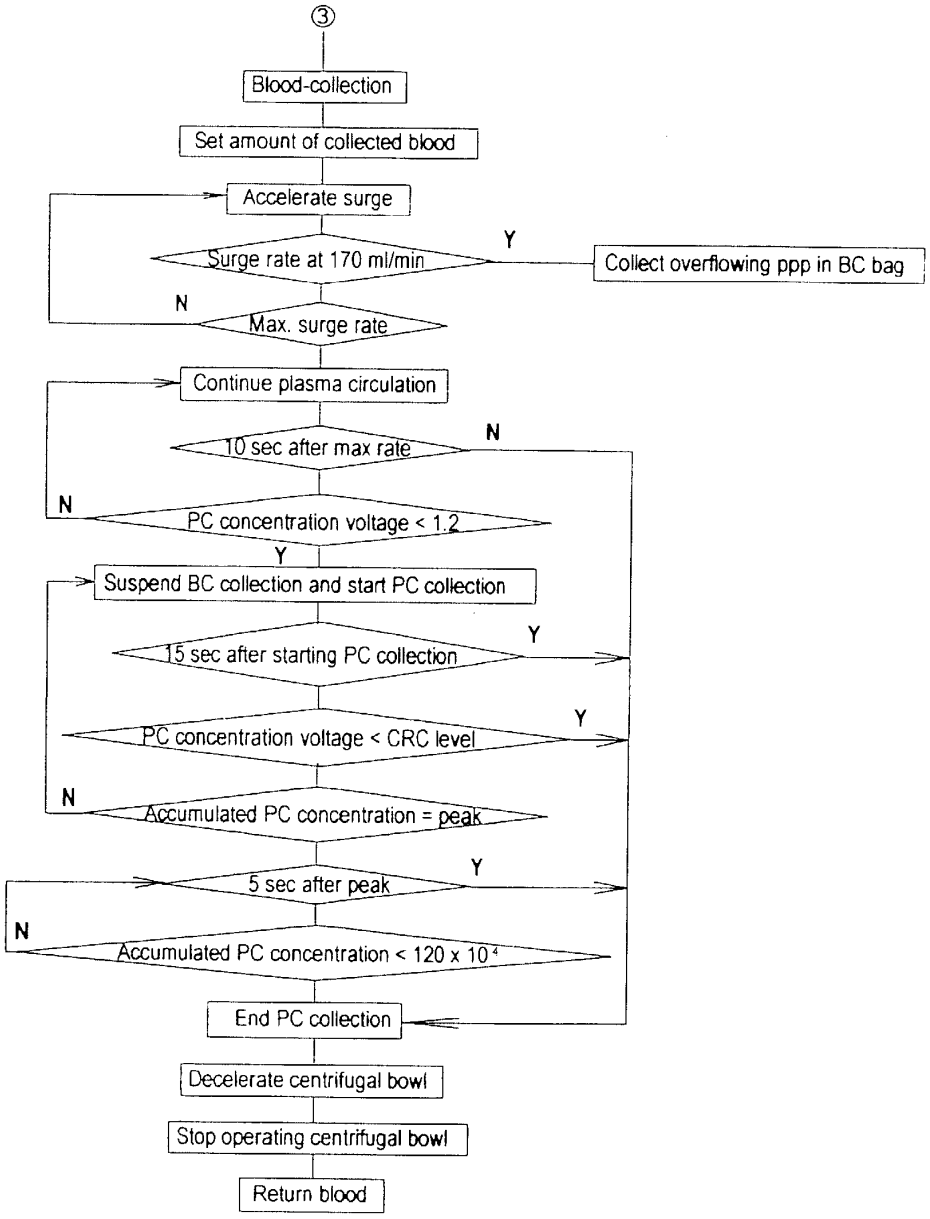
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Fig. 9



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Fig. 10



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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 40 1466

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	WO 96 40399 A (BAXTER INTERNATIONAL INC.) 19 December 1996 * page 9, line 1 - line 9 * * page 10, line 3 - line 24 * * page 11, line 16 - line 23 *	1,13	A61M1/36
D,A	WO 94 25086 A (HAEMONETICS CORP.) 10 November 1994 * page 6, line 30 - page 9, column 32 * * page 10, line 18 - line 34 * * page 11, line 5 - line 12 * * figure 6 *	1,13	
A	US 4 049 192 A (D KREBS) 20 September 1977 * column 2, line 54 - column 3, line 11 * * figure 2 *	13	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A61M

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	18 September 1998	Vereecke, A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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Espacenet

Bibliographic data: EP1057534 (A1) — 2000-12-06

Centrifugation bowl with filter core

Inventor(s): PAGES ETIENNE [FR] ± (PAGES, ETIENNE)

Applicant(s): HAEMONETICS CORP [US] ± (HAEMONETICS CORPORATION)

Classification: - international: ***A61M1/02; B01D63/08; B01D63/16; B04B11/02; B04B3/00; B04B5/04; B04B7/08; B04B7/16; G01N33/48;*** (IPC1-7): B04B5/04; B04B7/08
- cooperative: **B04B5/0442**; **B04B7/08**; B04B2005/0464; B04B2005/0478

Application number: EP20000303021 20000410 Global Dossier

Priority number(s): US19990325253 19990603

Also published as: CN1131729 (C) CN1276268 (A) JP2001017540 (A) JP3577444 (B2) US2002032112 (A1) more

Abstract of EP1057534 (A1)

A centrifugation bowl for separating blood products, includes a cylindrical filter core disposed within the bowl preferably coaxial with the bowl and preferably rotating with the bowl. The centrifugation bowl (214) includes a rotating bowl body (302) with a closed bottom (306) and defining an enclosed separation chamber (304). The filter core (328) includes a filter membrane (330) that is sized to block at least white blood cells, but to allow plasma to pass through. The filter core is generally arranged within the separation chamber such that plasma is forced to pass through the filter core radially inwards before being removed from the centrifugation bowl. To this end, the filter core includes at its bottom portion a truncated conical portion (332) converging downwardly and ending at a predetermined height above the bowl bottom. The addition of the filter core provides an efficient, low-cost method for recovering a "purer" plasma fraction from a donor, to the exclusion of white blood cells.

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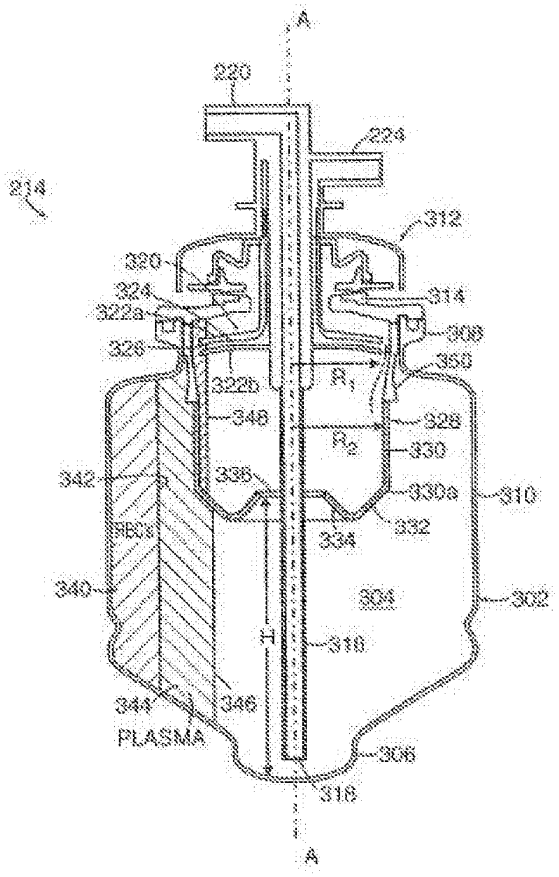


FIG. 3

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(54) Centrifugation bowl with filter core

(57) A centrifugation bowl for separating blood products, includes a cylindrical filter core disposed within the bowl preferably coaxial with the bowl and preferably rotating with the bowl. The centrifugation bowl (214) includes a rotating bowl body (302) with a closed bottom (306) and defining an enclosed separation chamber (304). The filter core (328) includes a filter membrane (330) that is sized to block at least white blood cells, but to allow plasma to pass through. The filter core is generally arranged within the separation chamber such that plasma is forced to pass through the filter core radially inwards before being removed from the centrifugation bowl. To this end, the filter core includes at its bottom portion a truncated conical portion (332) converging downwardly and ending at a predetermined height above the bowl bottom. The addition of the filter core provides an efficient, low-cost method for recovering a "purer" plasma fraction from a donor, to the exclusion of white blood cells.

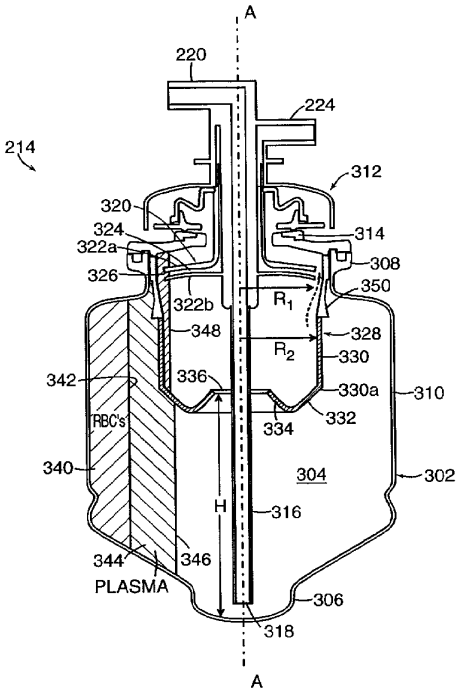


FIG. 3

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Description

FIELD OF THE INVENTION

[0001] The invention relates to centrifugation bowls for separating blood components and other similar fluids. More specifically, the present invention relates to a centrifugation bowl having a filter core for use in recovering filtered plasma fraction from whole blood.

BACKGROUND OF THE INVENTION

[0002] Human blood predominantly includes three types of specialized cells (i.e., red blood cells, white blood cells, and platelets) that are suspended in a complex aqueous solution of proteins and other chemicals called *plasma.* Although in the past blood transfusions have used whole blood, the current trend is to collect and transfuse only those blood components or fractions required by a particular patient. This approach preserves the available blood supply and in many cases is better for the patient, since the patient is not exposed to unnecessary blood components, especially white blood cells, which can transmit pathogens. Two of the more common blood fractions used in transfusions are red blood cells and plasma. Plasma transfusions, in particular, are often used to replenish depleted coagulation factors. Indeed, in the United States alone, approximately 2 million plasma units are transfused each year. Collected plasma is also pooled for fractionation into its constituent components, including proteins, such as Factor VIII, albumin, immune serum globulin, etc.

[0003] Individual blood components, including plasma, can be obtained from units of previously collected whole blood through "bag" centrifugation. With this method, a unit of anti-coagulated whole blood contained in a plastic bag is placed into a lab centrifuge and spun at very high speed, subjecting the blood to many times the force of gravity. This causes the various blood components to separate into layers according to their densities. In particular, the more dense components, such as red blood cells, separate from the less dense components, such as white blood cells and plasma. Each of the blood components may then be expressed from the bag and individually collected.

[0004] U.S. Patent No. 4,871,462 discloses another method for separating blood components. In particular, a filter includes a stationary cylindrical container that houses a rotatable, cylindrical filter membrane. The container and the membrane are configured so as to define only a narrow gap between the side wall of the container and the filter membrane. Blood is then introduced into this narrow gap. Rotation of the inner filter membrane at sufficient speed generates what are known as Taylor vortices in the fluid. The presence of Taylor vortices basically causes shear forces that drive plasma through the membrane and sweep red blood cells away.

[0005] Specific blood components may also be obtained through a process called *apheresis* in which whole blood is transported directly from the donor to a blood processing machine that includes an enclosed, rotating centrifuge bowl for separation of the blood. With this method, only the desired blood component is collected. The remaining components are returned directly to the donor, often allowing greater volumes of the desired component to be collected. For example, with *plasmapheresis,* whole blood from the donor is transported to the bowl where it is separated into its constituent components. The plasma is then removed from the bowl and transported to a separate collection bag, while the other components (e.g., red blood cells and white blood cells) are returned directly to the donor.

[0006] Fig. 1 is a block diagram of a plasmapheresis system 100 with an added filtration step. The system 100 includes a disposable harness 102 that is loaded onto a blood processing machine 104. The harness 102 includes a phlebotomy needle 106 for withdrawing blood from a donor's arm 108, a container of anti-coagulant solution 110, a temporary red blood cell (RBC) storage bag 112, a centrifugation bowl 114, a primary plasma collection bag 116 and a final plasma collection bag 118. An inlet line 120 couples the phlebotomy needle 106 to an inlet port 122 of the bowl 114, and an outlet line 124 couples an outlet port 126 of the bowl 114 to the primary plasma collection bag 116. The blood processing machine 104 includes a controller 130, a motor 132, a centrifuge chuck 134, and two peristaltic pumps 136 and 138. The controller 130 is operably coupled to the two pumps 136 and 138, and to the motor 132, which, in turn, drives the chuck 134.

[0007] In operation, the inlet line 120 is fed through the first peristaltic pump 136 and a feed line 140 from the anti-coagulant 110, which is coupled to the inlet line 120, is fed through the second peristaltic pump 138. The centrifugation bowl 114 is also inserted into the chuck 134. The phlebotomy needle 106 is then inserted into the donor's arm 108 and the controller 130 activates the two peristaltic pumps 136, 138, thereby mixing anti-coagulant with whole blood from the donor, and transporting anti-coagulated whole blood through inlet line 120 and into the centrifugation bowl 114. Controller 130 also activates the motor 132 to rotate the bowl 114 via the chuck 134 at high speed. Rotation of the bowl 114 causes the whole blood to separate into discrete layers by density. In particular, the denser red blood cells accumulate at the periphery of the bowl 114 while the less dense plasma forms an annular ring-shaped layer inside of the red blood cells. The plasma is then forced through an effluent port (not shown) of the bowl 114 and is discharged from the bowl's outlet port 126. From here, the plasma is transported by the outlet line 124 to the primary plasma collection bag 116.

[0008] When all the plasma has been removed and the bowl 114 is full of RBCs, the centrifugation bowl is stopped and the first pump 136 is reversed to transport the RBCs from the bowl 114 to the temporary RBC col-

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lection bag 112. Once the bowl 114 is emptied, the collection and separation of whole blood from the donor is resumed. At the end of the process, the RBCs in the bowl 114 and in the temporary RBC collection bag 112 are returned to the donor through the phlebotomy needle 106. The primary plasma collection bag 116, which is now full of plasma, may be removed from the harness 102 and shipped to a blood bank or hospital for subsequent transfusion.

[0009] Despite the system's generally high separation efficiency, the collected plasma can nonetheless contain some residual blood cells. For example, in a disposable harness utilizing a blow-molded centrifuge bowl from Haemonetics Corporation, of Braintree, Massachusetts, USA, the collected plasma typically contains from 0.1 to 30 white blood cells and from 5,000 to 50,000 platelets per micro-liter. This is due, at least in part, to the 8000 rpm rotational limit of the bowl 114 and the need to keep the bowl's filling rate in excess of 60 milliliters per minute (ml/min.) to minimize the collection time, causing slight re-mixing of blood components within the bowl. Furthermore, it is noteworthy that many countries continue to reduce the permissible level of white blood cells and other residual cells that may be present in their supply of blood components.

Discussion of System Not Found in the Prior Art

[0010] It has been suggested to install one or more filters, such as filter 142, to remove residual cells from the collected plasma in a manner similar to the filtration of collected platelets. Filter 142 may be disposed in a secondary outlet line 144 that couples the primary and final plasma collection bags 116, 118 together. After plasma has been collected in the primary plasma bag 116, a check valve (not shown) may be opened allowing plasma to flow through the secondary outlet line 144, the filter 142, and into the final plasma collection bag 118.

[0011] Although it may produce a "purer" plasma product, the disposable plasmapheresis harness including a separate filter element is disadvantageous for several reasons. In particular, the addition of a filter and another plasma collection bag increase the cost and complexity of the harness. Accordingly, an alternative system that can efficiently produce a "purer" plasma fraction at relatively low cost is desired.

SUMMARY OF THE INVENTION

[0012] Briefly, the present invention is directed to a centrifugation bowl with a rotating filter core disposed within the bowl.

[0013] The invention in its broad form resides in a blood processing centrifugal bowl for separating whole blood into blood fractions, the bowl comprising a bowl body (302) rotatable about a central axis and defining a generally enclosed separation chamber (304); a passage (324) including an outlet (224) disposed within the separation chamber for extracting one or more blood fractions from the bowl; and a filter core (328) disposed within the separation chamber (304), the filter core having a filter membrane (330) configured to block one or more types of residual cells contained within a first blood fraction, the filter core cooperating with the outlet such that the first blood fraction (348) passes through the filter membrane before reaching the outlet and being extracted from the bowl.

[0014] The invention also resides in a method for collecting a plasma fraction from whole blood, the method comprising the steps of supplying whole blood to a rotating centrifugation bowl having a separation chamber; centrifugally separating the whole blood into a plurality of fractions, including a plasma fraction, inside the separation chamber; forcing the plasma fraction radially inwards through a filter core disposed in the separation chamber to trap nonplasma material including any extraneous white blood cells, red blood cells and platelets; and extracting filtered plasma from an inside region of the filter core from within the centrifugation bowl.

[0015] In particular, the centrifugation bowl includes a rotating bowl body defining an enclosed separation chamber. A stationary header assembly that includes an inlet port for receiving whole blood and an outlet port from which a blood component may be withdrawn is mounted on top of the bowl body through a rotating seal. The inlet port is in fluid communication with a feed tube that extends into the separation chamber. The outlet port is in fluid communication with an effluent tube disposed within the separation chamber of the bowl body. The effluent tube includes an entryway at a first radial position relative to a central, rotating axis of the bowl. A generally cylindrical filter core is disposed inside the separation chamber and mounted for rotation with the bowl body. The filter core is sized to block one or more residual cells, but to allow plasma to pass through. The filter core is generally arranged at a second radial position that is slightly outboard of the first radial position that defines the entryway to the effluent tube.

[0016] A preferred embodiment is directed to A blood processing centrifugation bowl for separating centrifuged whole blood into blood fractions, the centrifugation bowl having an axis and comprising a bowl body (302) rotatable about its axis and generally defining a substantially enclosed centrifugal separation chamber and having a closed base portion; a passage including a plasma outlet disposed within the separation chamber for plasma separated from the centrifuged whole blood to be extracted as an effluent, said plasma outlet having an entrance located at a distance R_1, from the bowl axis; an inlet port (220) which brings in blood to be processed, said inlet port including a feed tube member (316) extending substantially to a bottom portion of the bowl body; a filter core having a filter membrane which will allow blood plasma to pass through but not nonplasma material including white blood cells, red blood cells and

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platelets, said filter member having a circular cross section disposed substantially coaxial with the centrifugation bowl axis, said filter membrane including at least a portion which is of a truncated conical configuration with its tapered converging end facing downwards and ending at a predetermined height H above the base portion of the bowl body, said truncated conical configuration having an upper end with an inside radius R_2, where $R_2 > R_1$.

[0017] In operation, the bowl is rotated at high speed by a centrifuge chuck. Anti-coagulated whole blood is delivered to the inlet port, flows through the feed tube and is delivered to the separation chamber of the bowl body. Due to the centrifugal forces generated within the separation chamber, the whole blood is separated into its discrete components. In particular, the denser red blood cells form a first layer against the periphery of the bowl body. Plasma, which is less dense than red blood cells, forms an annular-shaped second layer inside of the first layer of red blood cells. As additional whole blood is delivered to the separation chamber, the annular-shaped plasma layer closes in on and eventually contacts the rotating filter core. Plasma passes through the filtering core, enters the entryway of the effluent tube and is withdrawn from the bowl through the outlet port. Any residual cells contained in the plasma layer are trapped on the outer surface of the filter core and thus cannot reach the entryway of the effluent tube, which is inside of the filter core relative to the axis of rotation. Accordingly, the plasma extracted from the centrifugation bowl of the present invention is generally free of residual cells, eliminating the need for any downstream filter elements.

[0018] When all of the plasma has been extracted from the bowl, leaving primarily a volume of red blood cells in the separation chamber, the bowl is stopped. In the absence of the centrifugal forces, the red blood cells simply collect in the bottom of the bowl. To prevent the red blood cells from contacting the inner surface of the filter core, a solid skirt extends upwardly from the bottom of the filter core. The red blood cells may be withdrawn from the stopped bowl through the feed tube and the "inlet" port. With the red blood cells evacuated from the bowl, the bowl may be rotated again. Subsequent rotation of the bowl causes any residual cells that might have adhered to the outer surface of the filter core during the filter process to be flung off of the core, essentially "cleaning" the filter core. Thus, the centrifugation bowl is ready for any subsequent blood separation cycles.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] The invention description below refers to the accompanying drawings, of which:

Fig. 1, previously discussed, is a block diagram of a prior art plasmapheresis system;

Fig. 2 is a block diagram of a plasmapheresis system in accordance with an embodiment of the present invention;

Fig. 3 is a cross-sectional side view of the centrifugation bowl of Fig. 2 illustrating the rotating filter core;

Figs. 4 is a cross-sectional side view of an alternative embodiment of the centrifugation bowl of the present invention;

Fig. 5 is an isometric view of a preferred support structure for the filter core used in the present invention; and

Fig. 6 is a cross-sectional side view of the support structure of Fig. 5.

DETAILED DESCRIPTION OF AN ILLUSTRATIVE EMBODIMENT

[0020] Fig. 2. is a schematic block diagram of a blood processing system 200 in accordance with the invention. System 200 includes a disposable collection set 202 that may be loaded onto a blood processing machine 204. The collection set 202 includes a phlebotomy needle 206 for withdrawing blood from a donor's arm 208, a container of anti-coagulant 210, such as AS-3 from Haemonetics Corp., a temporary red blood cell (RBC) storage bag 212, a centrifugation bowl 214 and a final plasma collection bag 216. An inlet line 218 couples the phlebotomy needle 206 to an inlet port 220 of the bowl 214, and an outlet line 222 couples an outlet port 224 of the bowl 214 to the plasma collection bag 216. A feed line 225 connects the anti-coagulant 210 to the inlet line 218. The blood processing machine 204 includes a controller 226, a motor 228, a centrifuge chuck 230, and two peristaltic pumps 232 and 234. The controller 226 is operably coupled to the two pumps 232 and 234, and to the motor 228, which, in turn, drives the chuck 230.

[0021] A suitable blood processing machine for use with the present invention is the PCS®2 System from Haemonetics Corp., which is used to collect plasma.

Configuration of the Centrifuge Bowl of the Present Invention

[0022] Fig. 3 is a cross-sectional side view of the centrifugation bowl 214 of a preferred embodiment of the present invention. Bowl 214 includes a generally cylindrical bowl body 302 defining an enclosed separation chamber 304. The bowl body 302 includes a base 306, an open top 308 and a side wall 310. The bowl 214 further includes a header assembly 312 that is mounted to the top 308 of the bowl body 302 by a ring-shaped rotating seal 314. The inlet port 220 and outlet port 224 are part of the header assembly 312. Extending from the header assembly 312 into the separation chamber 304 is a feed tube 316 that is in fluid communication with inlet port 220. The feed tube 316 has an opening 318 that is preferably positioned proximate to the base 306

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of the bowl body 302 so that liquid flowing through the feed tube 316 is discharged at the base 306 of the bowl body 302. The header assembly 312 also includes an outlet, such as an effluent passage 320, that is disposed within the separation chamber 304. The effluent passage 320 may be positioned proximate to the top 308 of the bowl body 302. In the preferred embodiment, the effluent passage 320 is formed from a pair of spaced-apart disks 322a, 322b that define a passageway 324 whose generally circumferential entryway 326 is located at a first radial position, R_1, relative to a central, rotating axis A-A of the bowl 214.

[0023] A suitable header assembly and bowl body for use with the present invention are described in U.S. Patent No. 4,983,158. Nonetheless, it should be understood that other bowl configurations may be utilized.

[0024] Disposed within the separation chamber 304 of the bowl 302 is a filter core 328 having a generally cylindrical side wall 330. Side wall 330 is preferably disposed at a second radial position, R_2, that is slightly outboard of the first radial position, R_1, which, as described above, defines the location of the entryway 326 to the passageway 324. At a bottom 330a of the side wall 330 there is a first sloped section 332 that extends downward toward base 306 and is inclined toward the axis A-A. Extending upwardly from the first sloped section 332 is a solid skirt 334 that is also inclined toward the axis A-A. The skirt defines a circumference 336 opposite the sloped section 332 that, in the preferred embodiment, is spaced a height, H, from the base 306 of the bowl body 302. The filter core 328 is preferably mounted for rotation with the bowl body 302. In particular, an upper portion of the filter core 328 opposite the skirt 334 may be attached to the top 308 of the bowl body 302.

[0025] Both the side wall 330 and the first sloped section 332 of the filter core 328 are advantageously formed from or include a filter membrane that is sized to block one or more residual cells, such as least white blood cells, but to allow plasma to pass through. In the preferred embodiment, the filter membrane has a pore size of 2 to 0.8 microns. A suitable filter membrane for use with filter core 328 is the BTS-5 membrane from United States Filter Corp. of Palm Desert, California, USA or the Supor membrane from Pall Corp. of East Hills, New York, USA. The filter membrane may be additionally or alternatively configured to block red blood cells, platelets, different types of white blood cells and/or non-cellular blood components. The skirt 334 which is solid may be formed from plastic, silicone or other suitable material. Accordingly, none of the blood components, including plasma, pass through the skirt 334 portion of the filter core 328. The skirt 334 may also be truly cylindrical and extend upwardly inside the side wall 330.

[0026] It should be understood that the filter membrane of the present invention may take multiple forms. For example, it may be formed from an affinity media to which one or more residual cells (but not plasma) adheres, thereby removing the residual cells from the plasma passing through the membrane. The filter membrane may also be formed from micro-porous membranes of equal or unequal pore size preferably in the range of 0.5 to 2.0 microns. The filter membrane may also be a combination of affinity media and micro-porous membranes. The filter core 328 may also include two or more membrane layers of varying pore size or affinity that are spaced-apart or stacked together. Preferably, the pore size of such membrane layers successively decreases toward the entryway 326 of the effluent tube 320. In addition, one or more layers of the filter membrane may be formed from a non-woven media or material.

Operation of the Present Invention

[0027] In operation, the disposable collection set 202 (Fig. 2) is loaded onto the blood processing machine 204. In particular, the inlet line 218 is routed through the first pump 232 and the feed line 225 from the anti-coagulant container 210 is routed through the second pump 234. The centrifugation bowl 214 is securely loaded into the chuck 230, with the header assembly 312 held stationary. The phlebotomy needle 206 is then inserted into the donor's arm 208. Next, the controller 226 activates the two pumps 232, 234 and the motor 228. Operation of the two pumps 232, 234, causes whole blood from the donor to be mixed with anti-coagulant from container 210 and delivered to the inlet port 220 of the bowl 214. Operation of the motor 228 drives the chuck 230, which, in turn, rotates the bowl 214. The anti-coagulated whole blood flows through the feed tube 316 (Fig. 3) and enters the separation chamber 304. Centrifugal forces generated within the separation chamber 304 of the rotating bowl 214 forces the blood against side wall 310. Continued rotation of the bowl 214 causes the blood to separate into discrete layers by density. In particular, RBCs which are the densest component of whole blood form a first layer 340 against the periphery of side wall 310. The RBC layer 340 has a surface 342. Inboard of the RBC layer 340 relative to axis A-A, a layer 344 of plasma forms, since plasma is less dense than red blood cells. The plasma layer 344 also has a surface 346.

[0028] It should be understood that a buffy coat layer (not shown) containing white blood cells and platelets may form between the layers of red blood cells and plasma.

[0029] As additional anti-coagulated whole blood is delivered to the separation chamber 304 of the bowl 214, each layer 340, 344 "grows" and thus the surface 346 of the plasma layer 344 moves toward the central axis A-A. At some point, the surface 346 will contact the cylindrical side wall 330 of the filter core 328. Due to the flow resistance of the filter membrane of side wall 330, the surface 346 of the plasma layer 344 begins to "climb" up the first sloped section 332 of the filter core 328. Indeed, the plasma will continue to climb up the sloped section 332 until a sufficient pressure head is generated

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to "pump" plasma through the filter element. That is, the radial "height" of the plasma layer surface 346 relative to the fixed radial position of the cylindrical side wall 330 of the filter core 328 establishes a significant pressure head due to the large centrifugal forces generated within the separation chamber 304. For example, with an outer core radius, R_2, of 20 mm and plasma at a radial "height" of 4 mm "above" the outer core radius, a trans-membrane pressure of approximately 300 mm of mercury (Hg) will be generated across the filter core 328, which should be more than sufficient to pump plasma through the filter membrane. The height differences shown in the figures have been exaggerated for illustrative purposes. In addition, the radial "depth" of the filter core 328 is preferably sized to prevent unfiltered plasma from spilling over the rim or circumference 336 of the skirt 334 and being extracted from the bowl 214. That is, the rim 336, as defined by the radial extent of first sloped section 332 and skirt 334, is positioned closer to axis A-A than the plasma surface 346 during anticipated operating conditions of the bowl 214.

[0030] Due to the configuration of the filter membrane (e.g., pore size) at side wall 330 and sloped section 332, only plasma is allowed to pass through filter core 328. Any residual blood components, such white blood cells, still within the plasma layer 344 are trapped on the outer surface of the filter 328 core relative to axis A-A. After passing through the filter core 328, filtered plasma 348 enters the entryway 326 of the effluent tube 320 as shown by arrow P (Fig. 3) and flows along the passageway 326. From here, the filtered plasma is removed from the bowl 214 through the outlet port 224 which is in fluid communication with the effluent tube 320. The filtered plasma is then transported through the outlet line 222 (Fig. 2) and into the plasma collection bag 216.

[0031] As additional anti-coagulated whole blood is delivered to the bowl 214 and filtered plasma removed, the depth of the RBC layer 340 will grow. When the surface 342 of the RBC layer 340 reaches the filter core 328, indicating that all of the plasma in the separation chamber 304 has been removed, the process is preferably suspended. The fact that the surface 342 of the RBC layer 340 has reached the filter core 328 may be optically detected. In particular, the bowl 214 may further include a conventional optical reflector 350 that is spaced approximately the same distance (e.g., R_2) from the central axis A-A as the side wall 330 of the filter core 328. The reflector 350 cooperates with an optical emitter and detector (not shown) located in the blood processing machine 204 to sense the presence of RBCs at a preselected point relative to the filter core 328 causing a corresponding signal to be sent to the controller 226. In response, the controller 226 suspends the process.

[0032] It should be understood that the optical components and the controller 226 may be configured to suspend bowl filling at alternative conditions and/or upon detection of other fractions.

[0033] Specifically, the controller 226 de-activates the pumps 232, 234 and the motor 228, thereby stopping the bowl 214. Without the centrifugal forces, the RBCs in layer 340 drop to the bottom of the bowl 214. That is, the RBCs settle to the bottom of the separation chamber 304 opposite the header assembly 312. As mentioned above, the end rim 336 of the skirt 334 is preferably positioned so that the RBCs contained within the now stopped bowl 214 do not spill over and contact the inside surface of the filter membrane relative to axis A-A. For example, the height, H, of the end point 336 relative to the base 306 of the bowl body 302 is greater than the height of the RBCs when the bowl 214 is stopped. Thus, the RBCs do not contact any inner surface portion of the filter core 328. The significance of this feature is described in greater detail below.

[0034] After waiting a sufficient time for the RBCs to settle in the stopped bowl 214, the controller 226 activates pump 232 in the reverse direction. This causes the RBCs in the lower portion of the bowl 214 to be drawn up the feed tube 316 and out of the bowl 214 through the inlet port 220. The RBCs are then transported through the inlet line 218 and into the temporary RBC storage bag 212. It should be understood that one or more valves (not shown) may be operated to ensure that the RBCs are transported to bag 212. To facilitate the evacuation of RBCs from the bowl 214, the configuration of skirt 334 preferably allows air from plasma collection bag 216 to easily enter the separation chamber 304. That is, the end point 336 of the skirt 334 is spaced from the feed tube 316 and the skirt 334 does not otherwise block the flow of air from the effluent tube 320 to the separation chamber 304. Accordingly, air need not cross the wet filter core 328 in order to allow RBCs to be evacuated. It should be understood that this configuration and arrangement also facilitates air removal from the separation chamber 304 during bowl filling.

[0035] When all of the RBCs from bowl 214 have been moved to the temporary storage bag 212, the system 200 is ready to begin the next plasma collection cycle. In particular, controller 226 again activates the two pumps 232, 234 and the motor 228. In order to "clean" the filter core 328 prior to the next collection cycle, the controller 226 preferably activates the motor 228 and the pumps 232, 234 in such a manner (or in such a sequence) as to rotate the bowl 214, at its operating speed, for some period of time before anti-coagulated whole blood is allowed to reach the separation chamber 304. By rotating the filter core 328 in the empty bowl 214, residual blood cells that were "trapped" on its outer surface during the plasma collection process are flung off. Thus, the filter core 328 is effectively "cleaned" of residual blood cells that might be adhered to its surface. This intermediary "cleaning" step ensures that the entire surface area of the filter membrane is available for filtering during each plasma collection cycle and not just the first collection cycle.

[0036] With the filter cleaned of trapped cells, the plasma collection process proceeds as described

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above. In particular, anti-coagulated whole blood separates into its constituent components within the separation chamber 304 of the bowl 214 and plasma is pumped through the filter core 328. Filtered plasma is removed from the bowl 214 and transported along the outlet line 222 to the plasma collection bag 216 adding to the plasma collected during the first cycle. When the separation chamber 304 of the bowl 214 is again full of RBCs (as sensed by the optical detector), the controller 226 stops the collection process. Specifically, the controller deactivates the two pumps 232, 234 and the motor 228. If the process is complete (i.e., the desired amount of plasma has been donated), then the system returns the RBCs to the donor. In particular, controller 226 activates pump 232 in the reverse direction to pump RBCs from the bowl 214 and from the temporary storage bag 212 through the inlet line 218. The RBCs flow through the phlebotomy needle 206 and are thus returned to the donor.

[0037] After the RBCs have been returned to the donor, the phlebotomy needle 206 may be removed and the donor released. The plasma collection bag 216, which is now full of filtered plasma, may be severed from the disposable collection set 202 and sealed. The remaining portions of the disposable set 202, including the needle, bags 210, 212 and bowl 214 may be discarded. The filtered plasma may be shipped to a blood bank or hospital.

[0038] The significance of preventing any residual cells or non-plasma blood components from contacting the inside surface of the filter core 328 relative to axis A-A should now be appreciated. In particular, residual cells allowed to contact the inside surface of the filter core 328 would not be removed by rotating the bowl 214 while it is empty. Instead, these residual cells would simply remain stuck on the inside surface of the filer core 328. When the collection process is resumed, moreover, these residual cells would be pulled through the effluent tube 320 along with the plasma, thereby "contaminating" the filtered plasma in the collection bag 216. Accordingly, in the preferred embodiment, the filter core is configured so that non-plasma blood components are precluded from contacting the filter core's inner surface.

[0039] Furthermore, depending on the desired surface area of the filter membrane and the anticipated height of red blood cells in the stopped bowl, it may be possible to omit the skirt 332. That is, if sufficient filtration area can be achieved with the lowest extremity of the filter core still above the RBCs occupying the stopped bowl 214, then skirt 332 may be omitted. In the preferred embodiment, filter core 328 has a filtration area of approximately 50 cm^2. Additionally, those skilled in the art will recognize that, if only a single collection cycle is performed, residual cells could be permitted to contact the filter core's inner surface. More specifically, residual cells (such as the contents of the stopped bowl) could be allowed to contact the filter core's inner surface during evacuation of red blood cells.

[0040] As shown, the present invention provides an efficient, low-cost system for collecting a filtered or "purer" plasma product than currently possible with conventional centrifugation bowls. In the preferred embodiment, the system 200 further includes one or more means for detecting whether the filter core 328 has become clogged. In particular, the blood processing machine 204 may include one or more conventional fluid flow sensors (not shown) coupled to the controller 226 to measure flow of anticoagulated whole blood into the bowl 214 and the flow of filtered plasma out of the bowl 214. Controller 226 preferably monitors the outputs of the flow sensors and if the flow of whole blood exceeds the flow of plasma for an extended period of time, the controller 226 preferably suspends the collection process. The system 200 may further include one or more conventional line sensors (not shown) that detect the presence of red blood cells in the outlet line 222. The presence of red blood cells in the outlet line 222 may indicate that the blood components in the separation chamber 304 have spilled over the skirt 334.

[0041] It should be understood that the filter core may have alternative configurations. Fig. 4, for example, is a cross-sectional side view a centrifugation bowl 400 having a generally truncated-cone shaped filter core 402. Bowl 400 includes many similar elements to bowl 214. For example, bowl 400 has a generally cylindrical bowl body 404 having a base 406, an open top 408 and a side wall 410, for defining an enclosed separation chamber 412. A header assembly 414 is mounted to the bowl body 402 via a rotating seal 416. A feed tube 418 extends into the separation chamber 412 of the bowl 400, and the header assembly 414 includes an effluent tube 420 defining an entryway 422. The truncated-cone shaped filter core 402, which includes a large diameter section 424 and a small diameter section 426, also extends into the separation chamber 412. In particular, the large diameter section 424 of the filter core 402 is preferably disposed at a radial position, R_3, that is slightly outboard of a radial position, R_4, of the entryway 422 of the effluent tube 420. A solid skirt 428 is preferably formed at the small diameter section 426 of the filter core 402. Skirt 428 preferably extends upwardly relative to the header assembly 414 and may be sloped toward the central axis of rotation A-A. Skirt 428 similarly defines an end rim 430 that, in the preferred embodiment, is spaced a height, H, from the base 406 of the bowl body 404, for the reasons described above. The filter core 402, not including the skirt 428, is preferably formed from a filter membrane that is sized to block at least white blood cells, but to allow plasma to pass through.

[0042] In operation, anti-coagulated whole blood is similarly delivered to the separation chamber 412 of the rotating bowl 400. The whole blood separates into an RBC layer 432 and a plasma layer 434 having a surface 436. Due to the flow resistance presented by the filter membrane of filter core 402, the surface 436 of the plasma layer 434 "climbs" up a portion of the truncated cone-

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shaped filter core 402 until a sufficient pressure head is generated to "pump" plasma through the membrane, creating filtered plasma 438. Furthermore, by spacing the end rim 430 of the skirt 428 a height H from the base 406 of the bowl body 404, residual cells including RBCs are prevented from contacting the inner surface of the filter core 402 while the bowl 400 is stopped.

[0043] Figs. 5 and 6 are an isometric and a cross-sectional side view, respectively, of a preferred filter core support structure 500. The support structure 500 has a generally cylindrical shape defining an outer cylindrical surface 502, a first open end 504 and a second open end 506. Formed in the outer surface 502 of the support structure 500 are one or more underdrain regions, such as underdrain region 508, which preferably encompass a substantial portion of the surface area of the support structure 500. In the preferred embodiment, each underdrain region 508 is recessed relative to outer surface 502. Disposed within each underdrain region 508 are a plurality of spaced-apart ribs 510, each including a top surface 510a that is flush with the outer surface 502 of the support structure 500. Each underdrain region 508 also includes a plurality of drain holes 512 (Fig. 5) that provide fluid communication to the interior 514 (Fig. 6) of the support structure 500. More specifically, the spaces between adjacent ribs 510 define corresponding channels 516 that lead to the drain holes 512.

[0044] In place of sloped section 332 (Fig. 3) of filter core 328, support structure 500 includes an inwardly extending shelf 518 (Fig. 6) that is disposed at second open end 506. Support structure 500 also includes a skirt 520 that is similar to skirt 334 (Fig. 3). In particular, skirt 520, which has a truncated cone shape, is attached to shelf 518 and extends from second open end 506 toward first open end 504 within the interior 514 of support structure 500. Skirt 520 also defines an opening 522 opposite second open end 506 that provides fluid communication between first and second ends 504, 506.

[0045] Wrapped around the support structure 500 is a filter medium (not shown) configured to block one or more residual cells but to allow plasma to pass through. The filter medium may be attached to the support structure 500 by any suitable means, such as tape, ultrasonic welding, heat seal, etc. Due to the configuration of ribs 510, the filter medium is spaced from the respective underdrain region 508. That is, in the area of the underdrain region 508, the filter medium is supported by the top surfaces 510a of ribs 510. As plasma passes through the filter medium it enters the corresponding underdrain region 508. From here, the filtered plasma flows along the channels 516, through drain holes 512 and into the interior 514 of the support structure. Support structure 500 is preferably mounted to the bowl body 302 (Fig. 3) such that first open end 504 is proximate to header assembly 312. As described above, filtered plasma is extracted from the bowl 214 (Fig. 3) by the outlet 520 (Fig. 3). Furthermore, the configuration of skirt 520 prevents unfiltered plasma either from being extracted from the bowl 214 or from contacting the inner surface of the filter medium. Additionally, the opening 522 is the skirt 520 allows the feed tube 316 (Fig. 3) to extend through the support structure 500 and allows air to enter the separation chamber 304 of the bowl 214 during removing of red blood cells or other components.

[0046] Those skilled in the art will understand that other configurations of the filter core, including the support structure, are possible provided that the plasma is forced to pass through the filter core before reaching the outlet.

[0047] It should be further understood that the filter core of the present invention may be stationary relative to the rotatable bowl body. That is, the filter core may alternatively be affixed to the header assembly rather than to the bowl body. It should also be understood that the filter core of the present invention may be incorporated into centrifugation bowls having different geometries, including the bell-shaped Latham series of centrifugation bowls from Haemonetics Corp.

[0048] The foregoing description has been directed to specific embodiments of this invention. It will be apparent, however, that other variations and modifications may be made to the described embodiments with the attainment of some or all of their advantages. Accordingly, this description should be taken only by way of example and not by way of limitation. For example, the filter membrane may actually be inboard of the entryway of the effluent tube provided that some structure conveys the filtered plasma back out to the entryway. It is the object of the appended claims to cover all such variations and modifications.

Claims

1. A blood processing centrifugation bowl for separating whole blood into blood fractions, the bowl comprising:

   a bowl body (302) rotatable about a central axis and defining a generally enclosed separation chamber (304);
   a passage (324) including an outlet (224) disposed within the separation chamber for extracting one or more blood fractions from the bowl; and
   a filter core (328) disposed within the separation chamber (304), the filter core having a filter membrane (330) configured to block one or more types of residual cells contained within a first blood fraction, the filter core cooperating with the outlet such that the first blood fraction (348) passes through the filter membrane before reaching the outlet and being extracted from the bowl.

2. The blood processing centrifugation bowl of claim

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1 wherein the filter core (328) is mounted to the bowl body for rotation therewith, and includes pores of 0.5 to 2 microns.

3. The blood processing centrifugation bowl of claim 1 wherein the first blood fraction is plasma (344) and the one or more types of residual cells include white blood cells, red blood cells (340) and platelets.

4. The blood processing centrifugation bowl of claim 1 wherein the outlet is an effluent tube and wherein the passage includes an entryway, wherein the filter core includes a cylindrical portion co-axially aligned about the central axis, and wherein at least a portion of the filter core is located radially outside of the entryway relative to the central axis.

5. The blood processing centrifugation bowl of claim 4 wherein the centrifugation bowl includes a blood inlet port (220)having a feed tube member (316) which admits blood to be processed at (2200 substantially a bottom portion of the bowl, and wherein the cylindrical filter core (328) further includes a sloped section (332) that is inclined and converging downwards toward the central axis at a predetermined height above the bowl bottom portion.

6. The blood processing centrifugation bowl of claim 5 wherein the bowl body includes a base and the cylindrical filter core further includes an inner solid skirt (334) extending upwards from the sloped section opposite the bowl base.

7. The blood processing centrifugation bowl of claim 6 wherein the solid skirt of the filter core comprises plastics material and has a circumferential edge (336) that is spaced from the base of the bowl body such that one or more blood fractions remaining in the separation chamber are blocked from spilling over the skirt and contacting an inner surface of the filter core relative to the central axis.

8. The blood processing centrifugation bowl of claim 6 wherein the solid skirt comprises a substantially vertical cylindrical member made of silicone.

9. The blood processing centrifugation bowl of claim 8 wherein the truncated-cone shaped filter core has a large diameter section that is disposed radially outside of the entryway to the effluent tube relative to the central axis.

10. The blood processing centrifugation bowl of claim 1 wherein the filter membrane is formed, at least in part, from a medium having an affinity for one or more types of residual cells.

11. The blood processing centrifugation bowl of claim 10 wherein the filter membrane further includes a micro-porous section.

12. The blood processing centrifugation bowl of claim 1 wherein the filter membrane includes two or more layers.

13. The blood processing centrifugation bowl of claim 12 wherein each membrane layer has a pore size, and the pore size of the layers successively decreases toward the outlet.

14. A method for collecting a plasma fraction from whole blood, the method comprising the steps of:

supplying whole blood to a rotating centrifugation bowl having a separation chamber;
centrifugally separating the whole blood into a plurality of fractions, including a plasma fraction, inside the separation chamber;
forcing the plasma fraction radially inwards through a filter core disposed in the separation chamber to trap nonplasma material including any extraneous white blood cells, red blood cells and platelets; and
extracting filtered plasma from an inside region of the filter core from within the centrifugation bowl.

15. A blood processing centrifugation bowl for separating centrifuged whole blood into blood fractions, the centrifugation bowl having an axis and comprising:

a bowl body (302) rotatable about its axis and generally defining a substantially enclosed centrifugal separation chamber and having a closed base portion;
a passage including a plasma outlet disposed within the separation chamber for plasma separated from the centrifuged whole blood to be extracted as an effluent, said plasma outlet having an entrance located at a distance R_1, from the bowl axis;
an inlet port (220) which brings in blood to be processed, said inlet port including a feed tube member (316) extending substantially to a bottom portion of the bowl body;
a filter core having a filter membrane which will allow blood plasma to pass through but not nonplasma national including white blood cells, red blood cells and platelets, said filter member having a circular cross section disposed substantially coaxial with the centrifugation bowl axis, said filter membrane including at least a portion which is of a truncated conical configuration with its tapered converging end facing downwards and ending at a predetermined height H above the base portion of the bowl

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body, said truncated conical configuration having an upper end with an inside radius R_2, where $R_2 > R_1$.

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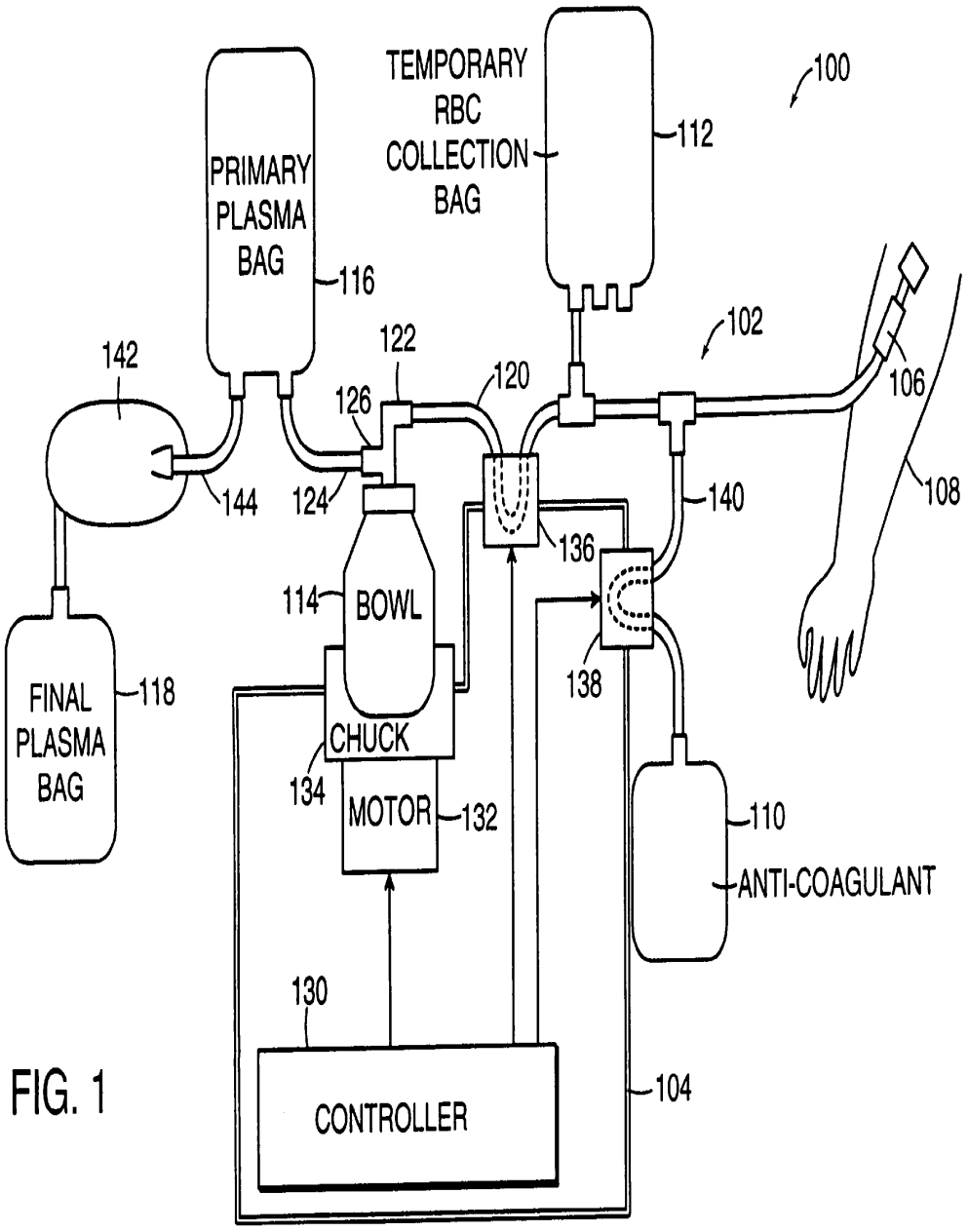


FIG. 1

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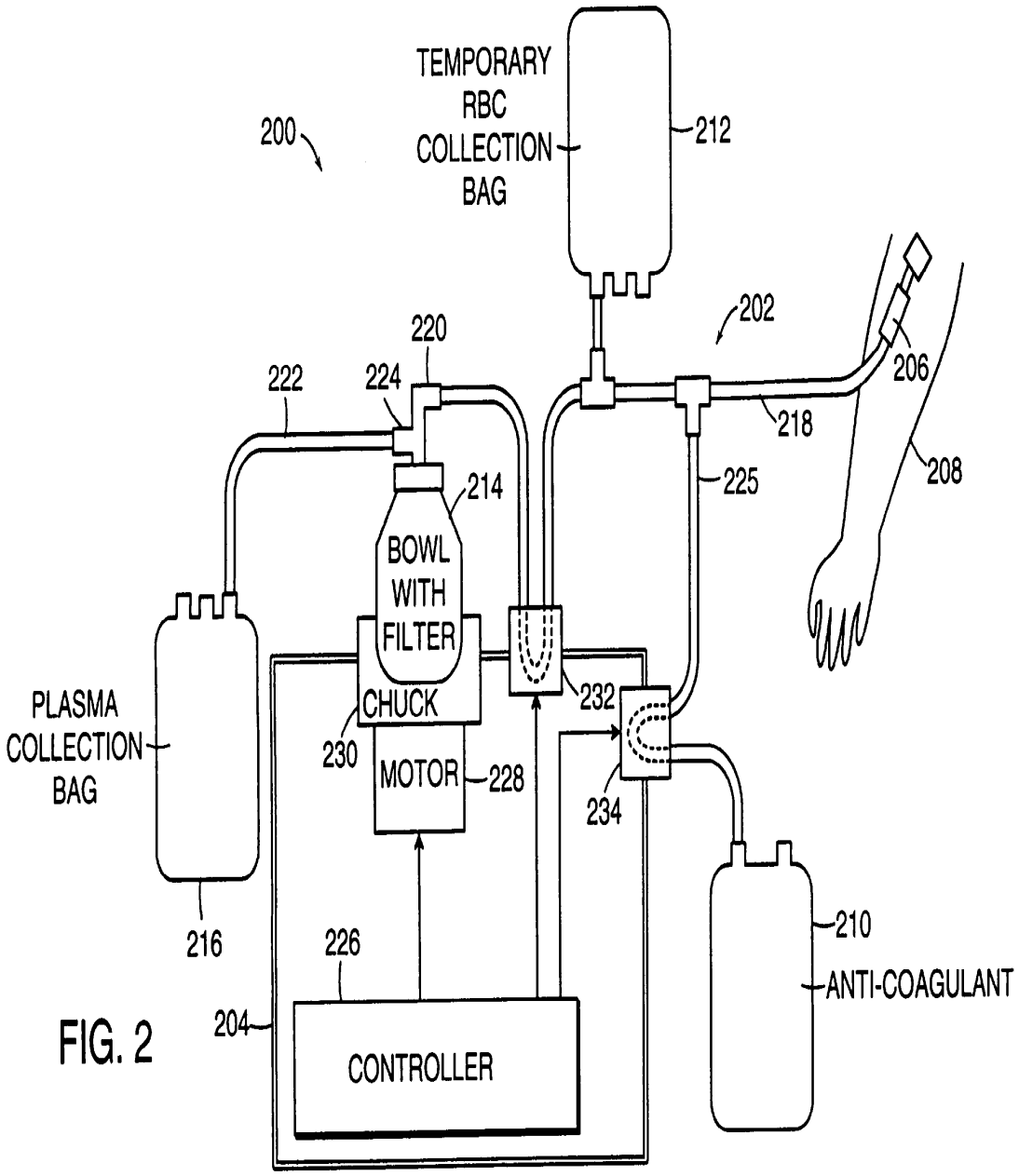


FIG. 2

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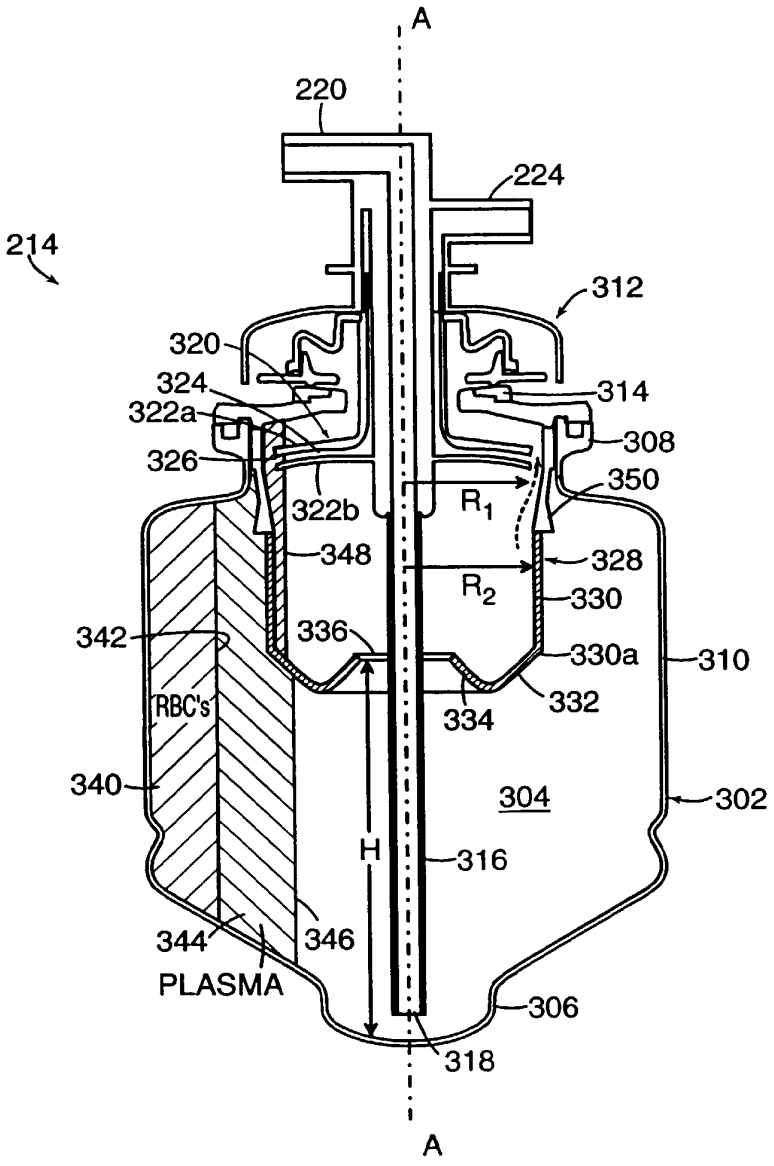


FIG. 3

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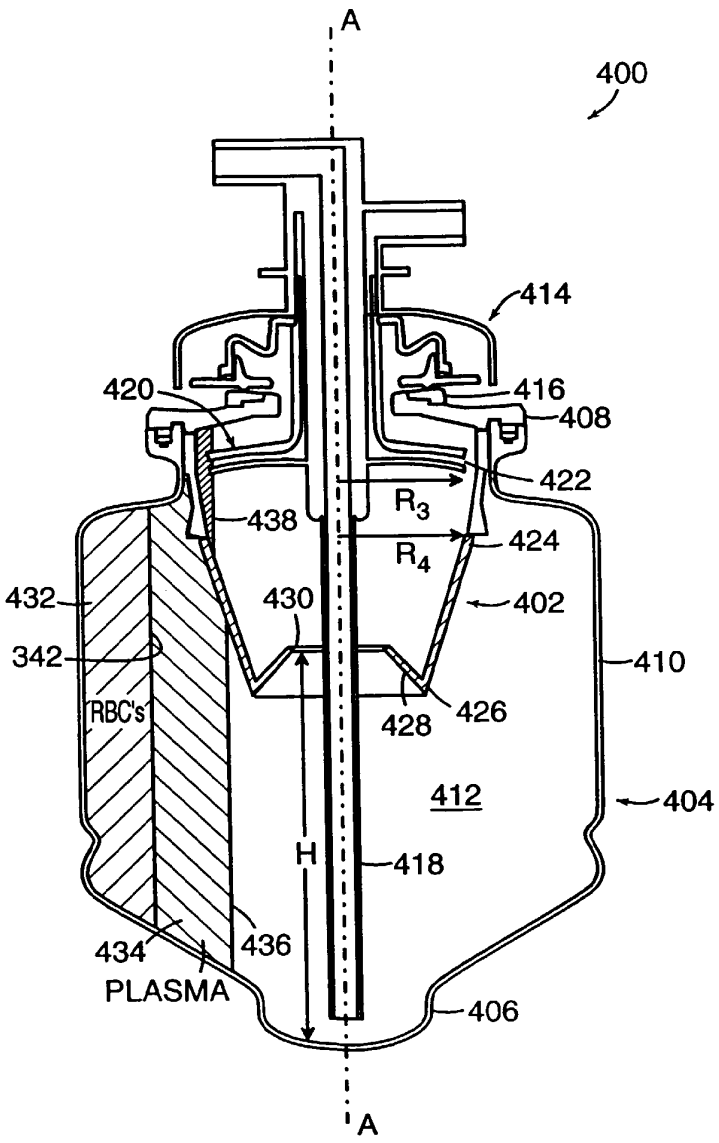


FIG. 4

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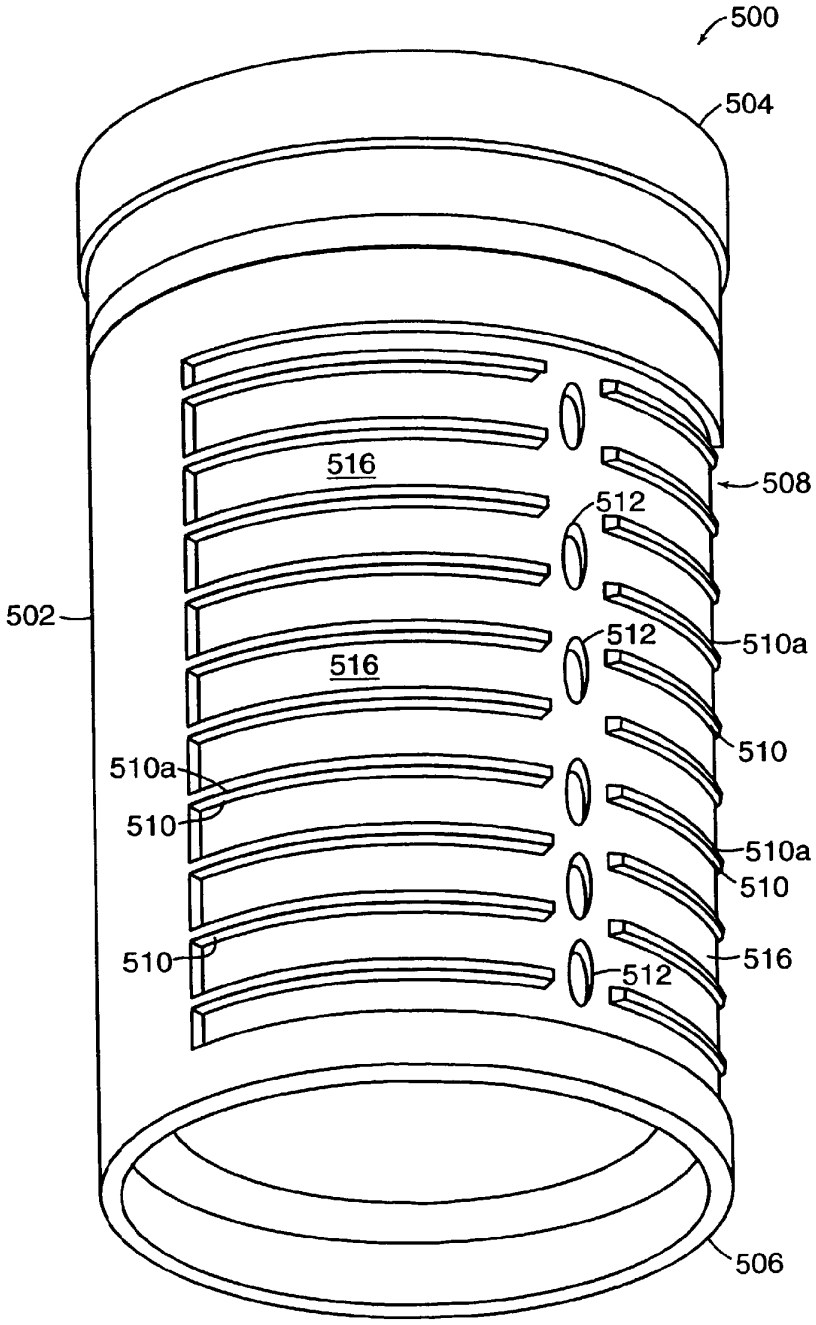


FIG. 5

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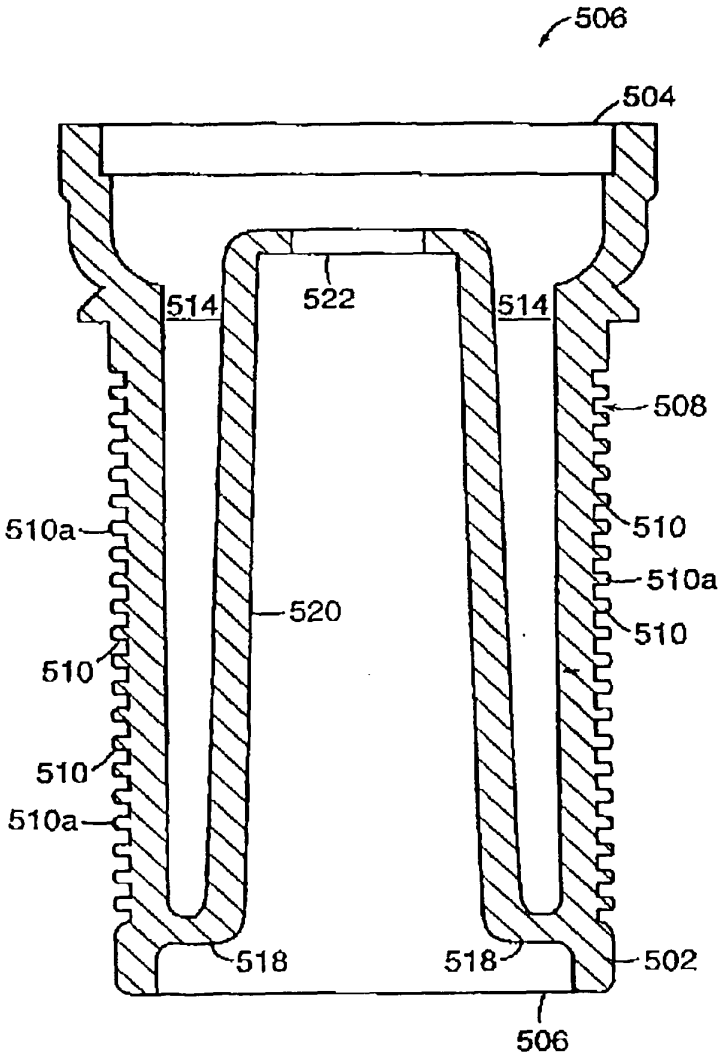


FIG. 6

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EUROPEAN SEARCH REPORT

Application Number
EP 00 30 3021

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 5 431 814 A (G. JORGENSEN) 11 July 1995 (1995-07-11) * column 1, line 48 - column 2, line 21 *	1-4, 12-14	B04B5/04 B04B7/08
Y A	* column 6, line 51 - column 7, line 33 * * column 10, line 50 - column 11, line 10; figures 2,3,8-11 *	10,11 5,15	
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TECHNICAL FIELDS SEARCHED (Int.Cl.7)

B04B
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A61M

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	28 August 2000	Leitner, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 30 3021

This annex lists the patent family members relating to the patent documents cited in the above–mentioned European search report. The members are as contained in the European Patent Office EDP file on
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Platelet collection apparatus

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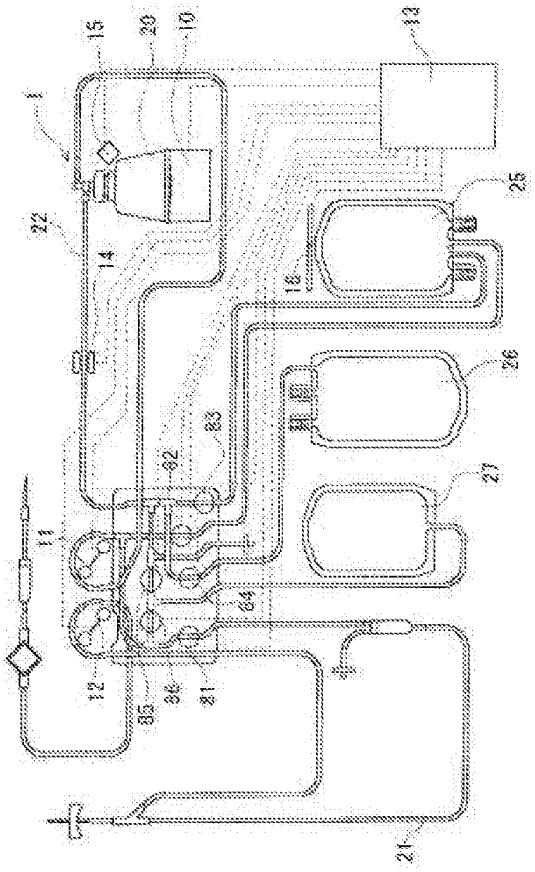
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Abstract of EP1295619 (A2)

A platelet collection apparatus (1) has a function of determining whether there is a tendency to increase or decrease in the number of collected platelets by using data, related to the concentration of platelets, obtained from a turbidity sensor (14), an expected number of to-be-collected platelets or a value related thereto; and a function of decreasing the amount of platelets to be collected in a subsequent platelet collection operation after plasma containing high-concentration platelets is collected in a plasma collection operation, if the function of determining on an increase/ decrease tendency in the number of collected platelets determines that there is a tendency to increase in the number of collected platelets.

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FIG. 3



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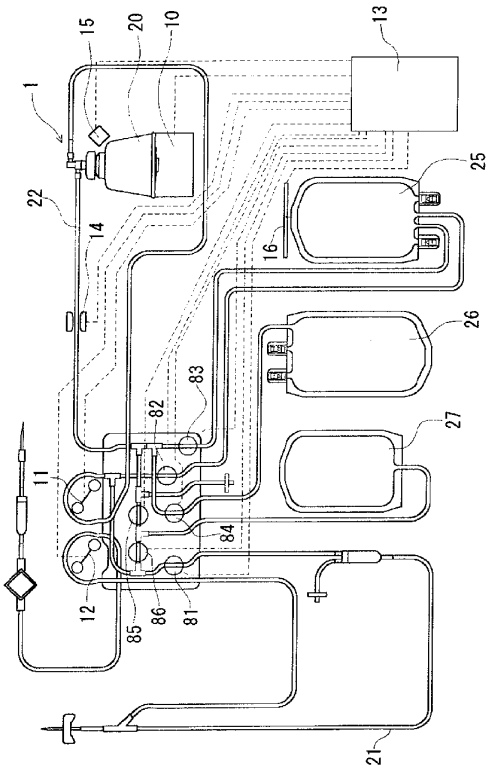
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(54) Platelet collection apparatus

(57) A platelet collection apparatus (1) has a function of determining whether there is a tendency to increase or decrease in the number of collected platelets by using data, related to the concentration of platelets, obtained from a turbidity sensor (14), an expected number of to-be-collected platelets or a value related thereto; and a function of decreasing the amount of platelets to be collected in a subsequent platelet collection operation after plasma containing high-concentration platelets is collected in a plasma collection operation, if the function of determining on an increase/ decrease tendency in the number of collected platelets determines that there is a tendency to increase in the number of collected platelets.

FIG. 3



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Description

BACKGROUND OF THE INVENTION

[0001] The present invention relates to a platelet collection apparatus for separating blood into predetermined blood components.

[0002] To effectively utilize collected blood and reduce donor's burden, the collected blood is separated into various components centrifugally and components required for a donee are collected, whereas remaining components are returned to the donor.

[0003] In obtaining a platelet product in this platelet collection process, the blood donated from the donor is introduced to a platelet collection circuit to separate it into four components of plasma, white cells, platelets, and red cells by a centrifugal separator called a centrifugal bowl installed in the platelet collection circuit. Then, the platelets are collected in a container to produce a platelet product, the plasma is collected in a separate container to produce a plasma product or the material for a plasma fraction product, and the remaining plasma, the white cells, and the red cells are returned to the donor.

[0004] As methods of collecting the platelets, the method disclosed in U.S.P. 5,637,082 is described below. In the method, blood is preliminarily collected from a donor before platelets are collected to obtain blood information (hematcrit value, platelet concentration) from the blood preliminarily collected. Data of the blood information and a target number of to-be-collected platelets are inputted to the platelet collection apparatus to thereby compute a necessary number of platelet collection operation cycles. A platelet collection operation is performed in a computed number of cycles.

[0005] However, an analyzing apparatus for providing blood information from the blood preliminarily collected may make an error in measurement or an operator may make an error in inputting information to the platelet collection apparatus. In this case, based on erroneous data of blood information, the number of platelet collection operation cycles is computed. The platelet collection operation is performed in the computed number of cycles. Therefore the operator think that a target number of platelets is obtained. However, an examination made after collection of platelets reveals that platelets have been collected more than a predetermined number of platelets. When an excessive amount of platelets is collected, the amount of platelets is adjusted before a blood transfusion is performed and an extra amount thereof is discarded to prevent an excessive amount of platelets from being administered to a patient.

[0006] Accordingly, it is an object of the present invention to provide a platelet collection apparatus capable of preventing collection of an excessive amount of platelets.

[0007] Depending on a blood condition of a donor, there is a case in which platelets can be collected in an amount more than expected. In this case, it is possible to alter a target number of units of to-be-collected platelets to a number larger than an initial target value. However, it is impossible to understand such a situation in a platelet collection operation. Thus an excessive amount of platelets is collected, as described above and an extra amount thereof is discarded.

SUMMARY OF THE INVENTION

[0008] The object described above is attained by a platelet collection apparatus separating blood into a plurality of components by means of a centrifugal separator having a blood-storage space therein and collecting at least platelets of said components which comprises a platelet collection circuit having a first line connecting an inlet of said centrifugal separator and a blood collection means with each other, a second line connected with an outlet of said centrifugal separator, and a platelet collection bag connected with said second line; a turbidity sensor disposed on said second line; and a function of computing a number of platelet collection cycles and an expected number of to-be-collected platelets or a value related thereto from data of a donor's hematcrit value, platelet concentration data, and a target number of said to-be-collected platelets, all of which are inputted to said platelet collection apparatus before a platelet collection operation is performed, a function of determining whether there is a tendency to increase or decrease in a number of collected platelets by using an estimated number of to-be-collected platelets computed by using an amount of plasma containing high-concentration platelets and a platelet concentration obtained from a turbidity sensor when said plasma containing high-concentration platelets is collected or data related to said platelet concentration and by using said expected number of to-be-collected platelets or said value related thereto; and a function of decreasing an amount of platelets to be collected in a subsequent platelet collection operation if said function of determining on an increase/decrease tendency in the number of collected platelets determines that there is a tendency to increase in the number of said collected platelets.

[0009] Further, the object described above is attained by a platelet collection apparatus separating blood into a plurality of components by means of a centrifugal separator having a blood-storage space therein and collecting at least platelets of said components which comprises a platelet collection circuit having a first line connecting an inlet of said centrifugal separator and a blood collection means with each other, a second line connected with an outlet of said centrifugal separator, and a pletelet collection bag connected with said second line: a turbidity sensor disposed on said second line; a platelet-concentration peak situation determination function of detecting a peak of a platelet concentration by using signals detected by said turbidity sensor, when high-concentration platelets-containing plasma is collected in a

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platelet collection operation and determining whether said detected peak of said platelet concentration is on a normal level or on an excessive level; and a function of decreasing a number of platelets to be collected in said platelet collection operation, when said platelet-concentration peak situation determination function determines that said peak of said platelet concentration is on said excessive level.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Fig. 1 is a plan view showing an example of the construction of a platelet collection circuit used in a platelet collection apparatus of the present invention.

[0011] Fig. 2 is a partially cutaway sectional view showing a state in which a drive unit is mounted on a centrifugal separator used in the platelet collection circuit.

[0012] Fig. 3 is a concept view showing a platelet collection apparatus, according to an embodiment of the present invention, having the platelet collection circuit mounted thereon.

[0013] Fig. 4 is a block diagram showing a controller used in the platelet collection apparatus of the present invention.

[0014] Fig. 5 is a flowchart for describing the operation of the platelet collection apparatus according to an embodiment of the present invention in the range from a start until an acceleration plasma circulation step.

[0015] Fig. 6 is a flowchart for describing the operation of the platelet collection apparatus according to an embodiment of the present invention in the range from a small-amount plasma collection step until a computation of a ROM value for computing an estimated number of to-be-collected platelets.

[0016] Fig. 7 is a flowchart for describing the operation of the platelet collection apparatus according to an embodiment of the present invention in the range from the computation of the estimated number of to-be-collected platelets until a blood return step.

[0017] Fig. 8 is a flowchart for describing an operation of a mode, for allowing alteration of number of units of to-be-collected platelets, to be executed in the platelet collection apparatus according to an embodiment of the present invention.

[0018] Fig. 9 is a flowchart for describing the operation of the platelet collection apparatus according to an embodiment of the present invention in the range from a buffy coat return step until the acceleration plasma circulation step.

[0019] Fig. 10 is a flowchart for describing the operation of the platelet collection apparatus according to an embodiment of the present invention in the range from small-amount plasma collection step until the computation of the ROM value for computing the estimated number of to-be-collected platelets.

[0020] Fig. 11 is a flowchart for describing the operation of the platelet collection apparatus according to an embodiment of the present invention in the range from the computation of the estimated number of to-be-collected platelets until the blood return step.

[0021] Fig. 12 is a flowchart for describing the operation of the platelet collection apparatus according to an embodiment of the present invention in the range from the small-amount plasma collection step until a platelet collection step.

[0022] Fig. 13 is a flowchart for describing the operation of the platelet collection apparatus according to an embodiment of the present invention in the range from the ROM value for computing the estimated number of to-be-collected platelets until the blood return step.

[0023] Fig. 14 is a flowchart for describing the operation of the platelet collection apparatus according to another embodiment of the present invention in the range from a start until an acceleration plasma circulation step.

[0024] Fig. 15 is a flowchart for describing the operation of the platelet collection apparatus according an embodiment of the present invention in the range from the small-amount plasma collection step until the platelet collection step.

[0025] Fig. 16 is a flowchart for describing the operation of the platelet collection apparatus according an embodiment of the present invention in the range from the ROM value for computing the estimated number of to-be-collected platelets until the blood return step.

[0026] Fig. 17 is a flowchart for describing the operation of the platelet collection apparatus according an embodiment of the present invention in the range from the buffy coat return step until the acceleration plasma circulation step.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0027] A platelet collection apparatus according to the present invention will be described with reference to embodiments shown in the accompanying drawings.

[0028] A platelet collection apparatus 1 according to the present invention has a platelet collection circuit 2 including a centrifugal separator 20 having a rotor 142 having an internal blood storage space and an inlet 143 and an outlet 144 both communicating with the blood internal storage space and centrifugally separating blood introduced into the internal blood storage space through the inlet 143 by a rotation of the rotor 142 into components; a first line 21 for connecting a Hood collection needle 29 or a connector (not shown) of a blood collection instrument and the inlet 143 of the centrifugal separator 20 with each other; a second line 22 connected to the outlet 144 of the centrifugal separator 20; a third line 23, connected to the first line 21, for injecting an anticoagulant to the blood; a plasma collection bag 25 having a first tube 25a connected with the first line 21 and a second tube 25b connected with the second line 22; and a platelet collection bag 26 connected with the second line 22.

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[0029] The platelet collection apparatus 1 of the present invention further includes a liquid supply pump 11 (first liquid supply pump) mounted on the first line 21. The platelet collection apparatus 1 has a function of computing the number of platelet collection cycles and the expected number of to-be-collected platelets or a value related thereto from the data of a donor's hematcrit value, platelet concentration data, and the target number of to-be-collected platelets or a value related thereto, all of which are inputted to the platelet collection apparatus 1 before a platelet collection operation is performed. The data of a donor's hematcrit value, platelet concentration data and the target number of to-be-collected platelets or a value related thereto are inputted to the platelet collection apparatus 1 before a platelet collection operation is performed.

[0030] The platelet collection apparatus of the present invention has a function (hereinafter referred to as function of determining on an increase/decrease tendency in the number of collected platelets) of determining whether there is a tendency to increase or decrease in the number of collected platelets after plasma (PC) containing high-concentration platelets is collected in a plasma collection operation. The function of determining on an increase/decrease tendency determines by using data, related to the concentration of platelets, obtained from a turbidity sensor when the plasma containing high-concentration platelets is collected, the expected number of to-be-collected platelets or a value related thereto And, the platelet collection apparatus 1 further includes a function of decreasing the amount of platelets to be collected in a subsequent platelet collection operation in the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that there is a tendency to increase in the number of collected platelets.

[0031] Also, The platelet collection apparatus of the present invention has a function (hereinafter referred to as function of determining on an increase/decrease tendency in the number of collected platelets) of determining whether there is a tendency to increase or decrease in the number of collected platelets after plasma (PC) containing high-concentration platelets is collected in a plasma collection operation. The function of determining on an increase/decrease tendency determines by using data, related to the concentration of platelets, obtained from a turbidity sensor when the plasma containing high-concentration platelets is collected, the expected number of to-be-collected platelets or a value related thereto. And, the platelet collection apparatus further includes a function of altering an inputted target number of units of to-be-collected platelets in the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that the number of units of collected platelets is on "unit-increased level". The platelet collection apparatus further includes a function of increasing the amount of platelets to be collected in a subsequent platelet collection operation in the case where the function of altering the target number of units of to-be-collected platelets has altered the target number of units of to-be-collected platelets.

[0032] It is preferable that the platelet collection apparatus of the present invention has the function of determining whether there is a tendency to increase or decrease in the number of collected platelets by using data, related to the concentration of platelets, obtained from the turbidity sensor, the expected number of to-be-collected platelets or a value related thereto and determining on a "level of tendency to increase" and a "unit-increased level" higher than the "level of tendency to increase" after the plasma (PC) containing high-concentration platelets is collected in the plasma collection operation. The platelet collection apparatus further includes the function of altering an inputted target number of units of to-be-collected platelets in the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that the number of units of platelets is on the "unit-increased level". The platelet collection apparatus further includes the function of increasing the amount of platelets to be collected in a subsequent platelet collection operation in the case where the function of altering the target number of units of to-be-collected platelets has altered the target number of units of to-be-collected platelets. The platelet collection apparatus further includes the function of decreasing the amount of platelets to be collected in a subsequent platelet collection operation in the case where the function of altering the target number of units of to-be-collected platelets has not altered the target number of units of platelets in a predetermined period of time after termination of the operation of the function of altering the target number of units of to-be-collected platelets and in the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that the number of collected platelets is on the "level of tendency to increase".

[0033] The platelet collection apparatus of the present invention has a platelet-concentration peak situation determination function of detecting a peak of the platelet concentration by using signals detected by the turbidity sensor when the high-concentration platelets-containing plasma is collected in the platelet collection operation and determining whether the detected peak of the platelet concentration is on a "normal level" or an "excessive level". The platelet collection apparatus further includes a function of decreasing the number of platelets to be collected in the platelet collection operation, when the platelet-concentration peak situation determination function has determined that the peak of the platelet concentration is on the "excessive level".

[0034] The platelet collection apparatus 1 has a centrifugal separator drive unit 10 for rotating the rotor 142 of the centrifugal separator 20; the first liquid supply pump 11 to be used for the first line 21; a second liquid

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supply pump 12 to be used for the third line 23; a plurality of flow path shutter means 81, 82, 83, 84, 85, and 86 for opening/closing flow paths of the platelet collection circuit 2, and a controller 13 for controlling the centrifugal separator drive unit 10, the first liquid supply pump 11, the second liquid supply pump 12, and a plurality of the flow path shutter means 81, 82, 83, 84, 85, and 86.

[0035] The platelet collection circuit 2 will be described in detail below.

[0036] The platelet collection circuit 2 is provided to collect platelets.

[0037] The platelet collection circuit 2 includes a blood collector such as a blood collection needle 29 or a connector (connector of blood collector) connected with the blood collection needle 29 or with a blood collector having a blood pool connector; the first line 21 (blood collection/blood return line) connecting the blood collection needle 29 or the connector of the blood collector and the inlet 143 of the centrifugal separator 20 with each other and having a first pump tube 21g; the second line 22 for connecting the outlet 144 of the centrifugal separator 20 and the first line 21 with each other; the third line (anticoagulant injection line) 23 connected with a position, of the first line 21, near the blood collection needle 29 and having a second pump tube 23a; a plasma collection bag 25 having the first tube 25a connected with a branch connector 21f positioned nearer to the collection needle 29 than a pump tube 21g of the first line 21 and the second tube 25b connected with the second line 22; the platelet collection bag 26 having a third tube 26a connected with the second line 22; and a buffy coat collection bag 27 having a fourth tube 27a connected with the second line 22. Instead of the blood collection needle 29, the platelet collection circuit 2 may employ a connector (such as a metal or plastic needle) to be connected with a blood pool such as a blood bag.

[0038] A known metal needle is used as the blood collection needle 29. The first line 21 includes a blood collection needle-side part 21a with which the blood collection needle 29 is connected and a centrifugal separator-side part 21b with which the inlet 143 of the centrifugal separator 20 is connected. The blood collection needle-side part 21a is formed of a plurality of soft plastic tubes. The blood collection needle-side part 21a has the following elements arranged as viewed from the side of the blood collection needle 29: a branching connector 21c for connecting the blood collection needle-side part 21a and the third line 23 with each other; a chamber 21d for removing bubbles and micro-aggregates; a branching connector 21e for connecting the blood collection needle-side part 21a and the second line 22 with each other; and a branching connector 21f for connecting the first line 21 and the first tube 25a of the plasma collection bag 25 with each other. The chamber 21d is connected to an air-permeable and germ-blocking filter 21i. The centrifugal separator-side part 21b is connected with the branching connector 21f connected with the first tube 25a and has the first pump tube 21g formed in the vicinity of the branching connector 21f.

[0039] The second line 22 connecting the outlet 144 of the centrifugal separator 20 and the first line 21 with each other has an end thereof connected to the outlet of the centrifugal separator 20 and the other end thereof connected to the branching connector 21e for connecting the blood collection needle-side part 21a and the second line 22 with each other. The second line 22 has the following elements arranged as viewed from the side of the centrifugal separator 20: a branching connector 22a for connecting the second line 22 with the second tube 25b of the plasma collection bag 25 and with the third tube 26a of the platelet collection bag 26; a branching connector 22c for connecting the second line 22 with a tube having a bubble-removing filter 22f; and a branching connector 22d for connecting the second line 22 with the fourth tube 27a connected with the buffy coat collection bag 27. The third line 23 is connected with the branching connector 21c having an end thereof connected to the first line 21. The third line 23 has the following elements arranged as viewed from the connector 21c: a pump tube 23a; a foreign matter removing filter 23b; a bubble removing chamber 23c; and an anticoagulant container-connecting needle 23d.

[0040] The plasma collection bag 25 includes the first tube 25a connected with the branching connector 21f located between the blood collection needle 29 and the pump tube 21g of the first line 21; and the second tube 25b connected with the branching connector 22a of the second line 22. The platelet collection bag 26 includes the third tube 26a connected with the branching connector 22a of the second line 22. The buffy coat collection bag 27 includes the fourth tube 27a connected with the branching connector 22d of the second line 22.

[0041] It is preferable to use polyvinyl chloride as the material for the tubes and the pump tubes used to form the first to third lines 21, 22, and 23 and the tubes connected to the bags. Materials similar to those for the tubes can be also used to form the branching connectors. The pump tubes strong enough to bear a pressure applied thereto by roller pumps are used in the embodiment.

[0042] Each of the plasma collection bag 25, the platelet collection bag 26, and the buffy coat collection bag 27 is composed of layers of flexible plastic sheets having the peripheral edges thereof fusion bonded (thermally or with high frequencies) or adhered. Soft polyvinyl chloride is the most favorable material for forming the bags 25, 26, and 27.

[0043] It is preferable to use a sheet material superior in gas permeability for the platelet collection bag 26 for assuring an improved platelet shelf life.

[0044] Essential portions of the platelet collection circuit 2 are housed in a cassette. The platelet collection circuit 2 includes a cassette housing 28 partially accommodating or partially holding all the lines (first, second, and third lines) and all the tubes (first, second, third, and fourth tubes). In other words, they are partially fixed to

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the cassette housing 28.

[0045] The centrifugal separator 20, a so-called centrifugal bowl, is mounted on the platelet collection circuit 2 to separate blood into components by a centrifugal force. As shown in Fig. 2, the centrifugal separator 20 includes a tubular member 141 extending vertically and having an inlet 143 formed at the upper end thereof and a hollow rotor 142 sealed to prevent liquid from flowing thereinto from an upper portion 145 of the centrifugal separator 20 and rotating around the tubular member 141. The rotor 142 has a flow path (blood storage space) formed along the bottom and the inner peripheral surface thereof. An outlet 144 is so formed as to communicate with the upper portion of the flow path. The volume of the rotor 142 ranges from 100 to 350 ml.

[0046] The rotor 142 is rotated under predetermined centrifugal conditions (rotational speed and rotation time) set by the rotor drive unit 10 of the platelet collection apparatus 1. Based on the centrifugal conditions, patterns (for example, the number of blood components to be separated) of blood separation to be made in the rotor 142 can be set. As shown in Fig. 2, according to the embodiment, the centrifugal conditions are set such that the blood is separated into a plasma layer (inner layer) 131, a buffy coat layer (intermediate layer) 132, and a red cell layer (outer layer) 133 laminated in the flow path of the rotor 142.

[0047] Referring to Fig. 3, the platelet collection apparatus 1 according to the present invention will be described.

[0048] The platelet collection apparatus 1 includes the centrifugal separator drive unit 10 for rotating the rotor 142 of the centrifugal separator 20; the first liquid supply pump 11 to be used individually for the first line 21; the second liquid supply pump 12 to be used individually for the third line 23; a plurality of the flow path shutter means 81,82, 83, 84, 85, and 86 for opening/closing the flow paths of the platelet collection circuit 2; and the controller 13 for controlling the centrifugal separator drive unit 10, the first liquid supply pump 11, the second liquid supply pump 12, and the flow path shutter means 81, 82, 83, 84, 85, and 86. The platelet collection apparatus 1 further includes a turbidity sensor 14 mounted on the portion, of the second line 22, located between the centrifugal separator 20 and the connector 22a for connecting the second tube 25b with the second line 22; an optical sensor 15 mounted above the centrifugal separator 20; and a weight sensor 16 for detecting the weight of the plasma collection bag 25.

[0049] The turbidity sensor 14 detects the turbidity of a fluid flowing through the second line 22 and outputs a voltage corresponding to the detected turbidity. Specifically, the turbidity sensor 14 outputs a low voltage when the turbidity is high, while it outputs a high voltage when the turbidity is low. As the turbidity sensor, an optical sensor (laser light source, LED light source, and the like) can be preferably used.

[0050] In the embodiment, the platelet collection apparatus computes the number of platelet collection cycles and the expected number of to-be-collected platelets or a value related thereto from the data of a donor's hematcrit value, platelet concentration data, and the target number of to-be-collected platelets or a value related thereto, all of which are inputted to the platelet collection apparatus 1 before a platelet collection operation is performed. Therefore the platelet collection apparatus has a hematcrit value input portion 61, a platelet concentration input portion 62, an input portion 63 of the target number of units of to-be-collected platelets related to the target number of to-be-collected platelets.

[0051] In the platelet collection apparatus of the present invention, blood to be analyzed is collected from a donor before performing the platelet collection operation, information of blood (hematcrit value, concentration of platelet) is obtained from the blood to be analyzed (preparatorily collected blood) by using a blood analyzer prepared separately. The data of the blood information and the target number of to-be-collected platelets (or target number of units of to-be-collected platelets) are inputted to the platelet collection apparatus to compute a necessary number of cycles of the platelet collection operation. Thereby the platelet collection operation is performed in the number of cycles.

[0052] The controller 13 includes a control part 50, a pump controller 53 for the first liquid supply pump 11 and a pump controller 54 for the second liquid supply pump 12, an input part 60, and a display part 52 serving as an warning means. The control part 50 which is the control mechanism of the controller 13 is electrically connected to the first liquid supply pump 11 and the second liquid supply pump 12 through the pump controllers 53 and 54 respectively. The turbidity sensor 14 mounted on the second liquid supply pump 22 is electrically connected to the control part 50. A operational amount detection part 56 mounted on the first liquid supply pump 11 is electrically connected to the control part 50. As the operational amount detection part 56, a rotational amount detection means can be used. More specifically, a rotary encoder can be preferably used as the operational amount detection part 56. The control part 50 is also electrically connected to a driving controller 55 of a driving apparatus (rotor-driving apparatus) for driving the centrifugal separator.

[0053] The control part 50 has a memory that stores necessary data, computing equations, and inputted hematcrit value data, and data of the platelet concentration; a function of computing the number of collected platelets (function of computing real time number of collected platelets) by using symbols, related to the platelet concentration, detected by the turbidity sensor; a function of computing the estimated number of to-be-collected platelets; the function of determining on an increase/decrease tendency in the number of collected platelets; the control function for the function of decreasing the number of to-be-collected platelets; and the function of controlling the function of increasing the number of to-

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be-collected platelets. The platelet collection apparatus of the embodiment is characterized in that it has both the function of decreasing the number of to-be-collected platelets and the function of increasing the number of to-be-collected platelets.

[0054] An input part 60 of the controller 13 has a hematcrit value input portion 61, a platelet concentration input portion 62, an input portion 63 of the target number of units of to-be-collected platelets, a start switch 64, and a switch 65 for altering the number of platelet collection cycles.

[0055] The platelet collection apparatus 1 computes the number of platelet collection cycles and the expected number of to-be-collected platelets or a value related thereto from the data of the hematcrit value obtained from the blood to be analyzed, the data of the platelet concentration from the blood to be analyzed, and the target number of to-be-collected platelets or a value related thereto. The value related to the target number of to-be-collected platelets means the target number of units of to-be-collected platelets. The value related to the expected number of to-be-collected platelets means the expected number of units of to-be-collected platelets.

[0056] The relationship between the number of units of platelets and the number of platelets is as follows:

20-unit platelet: not less than 4×10^{11}
15-unit platelet: not less than 3×10^{11}
10-unit platelet: not less than 2×10^{11}
5-unit platelet: not less than 1×10^{11}
The number of units = 5×number of platelets/10^{11}.
The number of platelets = number of units × 2 × 10^{10}

[0057] Description is made on the function of computing the number of platelet collection cycles and the expected number of to-be-collected platelets or the value related thereto from the data of the hematcrit value obtained from the blood to be analyzed, the data of the platelet concentration from the blood to be analyzed, and the target number of to-be-collected platelets or a value related thereto.

[0058] The control part 50 of the platelet collection apparatus of the embodiment computes the number of platelet collection cycles and the expected number of to-be-collected platelets or the value related thereto as follows: In the embodiment, upon input of the target number of units of to-be-collected platelets to the control part 50, the computing portion of the control part 50 computes the target number of to-be-collected platelets.

[0059] The expected number of to-be-collected platelets in the first cycle = amount of extracorporeally circulating blood × PLT concentration(platelet concentration) x expected recovery percentage ••• Equation 1

[0060] The equation 1 is fundamentally used. In addition, in the second cycle and subsequent cycles thereto, it is necessary to take extracorporeally circulating blood and the amount of blood remaining in the centrifugal bowl into consideration as the amount of treated blood. It is also necessary to consider an increase of the number of platelets owing to buffy coat recycled in the platelet collection apparatus of the embodiment.

[0061] The following computation is performed in the second cycle:

[0062] The expected number of platelets to be collected in the second cycle = amount of blood to be processed in the second cycle × expected platelet concentration in the second cycle × expected recovery percentage + amount of blood to be processed in the first cycle × expected PLT concentration in the first cycle × left-behind percentage × recycle percentage ••• Equation 2

[0063] The following computation is performed in the third cycle:

[0064] The expected number of platelets to be collected in the third cycle = amount of blood to be processed in the third cycle × expected platelet concentration in the third cycle × expected recovery percentage + amount of blood to be processed in the second cycle × expected platelet concentration in the second cycle × left-behind percentage × cycle percentage + amount of blood to be processed in the first cycle × expected PLT concentration in the first cycle × left-behind percentage × recycle percentage ••• Equation 3

[0065] In sequentially computing the expected number of platelets to be collected in the first cycle, the second cycle, and the third cycle, the number of cycles at which the expected number of platelets exceeds the target number of platelets to be collected is outputted as the number of platelet collection cycles. The number of platelets collected in each cycle is outputted as the expected number of platelets.

[0066] The amount of the extracorporeally circulating blood in the equation 1 is found by an equation shown below:

[0067] The amount of the extracorporeally circulating blood = K×B(%)÷HCT(%) ••• Equation 4

[0068] In the equations 1,2,3, and 4;

K: The volume (200 - 230ml) of red cells inside the centrifugal bowl at the time of termination of blood collection (start of platelet collection operation),
B(%): Percentage (60 - 95%) of the red cells in K,

[0069] The value of each of K and B is experimentally found, and a fixed value is used.

HCT(%): hematcrit value (obtained from blood collected for analysis),
PLT concentration: platelet concentration (obtained from the blood collected for analysis)

[0070] Expected recovery percentage: the ratio of the number of platelets that can be taken out into the recovery bag as thick platelets from the centrifugal separation

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container to the total platelets contained in blood supplied to the centrifugal separation container in each cycle. The experience value based on an experiment is used as expected recovery percentage. It is normally 60 ~ 85%.

[0071] Target number of to-be-collected platelets: target number of units of to-be-collected platelets $\times 2 \times 10^{10}$

[0072] Expected number of to-be-collected platelets = expected number of platelets to-be-collected in first cycle + expected number of platelets to-be-collected in second cycle + ••• expected number of platelets to-be-collected in last cycle •••• Equation 5

[0073] The platelet collection apparatus may compute the expected number of units of to-be-collected platelets. The display part 52 has the function of displaying the number of platelet collection operation cycles and the expected number of to-be-collected platelets or the expected number of units of to-be-collected platelets. From the number of platelet collection operation cycles, the control part 50 may have the function of computing an expected time period required to perform the platelet collection operation. The controller 13 may have the function of displaying an expected time when the platelet collection operation terminates.

[0074] The platelet collection apparatus of the present invention has the function of determining whether there is a tendency to increase or decrease in the number of collected platelets by using data, related to the concentration of platelets, obtained from the turbidity sensor, the expected number of to-be-collected platelets or a value related thereto and determining on a "level of tendency to increase" and a "unit-increased level" higher than the "level of tendency to increase" when the plasma (PC) containing high-concentration platelets is collected after blood is collected in a first plasma collection operation, namely, after platelets are collected in the first platelet collection operation is performed, namely, after the plasma containing high-concentration platelets (PC) is collected in a first cycle. The platelet collection apparatus further includes the function of altering an inputted target number of units of to-be-collected platelets in the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that the number of units of platelets is on the "unit-increased level". The platelet collection apparatus further includes the function of increasing the amount of platelets to be collected in a subsequent platelet collection operation in the case where the function of altering the target number of units of to-be-collected platelets has altered the target number of units of to-be-collected platelets. The platelet collection apparatus further includes the function of decreasing the amount of platelets to be collected in a subsequent platelet collection operation in the case where the function of altering the target number of units of to-be-collected platelets has not altered the target number of units of platelets in a predetermined period of time after termination of the operation of the function of altering the target number of units of to-be-collected platelets and in the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that the number of collected platelets is on the "level of tendency to increase".

[0075] The platelet collection apparatus of the embodiment has the function of decreasing the number of to-be-collected platelets and the function of increasing the number of to-be-collected platelets in addition to the function of determining on an increase/decrease tendency in the number of collected platelets.

[0076] The function of determining on an increase/decrease tendency in the number of collected platelets will be described in detail below.

[0077] The platelet collection apparatus of the embodiment has a expected collection-amount-group determination function of making a determination on to which of stored expected collection-amount-groups, by using the expected number of to-be-collected platelets or the value related thereto; and a function of computing the estimated number of to-be-collected platelets, by using data related to the collection amount of the high-concentration platelets-containing plasma in the platelet collection operation and data related to the platelet concentration obtained from the turbidity sensor when the high-concentration platelets-containing plasma is collected. The function of determining on an increase/decrease tendency in the number of collected platelets determines on an increase tendency by using the data of the corresponding collection-amount-group determined by the collection-amount-group determination function and the estimated number of to-be-collected platelets computed by the function of computing the estimated number of to-be-collected platelets.

[0078] The platelet collection apparatus of the embodiment has the collection-amount-group determination function of determining on which of stored expected collection-amount-groups corresponds to the number of collected platelets, by using the computed number of the estimated to-be-collected platelets or the value related thereto. More specifically, the expected collection-amount-groups are classified into a lower group, a medium group, and a higher group. In the lower group, the expected number of to-be-collected platelets is less than a reference value + a first predetermined value (for example, 0.3×10^{11}: PM1). The reference value is [target number of units of to-be-collected platelets $\times 2 \times 10^{10}$ - the predetermined value (for example, 0.15×10^{11}: PM5)]. In the medium group, the expected number of to-be-collected platelets is not less than the reference value + the first predetermined value (for example, 0.3×10^{11}: PM1) nor more than the reference value + a second predetermined value (for example, 0.65×10^{11}: PM2) with respect to the reference value. In the higher group, the expected number of to-be-collected platelets is more than the reference value + the second predetermined value (for example, 0.65×10^{11}: PM2)). The nu-

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merical values of the first predetermined value (PM1), the second predetermined value (PM2), and the predetermined value (PM5) are exemplified for the case where the target number of units of to-be-collected platelets is 10 units and can be altered in dependence on the target number of units of to-be-collected platelets. More specifically, it is preferable to set the values thereof to 1/2 when the target number of units of to-be-collected platelets is five and to 3/2 when the target number of units of to-be-collected platelets is 15.

[0079] The platelet collection apparatus of the embodiment has the function of computing the estimated number of to-be-collected platelets, by using data related to the collection amount of the high-concentration platelets-containing plasma in the platelet collection operation and data related to the platelet concentration obtained from the turbidity sensor when the high-concentration platelets-containing plasma is collected.

[0080] The platelet collection apparatus of the present invention has a function of computing a real-time number of collected platelets for the function of computing the estimated number of to-be-collected platelets. At the time when the plasma (PC) containing high-concentration platelets is collected, voltage signals detected by the turbidity sensor installed on the second line are sequentially inputted to the control part. The amount of the plasma containing the high-concentration platelet is computed by using an operation amount of the liquid supply pump at the time when the plasma containing high-concentration platelet is collected and a stored blood feeding amount per unit operation amount of the liquid supply pump. The control part stores data or an equation for computing the concentration of platelets in the plasma containing the high-concentration platelet from the voltage signal sent from the turbidity sensor. The control part computes the number of collected platelets (RTM value) from the computed platelet concentration and the computed blood-feeding amount. The number of collected platelets (RTM value) can be obtained by computing the platelet concentration in a predetermined time period on the basis of output signals of the turbidity sensor detected at predetermined intervals (for example, 0.02 - 2 seconds) and multiplying the platelet concentration by the blood-feeding amount in the predetermined time period to thereby obtain the number of collected platelets in each predetermined time period This operation is performed continuously in the time period in which the plasma containing the high-concentration platelet is collected. The total number of the collected platelets can be obtained by adding respective computed number of platelets to each other. The number (RTM value) of the collected platelets can be obtained by computing an average value of a predetermined number of times (for example, 10 times) of output signals of the turbidity sensor detected at predetermined intervals (for example, 0.001 - 0.5 seconds), computing a platelet concentration in a specified time period (for example, 10 times as large as the predetermined time period), and multiplying the platelet concentration by the blood-feeding amount in the specified time period to thereby obtain the number of collected platelets in each predetermined time period. This operation is performed continuously in the time period in which the plasma containing the high-concentration ' platelet is collected. The total number of the collected platelets can be obtained by adding respective computed number of platelets to each other.

[0081] The number of collected platelets (RTM value) may be computed without computing the platelet concentration. That is, the number of collected platelets (RTM value) can be computed by using a stored equation for computing the number of collected platelets and data related to the platelet concentration obtained by converting analog data provided by the turbidity sensor into digital data.

[0082] An RTM-corrected value is computed from the computed number of collected platelets (RTM value). When the RTM value is not less than the expected number of to-be-collected platelets $\times$ 1.5, the RTM-corrected value = the expected number of to-be-collected platelets $\times$ 1.2 (case A). When the RTM value is not less than the expected number of to-be-collected platelets $\times$ 1.2 nor more than the expected number of to-be-collected platelets $\times$ 1.5, the RTM-corrected value = the expected number of to-be-collected platelets $\times$ 1.1 (case B). When the RTM value is not less than the expected number of to-be-collected platelets nor more than the expected number of to-be-collected platelets $\times$ 1.2, the RTM-corrected value = the expected number of to-be-collected platelets (case C). When the RTM value is less than the expected number of to-be-collected platelets, the RTM-corrected value = RTM value (case D). A display number of collected platelets is also computed. The display number of collected platelets is the sum of the addition of the RTM-corrected values in the first platelet collection operation through the previous platelet collection operation and the RTM-corrected value in the current platelet collection operation. In other words, the display number of collected platelets is the addition of the RTM-corrected values in a terminated platelet collection operation.

[0083] The estimated number of to-be-collected platelets is computed by using the corresponding case of the cases A - D and the display number of collected platelets. More specifically, in the case of the cases A, B, and C, the estimated number of to-be-collected platelets is computed by the display number of collected platelets + the RTM-corrected value in the previous platelet collection operation $\times$ (set number of platelet collection operation cycles - the number of platelet collection operation cycles when collection operation terminated). In the case of the case D, the estimated number of to-be-collected platelets is computed by the display number of collected platelets + the expected number of to-be-collected platelets (value obtained by dividing the expected number of to-be-collected plate-

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lets by the number of cycles) × (set number of platelet collection operation cycles - the number of platelet collection operation cycles when collection operation terminated).

[0084] The function of determining on an increase/decrease tendency in the number of collected platelets makes a determination on to which of "level of proper range (no tendency to increase or decrease), "level of tendency to increase", and "unit-increased level" the estimated number of to-be-collected platelets corresponds. The function of determining on an increase/decrease tendency in the number of collected platelets may determine on "level of decrease range" (there is a tendency to decrease).

[0085] The function of determining on an increase/decrease tendency in the number of collected platelets determines that the number of collected platelets is on the level of proper range (there is no tendency to increase or decrease) [1] if a reference value □ the estimated number of to-be-collected platelets < the reference value + a second predetermined value (PM2: specifically 0.65×10^{11}), supposing that the expected collection-amount-group is "medium" or "high" and [2] if the reference value + the second predetermined value (PM2: specifically 0.65×10^{11}) □ the estimated number of to-be-collected platelets < the reference value + a third predetermined value (PM6: specifically 0.9×10^{11}), supposing that the expected collection-amount-group is "low".

[0086] The function of determining on an increase/decrease tendency in the number of collected platelets determines that the number of collected platelets is on "level of tendency to increase" (there is a tendency to increase) [3] if the reference value + the second predetermined value (PM2: specifically 0.65×10^{11}) □ the estimated number of to-be-collected platelets < the reference value + the third predetermined value (PM6: specifically 0.9×10^{11}), supposing that the expected collection-amount-group is "medium" or "high" and [4] if the reference value + the third predetermined value (PM6: specifically 0.9×10^{11}) □ the estimated number of to-be-collected platelets, supposing that the expected collection-amount-group is "low".

[0087] The function of determining on an increase/decrease tendency in the number of collected platelets determines that the number of collected platelets is on "unit-increased level" (there is a tendency to increase) if [5] the reference value + the third predetermined value (PM6: specifically 0.9×10^{11}) □ the estimated number of to-be-collected platelets, supposing that the expected collection-amount-group is "high".

[0088] In the embodiment, the function of determining on an increase/decrease tendency in the number of collected platelets determines on the number of collected platelets by distinguishing "level of tendency to increase" and "unit-increased level" from each other when there is a tendency to increase. This is because as described later, the platelet collection apparatus has the function of increasing the number of to-be-collected platelets. However, the platelet collection apparatus does not necessarily have to be provided with the function of increasing the number of to-be-collected platelets. In this case, the function of determining on an increase/decrease tendency in the number of collected platelets determines that the number of collected platelets is in the proper range (there is no tendency to increase or decrease) or there is a tendency to increase. In this case, the function of determining on an increase/decrease tendency in the number of collected platelets determines that the number of collected platelets is on the level of proper range (there is no tendency to increase or decrease) [1] if the reference value □ the estimated number of to-be-collected platelets < the reference value + the second predetermined value (PM2: specifically 0.65×1011), supposing that the expected collection-amount-group is "medium" or "high" and [2] if the reference value + the second predetermined value (PM2: specifically 0.65×10^{11}) □ the estimated number of to-be-collected platelets < the reference value + the third predetermined value (PM6: specifically 0.9×10^{11}), supposing that the expected collection-amount-group is "low". The function of determining on an increase/decrease tendency in the number of collected platelets determines that the number of collected platelets is on "level of tendency to increase" (there is a tendency to increase) if [3] the reference value + the second predetermined value (PM2: specifically 0.65×10^{11}) □ the estimated number of to-be-collected platelets, supposing that the expected collection-amount-group is "high" and [4] if the reference value + the third predetermined value (PM6: specifically 0.9×10^{11}) □ the estimated number of to-be-collected platelets, supposing that the expected collection-amount-group is "medium".

[0089] In the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that there is no tendency to increase in the number of collected platelets, the platelet collection apparatus performs a platelet collection operation on the basis of stored data of the platelet collection condition.

[0090] In the last platelet collection operation, the function of determining on an increase/decrease tendency in the number of collected platelets does not operate. That is, the determination of the tendency in the platelet collection is not made in the last platelet collection operation. However, the display number of collected platelets is computed.

[0091] The platelet collection apparatus of the present invention has the function of altering an inputted target number of units of to-be-collected platelets in the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that the number of units of collected platelets is on "unit-increased level". The platelet collection apparatus further includes the function of increasing the amount of platelets to be collected in a subsequent

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platelet collection operation in the case where the function of altering an inputted target number of units of to-be-collected platelets has altered the target number of units of to-be-collected platelets.

[0092] The platelet collection apparatus has a display function of giving warning of "unit-increased level" operates when the function of determining on an increase/decrease tendency in the number of collected platelets has determined that the number of units of collected platelets is on the increase level. At this time, the function of altering the target number of units of to-be-collected platelets also operates. Hence it is possible to alter the inputted target number of units of to-be-collected platelets. The target number of units of to-be-collected platelets is rewritten not automatically. An altered number of units can be inputted by an operator. The alteration of the number of units is inputted from the input portion 63 of the target number of units of to-be-collected platelets. The "unit-increased increase level" is displayed on the display part 52.

[0093] When the target number of units of to-be-collected platelets is altered, the warning display of "unit-increased level" is turned off, and the control part 50 computes and rewrites a necessary platelet collection condition for collecting the target number of units of platelets and executes subsequent platelet collection operations under a new platelet collection condition. Specifically, the control part 50 computes and rewrites the target collection amount of plasma containing high-concentration platelet and a target collection amount of platelet-removed of plasma. It is preferable not to alter the total amount of plasma to be collected from a donor. Because of the increase of the target number of units of to-be-collected platelets, the target collection amount of the plasma containing high-concentration platelets has increased. Thus the target collection amount of platelet-removed of plasma is decreased by the increased amount of the target collection amount of the plasma containing high-concentration platelets.

[0094] When the function of altering an inputted target number of units of to-be-collected platelets has altered the target number of units of to-be-collected platelets, the computing portion of the control part 50 re-computes the expected number of to-be-collected platelets or the value related thereto. The function of determining on an increase tendency in the number of collected platelets makes a determination by using the re-computed expected number of to-be-collected platelets or the value related thereto.

[0095] The platelet collection apparatus has a function of computing a re-computed expected number of to-be-collected platelets or a value related thereto when the function of altering an inputted target number of units of to-be-collected platelets alters a target number of units of to-be-collected platelets. The function of determining on an increase tendency in the number of collected platelets makes a determination by using a re-computed expected number of to-be-collected platelets or a value related thereto.

[0096] The platelet collection apparatus has the function of decreasing the amount of platelets to be collected in a subsequent platelet collection operation in the case where the function of altering the target number of units of to-be-collected platelets has not altered the target number of units of platelets in a predetermined period of time after termination of the operation of the function of altering the target number of units of to-be-collected platelets.

[0097] The platelet collection apparatus has the function of decreasing the amount of platelets to be collected in a subsequent platelet collection operation in the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that the number of collected platelets is on the "level of tendency to increase".

[0098] That is, the platelet collection apparatus of the embodiment has the function of decreasing the number of to-be-collected platelets operates in the case where the target number of units of to-be-collected platelets has not been altered in a predetermined period of time after the function of altering an inputted target number of units of to-be-collected platelets has start to operate and in the case where the function of determining on an increase tendency in the number of collected platelets has determined that the number of collected platelets is on the "level of tendency to increase".

[0099] The function of decreasing the number of to-be-collected platelets alters the stored data of the platelet collection termination condition to quicken the platelet collection operation and decrease the collection amount of the plasma containing high-concentration platelets (type 1 of the function of decreasing the number of to-be-collected platelets). The function of decreasing the number of to-be-collected platelets may alter the stored data of the platelet collection condition to decrease the concentration of platelets contained in the plasma containing the high-concentration platelets (type 2 of the function of decreasing the number of to-be-collected platelets).

[0100] Particularly, the platelet collection apparatus of the embodiment has both types 1 and 2.

[0101] More specifically, the platelet collection apparatus performs the platelet collection operation at least three times. In the platelet collection operation except the last platelet collection operation, the function of decreasing the number of to-be-collected platelets alters the stored data of the platelet collection termination condition to quicken the platelet collection operation and decrease the collection amount of the plasma containing high-concentration platelets. In the last platelet collection operation, the function of decreasing the number of to-be-collected platelets alters the stored data of the platelet collection condition to decrease the concentration of platelets contained in the plasma containing the high-concentration platelets.

[0102] The decrease type 1 of the function of decreas-

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ing the number of to-be-collected platelets alters the stored data of the platelet collection termination condition by decreasing the voltage of the collection termination turbidity sensor by a predetermined value to quicken the platelet collection operation. That is, the type 1 alters a platelet concentration (for example, about 400,000/ml) in a normal platelet collection termination to a platelet concentration (for example, about 900,000/ml) in an adjusted platelet collection termination. Thereby the time period for collecting the plasma containing the high-concentration platelets becomes short. Thus the collection amount of the plasma containing the high-concentration platelets becomes smaller. This type of adjustment can be simply and reliably accomplished. However, the amount of the plasma containing the high-concentration platelets decreases.

[0103] The decrease type 2 of the function of decreasing the number of to-be-collected platelets alters the stored data of the platelet collection termination condition in such a way that the concentration of platelets contained in the plasma containing the high-concentration platelets decreases, i.e., in such a way that the collection amount of the plasma is equal to or larger than that at the time when the adjusting function does not operate and that the platelet concentration decreases. More specifically, when the plasma containing high-concentration platelets is collected, the type 2 decreases the collection speed of the plasma containing the high-concentration platelets to a predetermined level after platelets flow out therefrom and increase the voltage of the collection termination turbidity sensor by a predetermined value to delay the platelet collection operation. That is, the type 2 alters a platelet concentration (for example, about 400,000/ml) in the normal collection termination to a platelet concentration (for example, about 300,000/ml) in the adjusted collection termination. Thereby the degree of the concentration platelets in the plasma decreases a little, and the collection amount thereof is more than that collected in the normal condition. By operating the decrease type 2 in the last platelet collection operation, the amount of the plasma containing the high-concentration platelets is almost equal to that collected in the normal condition.

[0104] It is preferable to provide both the type 1 and the type 2. However, one of the type 1 and the type 2 may be provided.

[0105] It is preferable that the platelet collection apparatus has an automatic function of terminating the operation of the function of decreasing the number of to-be-collected platelets and performing a platelet collection operation in accordance with data of the platelet collection condition which is used before the function of decreasing the number of to-be-collected platelets operates, when the function of determining on an increase tendency in the number of collected platelets has determined that the number of collected platelets has "there is no tendency to increase" after the function of decreasing the number of to-be-collected platelets operates. By doing so, it is possible to prevent an excessive reduction in the collection of the number of platelets which is caused by the operation of the function of decreasing the number of to-be-collected platelets.

[0106] In the platelet collection apparatus of the embodiment, the determination on the increase tendency in the number of collected platelets is continued after the function of decreasing the number of to-be-collected platelets starts its operation. Unlike the operation to be made after the function of increasing the number of to-be-collected platelets operates, the determination on the increase tendency in the number of collected platelets is made in accordance with the initial condition without altering the determination condition. In other words, the operation of the function of decreasing the number of to-be-collected platelets is effective only when a subsequent platelet collection operation is made, whereas the determination on the increase tendency in the number of to-be-collected platelets is executed in each platelet collection operation. Therefore when the function of decreasing the number of to-be-collected platelets operates because determination of "level of tendency to increase" and "unit-increased level" has been made in the first platelet collection operation, the function of decreasing the number of to-be-collected platelets does not operate if the determination of "level of proper range" has been made by the function of determining on an increase tendency in the number of collected platelets in the next platelet collection operation.

[0107] The platelet collection apparatus has a warning function that operates when it has been determined that there is a tendency to increase in the number of collected platelets and an operation display function of informing an operator of the operation of the function of decreasing the number of to-be-collected platelets.

[0108] In addition to the automatic type, the function of decreasing the number of to-be-collected platelets may be actuated by an operator's switching operation.

[0109] The platelet collection apparatus of the present invention is described below in other words. It is preferable that the platelet collection apparatus has the function of automatically computing the total number of platelets including the estimated number of platelets to be collected in remaining operation cycles after the operation cycle of each platelet collection operation terminates and the number of platelets collected in each cycle is automatically computed, has the function of determining on which of the four stages, namely, "level of tendency to decrease", "level of proper range", "level of tendency to increase" and "unit-increased level" corresponds to the number of to-be-collected platelets, and has the function of executing remaining operation cycles in dependence on each case of the four stages.

[0110] There is a case where the number of collected platelets corresponds to the case of "level of tendency to decrease". Thus it is preferable that the platelet collection apparatus has a function of informing the operator of the "level of tendency to decrease" by making a

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warning display such as "collected amount is short" and/or giving warning sound and automatically adjusting factors such as a collection amount of blood in the next cycle, a blood collection speed, a centrifuging separation speed, a plasma circulation speed for collection of platelets, and a platelet collection termination timing affecting the collection of platelets to increase the number of to-be-collected platelets. The platelet collection apparatus has a function of continuing an operation condition to be applied to the start of the blood collection operation when the tendency in the number of collected platelets is on the "level of proper range". When the tendency in the number of collected platelets corresponds to the case of "level of tendency to increase", it is preferable that the platelet collection apparatus has a function of informing the operator of that by making a warning display "collected amount is excessive" and/or giving warning sound so that the information allows the operator to issue an instruction of "prevent excessive collection" and automatically adjusting factors such as the collection amount of blood in the next cycle, the blood collection speed, the centrifuging separation speed, the plasma circulation speed for collection of platelets, and the platelet collection termination timing affecting the collection of platelets to decrease the collection the number of to-be-collected platelets. When the tendency in the number of collected platelets corresponds to the case of "unit-increased level", it is preferable to inform the operator of that by making a warning display "unit has increased" and/or giving a warning sound so that the information allows the operator to issue an instruction of "prevent excessive collection" and also issue an instruction of "unit has increased". In issuing the instruction of "prevent excessive collection", it is preferable that the platelet collection apparatus has the function of automatically adjusting factors such as the collection amount of blood in the next cycle, the blood collection speed, the centrifuging separation speed, the plasma circulation speed for collection of platelets, and the platelet collection termination timing affecting the collection of platelets to decrease the number of to-be-collected platelets. In issuing the instruction of "unit has increased", it is preferable that the platelet collection apparatus has the function of automatically altering the collection condition such as the target number of units of to-be-collected platelets, the collection amount of platelets, and the collection amount of plasma to values corresponding to the target number of units of to-be-collected platelets and the function of automatically releasing the warning of "unit has increased".

[0111] The controller 13 has a mechanism constructed of a microcomputer and a function of computing the number of rotations of the rotor. Detection signals outputted from the weight sensor 16, the optical sensor 15, and the turbidity sensor 14 are applied to the controller 13. The controller 13 controls the start and stop of the rotation and rotational direction (forward/backward) of each pump, based on the signals applied thereto from the turbidity sensor 14, the optical sensor 15, and the weight sensor 16. The controller 13 also controls the opening/closing of the flow path shutter means 81, 82, 83, 84, 85, and 86 and the operation (rotation of rotor) of the centrifugal separator drive unit 10.

[0112] The first flow path shutter means 81 is used to open/close the portion of the first line 21 located between the blood collection needle 29 and the pump tube 21g. The second flow path shutter means 82 is used to open/close the first tube 25a of the plasma collection bag 25. The third flow path shutter means 83 is used to open/close the second tube 25b of the plasma collection bag 25. The fourth flow path shutter means 84 is used to open/close the third tube 26a of the platelet collection bag 26. The fifth flow path shutter means 85 is used to open/close the portion of the second line 22 located between the centrifugal separator 20 and the connector 22d for connecting the second line 22 with the fourth tube 27a of the buffy coat collection bag 27.

[0113] The sixth flow path shutter means 86 is used to open/close the portion of the second line 22 located downstream from the connector 21e for connecting the first line 21 and the second line 22 with each other to the connector 22d for connecting the fourth tube 27a of the buffy coat collection bag 27 and the second line 22 with each other. Each of the flow path shutter means 81 through 86 has an insertion portion on which the lines or the tubes are installed. The insertion portion has a clamp to be operated by a drive source such as a solenoid, an electric motor, and a hydraulic or pneumatic cylinder. A clamp to be operated by a hydraulic pressure cylinder is preferable. The clamp of each of the flow path shutter means 81 through 86 is operated based on a signal transmitted thereto from the controller 13.

[0114] As shown in Fig. 2, the rotor drive unit 10 includes a rotor drive unit housing 151 accommodating the centrifugal separator 20, a pedestal 152, a motor 153 constituting the drive source, and a disk-shaped rest 155 for holding the centrifugal separator 20. The housing 151 is fixedly mounted on the pedestal 152. The motor 153 is fixed to the lower surface of the housing 151 with a bolt 156 via a spacer 157. The upper end of the rotary shaft 154 of the motor 153 is fitted in the rest 155 such that the rest 155 rotates coaxially and integrally with the rotational shaft 154. The upper portion of the rest 155 has a recess formed therein into which the bottom of the rotor 142 is fitted. The upper portion 145 of the centrifugal separator 20 is fixed to the housing 151 with a fixing member not shown. Once the motor 153 for the rotor drive unit 10 is started, the rest 155 and the rotor 142 fixed thereto are rotated at a rotational speed ranging from 3000 to 6000 rpm.

[0115] The rotor drive unit housing 151 has the optical sensor 15 fixedly mounted on an inner wall thereof with a mounting member 158. The optical sensor 15 optically detects the boundaries between separated blood components (for example, the interface B between the plasma layer 131 and the buffy coat layer 132 and the inter-

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face between the buffy coat layer 132 and the red cell layer 133) in the centrifugal separator 20. The optical sensor 15 is of a type capable of vertically scanning the peripheral surface of the rotor 142. The optical sensor 15 includes a light source for emitting a light beam to a shoulder portion of the centrifugal separator 20 and a light-receiving part for receiving a light beam reflected by the centrifugal separator 20 and returned therefrom. That is, a light emitting element such as an LED or laser and a light-receiving element are arrayed in a row. A light beam emitted by the light emitting element and reflected by a blood component is received by the light-receiving element, and the amount of the received light is photoelectrically converted.

[0116] Because the intensity of the reflected light varies depending on the separated blood component (for example, the interface B between the plasma layer 131 and the buffy coat layer 132), a position of the light-receiving element at which the amount of received light has changed is detected as the corresponding position of the interface B. More specifically, the arrival of the buffy coat layer at a light passage portion is detected, based on the difference between the amount of received light at the time when the light passage portion of the centrifugal separator 20 is filled with a transparent liquid (plasma or water) and the amount of received light at the time when the light passage portion thereof is filled with the buffy coat layer. The detection position of the buffy coat layer is adjusted by changing a light passage position in the centrifugal separator 20. Normally, the detection of the light passage position is unchangeably set.

[0117] The turbidity sensor 14 detects the turbidity of a fluid flowing through the second line 22 and outputs a voltage corresponding to the detected turbidity. Specifically, the turbidity sensor 14 outputs a low voltage when the turbidity is high, while it outputs a high voltage when the turbidity is low.

[0118] As each of the first liquid supply pump 11 on which the pump tube 21g of the first line 21 is mounted and the second liquid supply pump 12 on which the pump tube 23a of the third line 23 is mounted, a roller pump or a peristaltic pump which is kept out of contact with the blood is preferably used. A pump that can supply the blood in either direction is used as the first liquid supply pump 11 (blood pump). A roller pump capable of rotating forward/ backward is used.

[0119] Under the control of the controller, the following steps are executed: a plasma collection/plasma circulation step, to be executed at least one time, consisting of a plasma collection step for collecting anticoagulant-added blood, separating collected blood, and collecting separated plasma into the plasma collection bag and a plasma circulation step for circulating the plasma contained in the plasma collection bag by the plasma collection step to the centrifugal separator; a platelet collection step for flowing out platelets from the centrifugal separator by accelerating a plasma circulation speed by means of the first liquid supply pump after the plasma collection/plasma circulation step is executed and collecting platelets into the platelet collection bag; and a blood return step for returning the blood inside the centrifugal separator to a donor after the platelet collection step is executed.

[0120] The controller 13 of the platelet collection apparatus 1 according to the embodiment controls the centrifugal separator drive unit 10, the first liquid supply pump 11, the second liquid supply pump 12, and a plurality of the flow path shutter means to execute at least twice of the platelet collection operation including the plasma collection/constant-speed circulation step, the plasma collection/acceleration plasma circulation step, the platelet collection step, and the blood return step.

[0121] Subsequent to the termination of the execution of a platelet collection step and prior to the start of the execution of a blood return step, the controller 13 of the platelet collection apparatus 1 executes a buffy coat-collection step of flowing out the buffy coat from the centrifugal separator 20 and collecting it into the buffy coat collection bag 27 by setting a plasma circulation rate higher than a final plasma circulation rate in the platelet collection step by means of the first liquid supply pump 11.

[0122] After the execution of the buffy coat collection step terminates and before the execution of the subsequent blood collection step starts, the controller 13 controls the first liquid supply pump 11 and a plurality of the flow path shutter means 81 through 86 to execute the huffy coat return step of returning the collected huffy coat to the centrifugal separator 20.

[0123] The platelet collection operation includes a plasma collection/ circulation (preferably, constant-speed circulation) operation, the platelet collection operation (in other words, plasma containing high-concentration platelets collection operation or high-concentration platelets-containing plasma collection operation) after a plasma collection/circulation operation, and a blood return operation after the platelet collection operation. The platelet collection operation may include a plasma collection/acceleration plasma circulation operation after the plasma collection/constant-speed circulation operation and before the platelet collection operation (in other words, plasma containing high-concentration platelets collection operation).

[0124] The platelet collection operation will be described below with reference to Figs. 5 through 13.

[0125] As shown in Fig. 5, initially, blood cell components are measured beforehand by using sampling blood collected from the donor immediately before the operator starts to collect the components of the blood. A hematcrit value (HCT) of the donor, a platelet concentration (PLT concentration) measured at this time, and the target number of units of to-be-collected platelets are inputted to the platelet collection apparatus. The control part of the platelet collection apparatus computes a minimum value of the target number of to-be-

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collected platelets, the amount of extracorporeally circulating blood, the number of platelet collection operation cycles, and the expected number of to-be-collected platelets by using the above-described inputted values and data or computing equations stored therein. The control part may compute the expected number of units of to-be-collected platelets. Thereafter the number of platelet collection operation cycles and the expected number of to-be-collected platelets or the expected number of units of to-be-collected platelets are displayed on the display part 52. The control part 50 may have the function of computing an expected operation termination time, based on the number of platelet collection operation cycles and displaying the results. Then the control part makes a determination on to which of the stored expected three collection-amount-groups the computed expected value of the number of to-be-collected platelets corresponds. In other words, a group determination is executed. In the embodiment, the control part determines on to which of the three collection-amount-groups "low", "medium", and "high" the computed expected number of to-be-collected platelets, corresponds and results are stored.

[0126] The expected number of to-be-collected platelets is computed by the following equation 5: The expected number of to-be-collected platelets = expected number of platelets to-be-collecled in first cycle + expected number of platelets to-be-collected in second cycle + ••• expected number of platelets to-be-collected in last cycle •••• Equation 5

[0127] The expected number of platelets to-be-collected in the first cycle is computed by the above-described equation 1. The expected number of platelets to-be-collected in the second cycle is computed by the above-described equation 2. The expected number of platelets to-be-collected in the third cycle is computed by the above-described equation 3.

[0128] The expected recovery percentage is 65 - 80%. The target number of to-be-collected platelets is computed from the target number of units of platelets $\times$ 2×10^{10}.

[0129] First, the third line 23 and the blood collection needle 29 are primed with the anticoagulant. Then the blood collection needle 29 is stuck on the donor.

[0130] As shown in Fig. 5, the controller 13 executes the first plasma collection step of collecting the anticoagulant-added blood by starting the first and second liquid supply pumps 11, 12 and collecting the first predetermined amount of the plasma into the plasma collection bag 25 by activating the centrifugal separator drive unit 10.

[0131] When the first blood collection starts, the blood pump 11 is rotated at a predetermined rate (for example, 60 ml/min). At this time, a second pump constituting the anticoagulant pump supplies the anticoagulant (for example, ACD-A solution) at a predetermined rate (for example, 1/10 of the blood pump rate). The blood drawn from the donor is mixed with the ACD-A solution, flows through the first line 21, the chamber, and the first flow path shutter means 81, and flows into the centrifugal separator 20. At the above time point, the sixth flow path shutter means 86, the fifth flow path shutter means 85, the second flow path shutter means 82, and the third flow path shutter means 83 are dosed. Meanwhile the first flow path shutter means 81 and the fourth flow path shutter means 84 are open. When the ACD-A solution-added blood is fed to the centrifugal separator 20, sterilized air that has stayed in the centrifugal separator 20 flows into the platelet collection bag 26 through the second line 22 and the flow path shutter means 84.

[0132] Simultaneously with the start of the blood collection, the centrifugal separator 20 starts rotating at a predetermined speed while it is being supplied with the ACD-A solution-added blood. In the centrifugal separator 20, therefore, the blood is centrifugally separated into a plasma layer (inner layer), a buffy coat layer (BC layer, intermediate layer), and a red cell layer (outer layer). When the ACD-A solution-added blood (about 270 ml) is supplied in excess of the capacity of the centrifugal separator 20, the centrifugal separator 20 is completely filled with the blood, and the plasma overflows through the outlet of the centrifugal separator 20. The turbidity sensor 14 mounted on the second line 22 connected with the outlet of the centrifugal separator 20 detects that the fluid flowing through the second line 22 has changed from the air to the plasma. Upon receipt of the detection signal transmitted from the turbidity sensor 14, the controller 13 closes the fourth flow path shutter means 84 and opens the third flow path shutter means 83 to collect the plasma into the plasma collection bag 25.

[0133] The weight of the plasma collection bag 25 is measured in advance by the weight sensor 16, and a signal indicating the measured weight is transmitted to the controller 13. Thus, when the weight of the plasma collected in the plasma collection bag 25 is increased to a predetermined amount (for example, 10 to 150g, or 30g), the controller 13 doses the first flow path shutter means 81 and opens the second flow path shutter means 82 to proceed to the constant-speed plasma circulation step.

[0134] In the constant-speed circulation step, the blood collection is temporarily suspended, and the centrifugal separator drive unit 10 is activating. The plasma contained in the plasma collection bag 25 is circulated to the centrifugal separator 20 at a constant speed.

[0135] Upon start of the execution of the constant-speed circulation step, the controller 13 keeps the first flow path shutter means 81 dosed and the second flow path shutter means 82 opened, stops the ACD pump 12, and starts the blood pump 11 at the predetermined rate (60 to 250 ml/min, for example, 200 ml/min). The plasma collected in the plasma collection bag 25 is fed to the centrifugal separator 20 rotating at a predetermined speed (computed initial number of rotations of rotor) through the second flow path shutter means 82. At

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the same time, the plasma which has flowed from the centrifugal separator 20 flows into the plasma collection bag 25 through the turbidity sensor 14 and the third flow path shutter means 83. With the lapse of a predetermined length of time (10 to 90 sec, for example, 30 seconds) from the start of the constant-speed circulation step, the controller 13 closes the second flow path shutter means 82 and opens the first flow path shutter means 81 to proceed to the second plasma collection step. The first plasma circulation step is executed preferably at the flow rate of 60 ml/min or more for at least 10 seconds.

[0136] In the second plasma collection step, the first and second liquid supply pumps 11, 12 are started to collect the anticoagulant-added blood. Upon detection of the buffy coat layer in the centrifugal separator 20 because of an increase in the amount of the plasma in the platelet collection bag 26, a detection signal is transmitted from the optical sensor 15 to the controller 13. Upon receipt of the signal, the controller 13 doses the first flow path shutter means 81 and opens the second flow path shutter means 82 to proceed to the acceleration plasma circulation step.

[0137] More specifically, the first blood pump 11 is activated to collect the blood at a predetermined rate (for example, 60 ml/min). At this time, the second pump constituting the anticoagulant pump supplies the anticoagulant (for example, ACD-A solution) at a predetermined rate (for example, 1/10 of the rate of the blood pump).

[0138] The blood drawn from the donor is mixed with the ACD-A solution. The ACD-A solution-added blood flows into the centrifugal separator 20 rotating at a predetermined rate (computed initial number of rotations of rotor), and the plasma is collected in the plasma collection bag 25. Normally, upon detection of the buffy coat layer in the centrifugal separator 20 because of an increase in the amount of the plasma in the platelet collection bag 26, a detection signal is transmitted from the optical sensor 15 to the controller 13. Upon receipt of the signal, the controller 13 doses the first flow path shutter means 81 and opens the second flow path shutter means 82 to proceed to the acceleration plasma circulation step. In the second plasma collection step, the plasma is collected until the optical sensor 15 detects the buffy coat (BC interface: interface between plasma layer and buffy coat layer).

[0139] In the acceleration plasma circulation step, the blood collection is temporarily suspended and the centrifugal separator drive unit 10 is activated to circulate the plasma in the plasma collection bag 25 to the centrifugal separator 20. In the processing, the blood pump operates at an initial rate, for example, at 60 ml/min lower than that in the constant-speed plasma circulation step and accelerated until a final rate reaches 150 ~ 200 ml/min. The acceleration of the pomp is carried out at 2 - 10ml/min for 14 - 70 seconds until a final rate reaches 200 ml/min. Upon completion of the acceleration plasma circulation step, the processing proceeds to ① of the flowchart of Fig. 6 showing the step of collecting a small amount of plasma for interface adjustment.

[0140] As shown in Fig. 6, in the small-amount blood collection step for interface adjustment, to keep the position of the buffy coat layer constant, irrespective of donors in the subsequent platelet collection step, the blood is collected in correspondence to a predetermined amount of red cells to be supplied. The supply amount of the red cells is defined as a value derived from dividing a collected amount of blood by the hematocrit value of the donor. Practically about 12 ml of the blood is collected. The blood collection starts by rotating the first liquid supply pump 11 at a predetermined rate (for example, 60 ml/min). At this time, the second pump constituting the anticoagulant pump also supplies the anticoagulant (such as the ACD-A solution) at a predetermined rate (for example, 1/10 of the blood pump rate). The blood collected from the donor is mixed with the ACD-A solution. The ACD-A solution-added blood flows into the centrifugal separator 20 rotating at a predetermined rate (computed initial number of rotations of rotor), and a small amount of plasma is collected. Based on a set collection amount and a set pump rotation rate, the controller 13 computes a blood collection time, and terminates the blood collection when the computed blood collection time expires. Then the controller 13 closes the first flow path shutter means 81 and opens the second flow path shutter means 82 to proceed to the platelet collection step.

[0141] Upon termination of the acceleration plasma circulation step, the controller 13 executes the platelet collection step of flowing out platelets from the centrifugal separator 20 and collecting them into the platelet collection bag 26 by accelerating the plasma circulation rate by means of the first liquid supply pump 11. The platelet collection step is called acceleration processing. In this step, the controller 13 controls the rotational speed of the blood pump to increase it stepwise by 10 ml/min every predetermined time period (for example, every one second) from 60 ml/min to 200 ml/min. When the rotational speed of the blood pump reaches 200 ml/min, it is maintained until the platelet collection step terminates.

[0142] Upon start of the platelet collection step, the turbidity sensor 14 detects the turbidity of a liquid passing therethrough and outputs a voltage corresponding to a detected turbidity. The output signal of the turbidity sensor 14 is applied to the controller 13. When the rotational speed of the blood pump increases and reaches a rate ranging from 160 to 200 ml/min, platelets contained in the buffy coat layer that have stayed in the centrifugal separator 20 flow out therefrom. As a result of the release of the platelets, the turbidiy of the liquid passing through the turbidity sensor 14 becomes high. At a time point when a voltage outputted from the turbidity sensor 14 drops by 0.2 V, the third flow path shutter means 83 is closed and the fourth flow path shutter means 84 is opened. Thus the platelet-rich plasma released from the centrifugal separator 20 is collected in

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the platelet collection bag 26. The controller 13 converts the voltage outputted from the turbidity sensor 14 into a platelet concentration to compute the number of platelets collected in the platelet collection bag 26 by driving the liquid supply pump. The concentration of high-concentration platelets-containing plasma passing through the turbidity sensor drops after reaching a maximum value. At a time point when it is detected that a termination level (CRC level) is attained, the execution of the platelet collection step finishes and the processing proceeds to the buffy coat collection step.

[0143] As shown in Fig. 6, simultaneously with the start of the collection of the high-concentration platelets-containing plasma (PC), computation and measurement of the collection amount of the high-concentration platelets-containing plasma and computation of the number of collected platelets start. Voltage signals detected by the turbidity sensor are sequentially inputted to the control part. The amount of the plasma containing the high-concentration platelet is computed by using an operation amount of the liquid supply pump and a stored blood feeding amount per unit operation amount. The control part computes the number of collected platelets (RTM value) from the platelet concentration computed by using the voltage signal sent from the turbiditv sensor and a computed blood-feeding amount computed as described above and displays the number of collected platelets. The number of collected platelets (RTM value) can be obtained by computing the platelet concentration in a predetermined time period from output signals of the turbidity sensor detected at predetermined intervals (for example, 0.01 - 2 seconds) and multiplying the platelet concentration by the blood-feeding amount in the predetermined time period to thereby obtain the number of collected platelets in each predetermined time period. This operation is performed continuously in the time period in which the plasma containing the high-concentration platelet is collected The total number of the collected platelets can be obtained by adding respective computed number of platelets to each other. The RTM-corrected value is computed from the computed number of collected platelets (RTM value). When the RTM value is not less than the expected number of to-be-collected platelets × 1.5, the RTM-corrected value = the expected number of to-be-collected platelets × 1.2 (case A). When the RTM value is not less than the expected number of to-be-collected platelets × 1.2 nor more than the expected number of to-be-collected platelets × 1.5, the RTM-corrected value = the expected number of to-be-collected platelets × 1.1 (case B). When the RTM value is not less than the expected number of to-be-collected platelets nor more than the expected number of to-be-collected platelets × 1.2, the RTM-corrected value = the expected number of to-be-collected platelets (case C). When the RTM value is less than the expected number of to-be-collected platelets, the RTM-corrected value = RTM value (case D). The control part computes display number of collected platelets which is the sum of the addition of the RTM-corrected values in an initial platelet collection operation through a previous platelet collection operation and the RTM corrected value in a current platelet collection operation.

[0144] Then the processing proceeds to ② of Fig. 7 in which the estimated number of to-be-collected platelets is computed by using the corresponding case of the cases A - D and the display number of collected platelets. More specifically, in the case of the cases A, B, and C, the estimated number of to-be-collected platelets is computed by the display number of collected platelets + the RTM-corrected value in the previous platelet collection operation × (set number of platelet collection operation cycles - the number of platelet collection operation cycles when collection operation terminated). In the case of the case D, the estimated number of to-be-collected platelets is computed by the display number of collected platelets + the expected number of to-be-collected platelets × (set number of platelet collection operation cycles - the number of platelet collection operation cycles when collection operation terminated).

[0145] The function of determining on an increase/decrease tendency in the number of collected platelets determines whether there is a tendency to increase in the number of collected platelets. As shown in Fig. 7, the function of determining on an increase/decrease tendency in the number of collected platelets determines on to which of the three stages, namely, "there is no tendency to increase (level of proper range)", "level of tendency to increase", and "unit-increased level" the estimated number of collected platelets corresponds. More specifically, the function of determining on an increase/decrease tendency in the number of collected platelets determines on whether the number of collected platelets has a tendency to increase or decrease, based on the estimated number of platelets and corresponding groups ("low", "medium", and "high") determined from the above-described computed value of the expected number of platelets. More specifically, the function of determining on an increase/decrease tendency in the number of collected platelets determines that the number of collected platelets is on the proper range level (there is no tendency to increase or decrease) [1] if a reference value □ the estimated number of to-be-collected platelets < the reference value + a second predetermined value (PM2: specifically 0.65×10^{11}), supposing that the expected collection-amount-group is "medium" or "high" and [2] if the reference value + the second predetermined value (PM2: specifically 0.65×10^{11}) □ the estimated number of to-be-collected platelets < the reference value + a third predetermined value (PM6: specifically 0.9×10^{11}), supposing that the expected collection-amount-group is "low". The function of determining on an increase/decrease tendency in the number of collected platelets determines that the number of collected platelets is on "level of tendency to increase" (there is a tendency to increase) if [3] the ref-

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erence value + the second predetermined value (PM2: specifically 0.65×10^{11}) □ the estimated number of to-be-collected platelets < the reference value + the third predetermined value (PM6: specifically 0.9×10^{11}), supposing that the expected collection-amount-group is "high" and [4] if the reference value + the third predetermined value (PM6: specifically 0.9×10^{11}) □ the estimated number of to-be-collected platelets, supposing that the expected collection-amount-group is "medium". The function of determining on an increase/decrease tendency in the number of collected platelets determines that the number of collected platelets is on "unit-increased level" (there is a tendency to increase) if [5] the reference value + the third predetermined value (PM6: specifically 0.9×10^{11}) □ the estimated number of to-be-collected platelets, supposing that the expected collection-amount-group is "high".

[0146] If it is determined that there is "no tendency to increase (level of proper range)" in the number of collected platelets, the collection condition is not changed and the processing proceeds to a buffy coat collection step. If it is determined that the number of collected platelets has the "tendency to increase", whether the number of collected platelets is on the "unit-increased level" is determined. If it is determined that the number of collected platelets is not on the "unit-increased level", it is determined that the number of collected platelets is on the "level of tendency to increase". As a result, a program for preventing collection of an excessive amount of platelets (function of decreasing the number of to-be-collected platelets) operates, which is displayed on the display part 52. When the program for preventing collection of an excessive amount of platelets operates, in the platelet collection operation except the last platelet collection operation, the stored data of the platelet collection condition, namely, the voltage of the collection termination turbidity sensor is dropped by a predetermined value to quicken the platelet collection operation. That is, the platelet concentration (for example, about 400,000/ml) in the normal platelet collection termination is altered to the platelet concentration (for example, about 900,000/ml) in the adjusted platelet collection termination. Thereby the time period for collecting the plasma containing high-concentration platelets becomes short. Thus the collection amount of platelets becomes smaller.

[0147] When it is determined that the number of collected platelets is on the "unit-increased level", a message indicating an increase in the number of units of collected platelets is displayed on the display part 52. Then the processing proceeds to a mode for allowing alteration of number of units of to-be-collected platelets shown in Fig. 8. In the mode for allowing alteration of number of units of to-be-collected platelets, it is possible to increase the target number of units of to-be-collected platelets. When the target number of units of to-be-collected platelets is increased, the target number of units of to-be-collected platelets is rewritten. Thereby the target collection amount of the plasma containing high-concentration platelets, the target collection amount of the platelets and plasma (PPP), and the collection condition are re-computed. Thereafter the message indicating an increase in the number of units of collected platelets is erased, and the execution of the mode for allowing alteration of number of units of to-be-collected platelets terminates. As described above, after whether the number of collected platelets is on the tendency to increase is determined, the buffy coat is collected, as shown in Fig. 7.

[0148] Upon completion of the platelet collection step, the huffy coat collection step is executed. In this step, the controller 13 doses the fourth flow path shutter means 84 and opens the fifth flow path shutter means 85. The plasma in the plasma collection bag 25 is fed to the centrifugal separator 20 by the blood pump 11. At the same time, the liquid that has been released (the huffy coat layer that has flowed out) from the centrifugal separator 20 flows into the buffy coat collection bag 27. In the huffy coat collection step, the final rate of the rotational speed of the blood pump in the platelet collection step is maintained, and the rotational speed of the centrifugal separator 20 is increased to the predetermined speed or a speed a little higher (higher by 50 - 200 rpm than the predetermined speed, for example, higher by 100 rpm) than the predetermined speed. In this manner, the huffy coat is released from the centrifugal separator 20 and collected in the buffy coat collection bag 27. At a time point when the amount of the collected buffy coat reaches a value computed based on the hematocrit value of the donor and the amount of collected platelet, the blood pump 11 is stopped and all the valves are closed. Thus the centrifugal separator 20 stops rotating, i.e., the execution of the buffy coat collection step terminates.

[0149] Then, the blood return step of returning the blood in the centrifugal separator 20 to the donor is executed. The controller 13 rotates the blood pump 11 in a reverse direction, opens the first flow path shutter means 81, and returns the red cell layer remaining in the centrifugal separator 20 to the donor through the first line 21.

[0150] Thus, the first (initial) platelet collection operation terminates.

[0151] Then, the processing proceeds to a second platelet collection operation, as shown in Fig. 9.

[0152] Referring to Fig. 9, in the second cycle, initially the controller 13 executes the buffy coat return step of returning the buffy coat collected in the first platelet collection step to the centrifugal separator 20 before the next blood collection step is executed. Once the processing proceeds to the huffy coat return step, the controller 13 rotates the centrifugal separator 20 at a predetermined rotational speed (computed initial number of rotations of rotor), opens the fifth flow path shutter means 85 and the fourth flow path shutter means 84, and starts the blood pump 11 at a predetermined

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rate (default value: 100 ml/min). The huffy coat contained in the buffy coat collection bag 27 is fed to the centrifugal separator 20 through the fifth flow path shutter means 85. The air in the centrifugal separator 20 is sent to the platelet collection bag 26 through the second line 22 and the fourth flow path shutter means 84. After the blood pump 11 rotates in an amount corresponding to the set collection amount of the buffy coat, the execution of the buffy coat return step is completed.

[0153] Then, as shown in Fig. 9, the first plasma collection step and the constant-speed plasma circulation step are executed.

[0154] Whether the processing has proceeded to the mode for allowing alteration of number of units of to-be-collected platelets is determined. If YES, the execution of the determination processing terminates. Then the program for preventing collection of an excessive amount of platelets (function of decreasing the number of to-be-collected platelets) operates, which is displayed on the display part 52.

[0155] As shown in Fig. 9, after the second plasma collection step and the plasma circulation step are executed, the processing proceeds to the program referred to as ③ in Fig. 10 in which the small-amount plasma collection step and the platelet collection step are executed. In the platelet collection step, when the program for preventing collection of an excessive amount of platelets is in operation, the platelet collection operation terminates not when the platelet concentration reaches the CRC level (for example, about 400,000/ml in the normal platelet collection termination) but when the platelet concentration reaches about 900,000/ml (in the adjusted platelet collection termination). Thereby the time period for collecting the plasma containing high-concentration platelets becomes short. Thus the collection amount of platelets becomes smaller.

[0156] At the platelet collection step, regardless of whether the program for preventing collection of an excessive amount of platelets is in operation, similarly to the first cycle, computation and measurement of the collection amount of the plasma containing high-concentration platelets and computation of the number of collected platelets start, the number of collected platelets (RTM value) is computed, and the RTM-corrected value (RTM value for computation of estimated number of to-be-collected platelets) is computed. Then the processing proceeds to ④ of Fig. 11 in which it is determined whether the number of collected platelets has a tendency to increase.

[0157] If it is determined that there is "no tendency to increase (level of proper range)" in the number of collected platelets, the collection condition is not changed and the processing proceeds to the buffy coat collection step. If it is determined that the number of collected platelets has the "tendency to increase", it is determined whether the number of collected platelets is on the "unit-increased level". If it is determined that the number of collected platelets is not on the "unit-increased level", it is determined that the number of collected platelets is on the "level of tendency to increase". As a result, the program for preventing collection of an excessive amount of platelets (function of decreasing the number of to-be-collected platelets) operates, which is displayed on the display part 52. When it is determined that the number of collected platelets is on the "unit-increased level", the processing proceeds to the mode for allowing alteration of number of units of to-be-collected platelets. After whether the number of collected platelets is on the tendency to increase is determined, the buffy coat is collected, as shown in Fig. 11.

[0158] Then the buffy coat collection step and the blood return step are sequentially executed. In this manner, the second platelet collection operation terminates.

[0159] Description will be made on the last platelet collection operation with reference to Fig. 9. In this embodiment, the third operation is the last one. However, the fourth or subsequent platelet collection operations may be the last one. Each of these platelet collection operations except the last one is identical to the second platelet collection operation (Figs. 7 and 8).

[0160] In the last platelet collection operation, initially, as shown in Fig. 9, the buffy coat return step is executed. In this step, the buffy coat collected by the second platelet collection operation (previous platelet collection operation) is returned to the centrifugal separator 20 prior to the execution of the next plasma collection step.

[0161] When the processing proceeds to the buffy coat return step, the controller 13 rotates the centrifugal separator 20 at a predetermined rotational speed (for example, 4800 rpm), opens the fifth flow path shutter means 85 and the fourth flow path shutter means 84, and activates the blood pump 11 at a predetermined rate (default value: 100 ml/min). The buffy coat contained in the buffy coat collection bag 27 passes through the fifth flow path shutter means 85 and is supplied to the centrifugal separator 20. The air in the centrifugal separator 20 is sent to the platelet collection bag 26 through the second line 22 and the fourth flow path shutter means 84. After the blood pump 11 rotates in an amount corresponding to the set collection amount of the buffy coat, the execution of the buffy coat return step terminates.

[0162] Then, the first plasma collection step is executed. That is, the first and second liquid supply pumps 11, 12 are started to collect the anticoagulant-added blood, and the centrifugal separator drive unit 10 is activated to collect a first predetermined amount of plasma from the blood and flow it into the plasma collection bag 25.

[0163] Upon start of the first blood collection, the first liquid supply pump 11 is rotated at a predetermined rate (for example, 60 ml/min). At this time, the second pump constituting the anticoagulant pump supplies the anticoagulant (such as the ACD-A solution) at the predetermined rate (for example, 1/10 of the blood pump rate). Blood supplied from the donor is mixed with the ACD-A solution. The ACD-A solution-added blood flows through the first line 21, passes through the chamber

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and the first flow path shutter means 81, and flows into the centrifugal separator 20.

[0164] At this time, the sixth flow path shutter means 86, the fifth flow path shutter means 85, the second flow path shutter means 82, and the third flow path shutter means 83 are closed. Meanwhile the first flow path shutter means 81 and the fifth flow path shutter means 85 are opened. When the ACD-A solution-added blood is supplied to the centrifugal separator 20, the sterilized air that has been admitted into the centrifugal separator 20 flows into the buffy coat collection bag 27 through a line sensor and the fifth flow path shutter means 85. Simultaneously with the start of the blood collection step, the centrifugal separator 20 starts rotating at the predetermined speed. The centrifugal separator 20 is supplied with the ACD-A solution-added blood during its rotation. Thus, the centrifugal separator 20 separates it centrifugally into the plasma layer (inner layer), the buffy coat layer (BC layer, intermediate layer), and the red cell layer (outer layer). When about 270 ml of the ACD-A solution-added blood exceeding the capacity of the centrifugal separator is supplied to the centrifugal separator 20, it is filled with the blood, and the plasma overflows through the outlet of the centrifugal separator 20.

[0165] The turbidity sensor 14 mounted on the second line 22 connected to the outlet of the centrifugal separator 20 detects that the fluid flowing through the line has changed from the air to the plasma. Based on the detection signal outputted from the turbidity sensor 14, the controller 13 closes the fifth flow path shutter means 85 and opens the third flow path shutter means 83 to collect the plasma into the plasma collection bag 25. The weight of the plasma collection bag 25 is measured in advance by the weight sensor 16, and a signal indicating the measured weight is transmitted therefrom to the controller 13. Thus, when the weight of the plasma collected in the plasma collection bag 25 is increased to a predetermined amount (for example, 30 g), the controller 13 doses the first flow path shutter means 81 and opens the second flow path shutter means 82 to proceed to the constant-speed plasma circulation step.

[0166] Thereafter it is determined whether the processing has proceeded to the mode for allowing alteration of number of units of to-be-collected platelets. If YES, the determination processing terminates. Then the program for preventing collection of an excessive amount of platelets (function of decreasing the number of to-be-collected platelets) operates, which is displayed on the display part 52

[0167] After the second plasma collection step and the acceleration plasma circulation step are executed, the processing proceeds to the program referred to as ⑤ in Fig. 12 in which a small-amount plasma collection step for interface adjustment and a platelet collection step are executed.

[0168] At the platelet collection step, when the program for preventing collection of an excessive amount of platelets is in operation after start of the collection of the plasma containing high-concentration platelets, the collection speed of the plasma containing high-concentration platelets is reduced to a predetermined level after platelets flow out. More specifically, the collection speed of the plasma containing high-concentration platelets is reduced from 200ml/min to 170ml/min. When the program for preventing collection of an excessive amount of platelets is in operation, the platelet concentration (for example, about 400,000/ml) in the normal platelet collection termination is altered to the platelet concentration (for example, about 300,000/ml) in the adjusted platelet collection termination. Thereby the degree of the concentration platelets in the plasma decreases a little, and the collection amount thereof is more than that collected in the normal condition.

[0169] At the platelet collection step, regardless of whether the program for preventing collection of an excessive amount of platelets is in operation, similarly to the first cycle, computation and measurement of the collection amount of the plasma containing high-concentration platelets and computation of the number of collected platelets start, and the number of collected platelets (RTM value) is computed. Then the processing proceeds to ⑥ of Fig. 13 in which the RTM-corrected value (RTM value for computation of estimated number of to-be-collected platelets) is computed, and the estimated number of to-be-collected platelets is computed.

[0170] When the platelet collection step terminates, the blood return step is executed. Thereby the last platelet collection operation terminates.

[0171] The platelet collection apparatus has both the function of decreasing the number of to-be-collected platelets and the function of increasing the number of to-be-collected platelets. It is desirable that the platelet collection apparatus has both the functions. However, the platelet collection apparatus may have one of the two functions.

[0172] More specifically, the platelet collection apparatus may have only the function of decreasing the number of to-be-collected platelets. In this case, the platelet collection apparatus does not determine on "unit-increased level" in determining whether the number of collected platelets has a tendency to increase.

[0173] As shown in Fig. 15, even in the first platelet collection operation (first cycle), the platelet collection apparatus not having the function of increasing the number of to-be-collected platelets may have the function of decreasing the number of to-be-collected platelets by altering a set condition of the platelet collection operation. The platelet collection apparatus of this embodiment has the peak platelet concentration situation determination function of detecting the peak of the platelet concentration by using signals detected by the turbidity sensor when the high-concentration platelets-containing plasma is collected in the initial platelet collection operation and determining whether the detected peak of the platelet concentration is on the "normal lev-

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el" or the "excessive level"; and the function of decreasing the number of platelets to be collected in the platelet collection operation, when the platelet-concentration peak situation determination function has determined that the peak of the platelet concentration is on the "excessive level".

[0174] The platelet collection apparatus of another embodiment is described below.

[0175] The platelet collection apparatus of this embodiment has a construction similar to that of the embodiment shown in Figs. 1 through 3.

[0176] The platelet collection apparatus of this embodiment has the peak platelet concentration situation determination function of detecting the peak of the platelet concentration by using signals detected by the turbidity sensor when the high-concentration platelets-containing plasma is collected in the platelet collection operation and determining whether the detected peak of the platelet concentration is on the "normal level" or the "excessive level"; and the function of decreasing the number of platelets to be collected in the platelet collection operation, when the platelet-concentration peak situation determination function has determined that the peak of the platelet concentration is on the "excessive level".

[0177] The platelet collection apparatus of this embodiment has only the function of decreasing the number of to-be-collected platelets.

[0178] The embodiment is described below with reference to Figs. 13 through 17.

[0179] The platelet collection apparatus of this embodiment has the function of decreasing the collection amount of platelets in the case where it is expected that the number of platelets to be collected in each platelet collection operation is more than a predetermined amount.

[0180] The peak platelet concentration situation determination function of this embodiment is similar to that of the above-described embodiment. The function of decreasing the collection amount of platelets of this embodiment is similar to that of the above-described embodiment.

[0181] It is preferable the platelet collection apparatus has an operation display function of informing an operator of the operation of the function of decreasing the collection amount of platelets. In addition to the automatic type, this function may be actuated by an operator's switching operation.

[0182] The platelet collection operation to be performed by the platelet collection apparatus of this embodiment is described in detail below with reference to Figs. 14 through 17.

[0183] As shown in Fig. 14, initially blood cell components are measured beforehand by using sampling blood collected from the donor immediately before an operator starts to collect the components of the blood. The hematcrit value (HCT) of the donor, a platelet concentration (PLT concentration) measured at this time, and the target number of units of to-be-collected platelets are inputted to the platelet collection apparatus. The control part of the platelet collection apparatus computes the minimum value of the target to-be-collected platelets, the amount of extracorporeally circulating blood, the number of platelet collection operation cycles, and the expected number of to-be-collected by using the above-described inputted values and data or computing equations stored therein. The control part may compute the expected number of units of to-be-collected platelets. Thereafter the number of platelet collection operation cycles and the expected number of to-be-collected platelets or the expected number of units of to-be-collected platelets are displayed on the display part 52. The control part 50 may have the function of computing an expected operation termination time, based on the number of platelet collection operation cycles and displaying results. The expected number of to-be-collected platelets that is computed by a method similar to that of the embodiment can be utilized.

[0184] First, the third line 23 and the blood collection needle 29 are primed with the anticoagulant. Then the blood collection needle 29 is stuck on the donor.

[0185] As shown in Figs. 14 and 15, between the first plasma collection step and the collection of the plasma containing high-concentration platelets (PC) at the platelet collection step, an operation similar to those of the above-described embodiments is performed (see Figs. 5 and 6). Thus description thereof is omitted herein.

[0186] Simultaneously with the start of the collection of the high-concentration platelets-containing plasma (PC), computation and measurement of the collection amount of the high-concentration platelets-containing plasma and computation of the number of collected platelets start. The voltage signals detected by the turbidity sensor are sequentially inputted to the control part. The amount of the plasma containing the high-concentration platelet is computed by using an operation amount of the liquid supply pump and a stored blood feeding amount per unit operation amount. The control part computes the number of collected platelets (RTM value) from the platelet concentration computed by using the voltage signal sent thereto from the turbidity sensor and a computed blood-feeding amount computed as described above and displays the number of collected platelets. The number of collected platelets (RTM value) can be obtained by computing the platelet concentration in a predetermined time period from output signals of the turbidity sensor detected at predetermined intervals (for example, 0.01 - 2 seconds) and multiplying the platelet concentration by the blood-feeding amount in the predetermined time period to thereby obtain the number of collected platelets in each predetermined time period. This operation is performed continuously in the time period in which the plasma containing the high-concentration platelet is collected. The total number of the collected platelets can be obtained by adding re-

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spective computed number of platelets to each other.

[0187] As shown in Fig. 15, when the collection of the plasma containing high-concentration platelets (PC) starts, whether the peak of the platelet concentration has been attained is determined, by using detection signals sent from the turbidity sensor. After the peak of the platelet concentration is attained, the situation of the peak of the platelet concentration is determined. If the peak of the platelet concentration corresponds to "excessive level 2", the platelet concentration (for example, about 400,000/ml) in the normal platelet collection termination is altered to a second platelet concentration (for example, about 900,000/ml) in the adjusted platelet collection termination. If the peak of the platelet concentration does not correspond to the "excessive level 2" but to an "excessive level 1", the platelet concentration (for example, about 400,000/ml) in the normal platelet collection termination is altered to a first platelet concentration (for example, about 900,000/ml) in the adjusted platelet collection termination. If the peak of the platelet concentration corresponds to neither the "excessive level 2" nor the "excessive level 1", the platelet concentration (for example, about 400,000/ml) in the normal platelet collection termination is maintained. When the peak of the platelet concentration reaches the platelet concentration in the normal platelet collection termination, the collection of the plasma containing high-concentration platelets terminates.

[0188] After the collection of the plasma containing high-concentration platelets terminates, the number of collected platelets (RTM value) is computed. Then the processing goes to ⑧ of Fig. 16 in which the RTM-corrected value (for computing estimated number of to-be-collected platelets) is computed. Then the display number of collected platelets is computed. Thereafter the buffy coat is collected The buffy coat collection step can be executed by a method similar to that of the above-described embodiments.

[0189] Then, the blood return step of returning the blood in the centrifugal separator 20 to the donor is executed. The blood return step can be executed by a method similar to that of the above-described embodiments. Thereby the first (initial) platelet collection operation terminates.

[0190] Then the processing proceeds to a second platelet collection operation.

[0191] Referring to Fig. 17, in the second cycle, initially the controller 13 executes the buffy coat return step of returning the buffy coat collected in the first platelet collection step to the centrifugal separator 20 before the next blood collection step is executed. The buffy coat return step is executed by a method similar to that of the above-described embodiments.

[0192] Then, as shown in Fig. 17, the first plasma collection step, the constant-speed plasma circulation step, a second plasma collection step, and an acceleration plasma circulation step are executed. Then the processing proceeds to ⑦ of Fig. 15 in which the small-amount blood collection step and the platelet collection step are executed.

[0193] The platelet collection step is executed in a manner similar to that of the first cycle. That is, in a manner similar to that of the first cycle, when the collection of the plasma containing high-concentration platelets (PC) starts, computation and measurement of the collection amount of the plasma containing high-concentration platelets and computation of the number of collected platelets start. Computed number of collected platelets (RTM value: in second operation cycle and an n-th operation cycle, computed number of collected platelets in first operation cycle through (n-1)th operation cycle + RTM value in n-th operation cycle: total number of number of collected platelets) is displayed on the display part 52. While the plasma containing high-concentration platelets is being collected, it is determined whether the peak has been attained, by using signals detected by the turbidity sensor. When it is detected that the peak voltage has been attained, the peak platelet concentration situation is determined by using a detected result. As shown in Fig. 15 and as described previously, according to a result obtained by a determination made by peak platelet concentration situation determination function, the concentration of collected platelets is adjusted depending on necessity.

[0194] Then the RTM value for computing the estimated number of to-be-collected platelets is computed from the computed number of collected platelets (RTM). Thereafter the processing goes to ⑧ of Fig. 16 in which estimated number of to-be-collected platelets is computed from the computed RTM value for computing the estimated number of to-be-collected platelets. Then as shown in Fig. 16, the buffy coat step and the blood return step are sequentially executed. In this manner, the second platelet collection operation terminates.

[0195] Description will be made on the last platelet collection operation. In this embodiment, the third operation is the last one. However, the fourth or subsequent platelet collection operation may be the last one. Each of these platelet collection operations except the last one is identical to the second platelet collection operation (Figs. 7 and 8). The second platelet collection operation may be the last platelet collection operation.

[0196] In the last platelet collection operation, initially, as shown in Fig. 17, the huffy coat return step is executed. In this step, the buffy coat collected in the second platelet collection operation (previous platelet collection operation) is returned to the centrifugal separator 20 prior to the execution of the next plasma collection step. The buffy coat return step is executed by a method similar to that of the above-described embodiments.

[0197] Then, the first plasma collection step is executed. That is, the first and second liquid supply pumps 11, 12 are started to collect the anticoagulant-added blood, and the centrifugal separator drive unit 10 is activated to collect a first predetermined amount of plasma from the blood and flow it into the plasma collection bag 25.

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The first plasma collection step may be executed by a method similar to that of the above-described embodiments.

[0198] After the second plasma collection step and the acceleration plasma circulation step are executed, the processing proceeds to the program referred to as ⑦ in Fig. 15 in which the small-amount plasma collection step for interface adjustment and the platelet collection step are executed. The second plasma collection step, the acceleration plasma circulation step, and the small-amount plasma collection step for interface adjustment can be executed by a method similar to that of the first cycle or the above-described embodiments.

[0199] The platelet collection step is executed by a method similar to that of the first cycle. Upon termination of the platelet collection step, the blood return step is executed. Thereby the last platelet collection operation terminates.

[0200] The platelet collection apparatus of the present invention has a function of determining whether there is a tendency to increase or decrease in the number of collected platelets by using an estimated number of to-be-collected platelets computed by using an amount of plasma containing high-concentration platelets and a platelet concentration obtained from a turbidity sensor when the plasma is collected or data related to the platelet concentration and by using an expected number of to-be-collected platelets or a value related thereto; and a function of decreasing the amount of platelets to be collected in a subsequent platelet collection operation in the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that there is a tendency to increase in the number of collected platelets.

[0201] Therefore it is possible to prevent platelets from being collected in an amount much larger than the target number of to-be-collected platelets.

[0202] The platelet collection apparatus of the present invention has a function of determining whether there is a tendency to increase or decrease in the number of collected platelets by using data, related to the concentration of platelets, obtained from a turbiditv sensor, the expected number of to-be-collected platelets or a value related thereto after the plasma (PC) containing high-concentration platelets is collected in a plasma collection operation; a function of altering an inputted target number of units of to-be-collected platelets in the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that the number of units of collected platelets is on "unit-increased level"; and a function of increasing the amount of platelets to be collected in a subsequent platelet collection operation in the case where the function of altering the target number of units of to-be-collected platelets has altered the target number of units of to-be-collected platelets.

[0203] Therefore in the case where it is possible to increase the target number of units of platelets in dependence on a platelet-collected situation, it is possible to alter the target number of units of platelets and collect platelets at an altered target number of units thereof.

[0204] The platelet collection apparatus of the present invention has a function of determining whether there is a tendency to increase or decrease in the number of collected platelets by using data, related to the concentration of platelets, obtained from a turbidity sensor, an expected number of to-be-collected platelets or a value related thereto and determining on a "level of tendency to increase" and a "unit-increased level" which is higher than the "level of tendency to increase" after plasma (PC) containing high-concentration platelets is collected in a plasma collection operation; a function of altering an inputted target number of units of to-be-collected platelets in the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that the number of units of platelets is on the "unit-increased level"; and a function of increasing an amount of platelets to be collected in a subsequent platelet collection operation in the case where the function of altering the target number of units of the to-be-collected platelets has altered the target number of units of the to-be-collected platelets; and a function of decreasing an amount of platelets to be collected in a subsequent platelet collection operation in the case where the function of altering the target number of units of the to-be-collected platelets has not altered the target number of units of platelets in a predetermined period of time after termination of an operation of the function of altering the target number of units of the to-be-collected platelets and in the case where the function of determining on an increase/decrease tendency in the number of collected platelets has determined that the number of the collected platelets is on the "level of tendency to increase".

[0205] Therefore in the case where it is possible to increase the target number of units of platelets in dependence on a platelet-collected situation, it is possible to alter the target number of units of platelets and collect platelets at an altered target number of units thereof. Further it is possible to prevent platelets from being collected in an amount much larger than the target number of to-be-collected platelets in the case where an increase is not desired in the target number of units of platelets or in the case where the target number of units of platelets is not on an increasable level although the target number of units of platelets has a tendency to increase.

[0206] The platelet collection apparatus of the present invention has a platelet-concentration peak situation determination function of detecting a peak of a platelet concentration by using signals detected by a turbidity sensor when the high-concentration platelets-containing plasma is collected in a platelet collection operation and determining whether a detected peak of the platelet concentration is on a "normal level" or an "excessive level"; and a function of decreasing the number of platelets to

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be collected in the platelet collection operation, when the platelet-concentration peak situation determination function has determined that the peak of the platelet concentration is on the "excessive level".

[0207] Therefore in the case where it is possible to increase the target number of units of platelets in dependence on a platelet-collected situation, it is possible to alter the target number of units of platelets and collect platelets at an altered target number of units thereof.

[0208] A platelet collection apparatus (1) has a function of determining whether there is a tendency to increase or decrease in the number of collected platelets by using data, related to the concentration of platelets, obtained from a turbidity sensor (14), an expected number of to-be-collected platelets or a value related thereto; and a function of decreasing the amount of platelets to be collected in a subsequent platelet collection operation after plasma containing high-concentration platelets is collected in a plasma collection operation, if the function of determining on an increase/ decrease tendency in the number of collected platelets determines that there is a tendency to increase in the number of collected platelets.

Claims

1. A platelet collection apparatus separating blood into a plurality of components by means of a centrifugal separator having a blood-storage space therein and collecting at least platelets of said components, comprising:

   a platelet collection circuit having a first line connecting an inlet of said centrifugal separator and a blood collection means with each other, a second line connected with an outlet of said centrifugal separator, and a platelet collection bag connected with said second line;
   a turbidity sensor disposed on said second line; and
   a function of computing a number of platelet collection cycles and an expected number of to-be-collected platelets or a value related thereto from data of a donor's hematcrit value, platelet concentration data, and a target number of said to-be-collected platelets, all of which are inputted to said platelet collection apparatus before a platelet collection operation is performed,
   a function of determining whether there is a tendency to increase or decrease in a number of collected platelets by using an estimated number of to-be-collected platelets computed by using an amount of plasma containing high-concentration platelets and a platelet concentration obtained from a turbidity sensor when said plasma containing high-concentration platelets is collected or data related to said platelet concentration and by using said expected number of to-be-collected platelets or said value related thereto; and
   a function of decreasing an amount of platelets to be collected in a subsequent platelet collection operation if said function of determining on an increase/decrease tendency in the number of collected platelets determines that there is a tendency to increase in the number of said collected platelets.

2. A platelet collection apparatus according to claim 1, wherein said function of determining whether there is a tendency to increase or decrease in the number of collected platelets determines on a level of tendency to increase and a unit-increased level which is higher than said level of tendency to increase, if it is determined that there is a tendency to increase in the number of collected platelets.

3. A platelet collection apparatus according to claim 2, further comprising a function of altering an inputted target number of units of to-be-collected platelets, if said function of determining on an increase/decrease tendency in the number of collected platelets determines that the number of units of platelets is on the unit-increased level.

4. A platelet collection apparatus according to claim 3, further comprising a function of increasing an amount of platelets to be collected in a subsequent platelet collection operation, if said function of altering the target number of units of to-be-collected platelets has altered said target number of units of said to-be-collected platelets; and
   a function of decreasing an amount of platelets to be collected in a subsequent platelet collection operation, if said function of altering said target number of units of the to-be-collected platelets has not altered the target number of units of platelets in a predetermined period of time after termination of an operation of said function of altering the target number of units of the to-be-collected platelets and if said function of determining on an increase/decrease tendency in the number of collected platelets determines that the number of the collected platelets is on said level of tendency to increase.

5. A platelet collection apparatus according to claim 3 or 4, wherein when said function of altering an inputted target number of units of to-be-collected platelets alters a target number of units of to-be-collected platelets, a computing portion of a control part re-computes an expected number of to-be-collected platelets or a value related thereto; and a function of determining on an increase tendency in the number of collected platelets makes a determination by using a re-computed expected number of

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to-be-collected platelets or a value related thereto.

6. A platelet collection apparatus according to any one of claims 1 to 5, wherein said platelet collection operation includes a plasma collection/circulation operation, the plasma containing high-concentration platelets collection operation after the plasma collection/circulation operation and a blood return operation after the plasma containing high-concentration platelets collection operation.

7. A platelet collection apparatus separating blood into a plurality of components by means of a centrifugal separator having a blood-storage space therein and collecting at least platelets of said components, comprising:

a platelet collection circuit having a first line connecting an inlet of said centrifugal separator and a blood collection means with each other, a second line connected with an outlet of said centrifugal separator, and a pletelet collection bag connected with said second line;
a turbidity sensor disposed on said second line;
a platelet-concentration peak situation determination function of detecting a peak of a platelet concentration by using signals detected by said turbidity sensor, when high-concentration platelets-containing plasma is collected in a platelet collection operation and determining whether said detected peak of said platelet concentration is on a normal level or on an excessive level; and
a function of decreasing a number of platelets to be collected in said platelet collection operation, when said platelet-concentration peak situation determination function determines that said peak of said platelet concentration is on said excessive level.

8. A platelet collection apparatus according to claim 7, wherein said function of decreasing the number of to-be-collected platelets alters stored data of a platelet collection termination condition to quicken a platelet collection operation and decrease a collection amount of said plasma containing high-concentration platelets.

9. A platelet collection apparatus according to claim 7 or 8, wherein said platelet-concentration peak situation determination function determines whether a peak of a platelet concentration is on a normal level, a first excessive level or a second excessive level higher than said first excessive level, and

said function of decreasing the number of to-be-collected platelets alters data of a platelet collection termination condition, namely, a termination voltage of a turbidity sensor to a first predetermined value, if said platelet-concentration peak situation determination function determines that said peak of said platelet concentration is on said first excessive level, and alters said termination voltage of said turbidity sensor to a second predetermined value, if said platelet-concentration peak situation determination function determines that said peak of said platelet concentration is on said second excessive level.

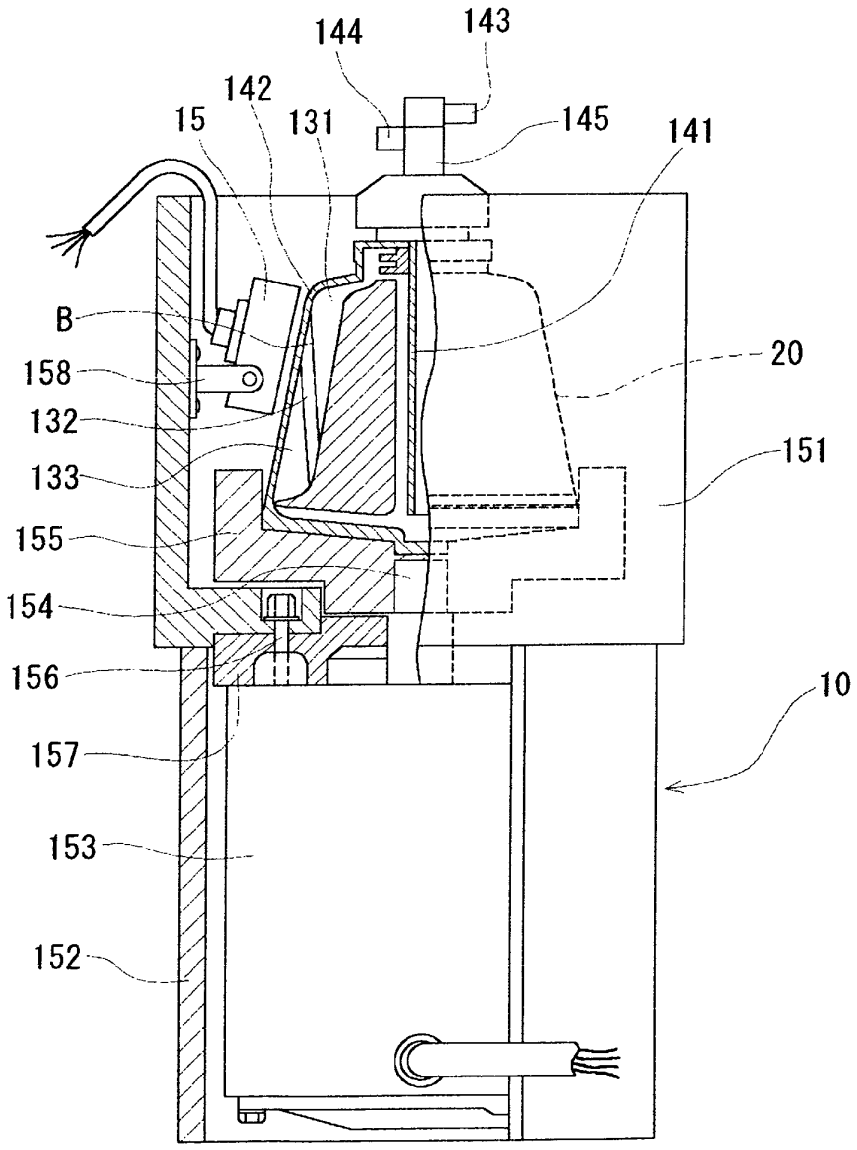
10. A platelet collection apparatus according to any one of claims 7 to 9, wherein said platelet collection operation includes a plasma collection/circulation operation, a high-concentration platelets-containing plasma collection operation after the plasma collection/circulation operation and a blood return operation after the plasma containing high-concentration platelets collection operation.

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FIG. 1

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FIG. 2

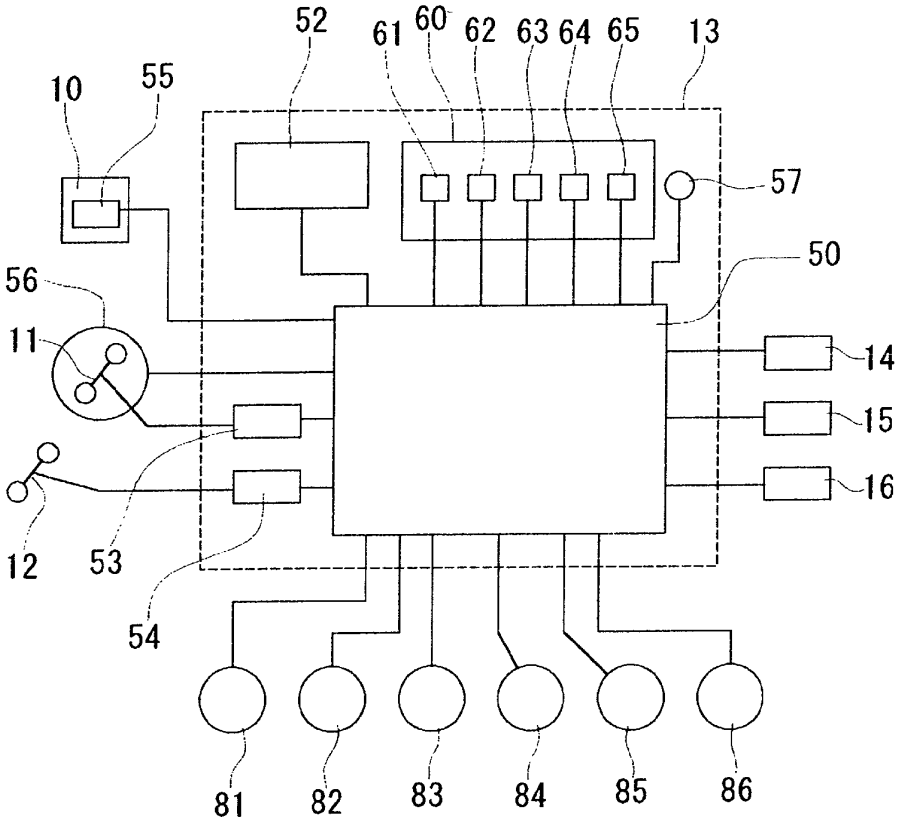


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FIG. 3

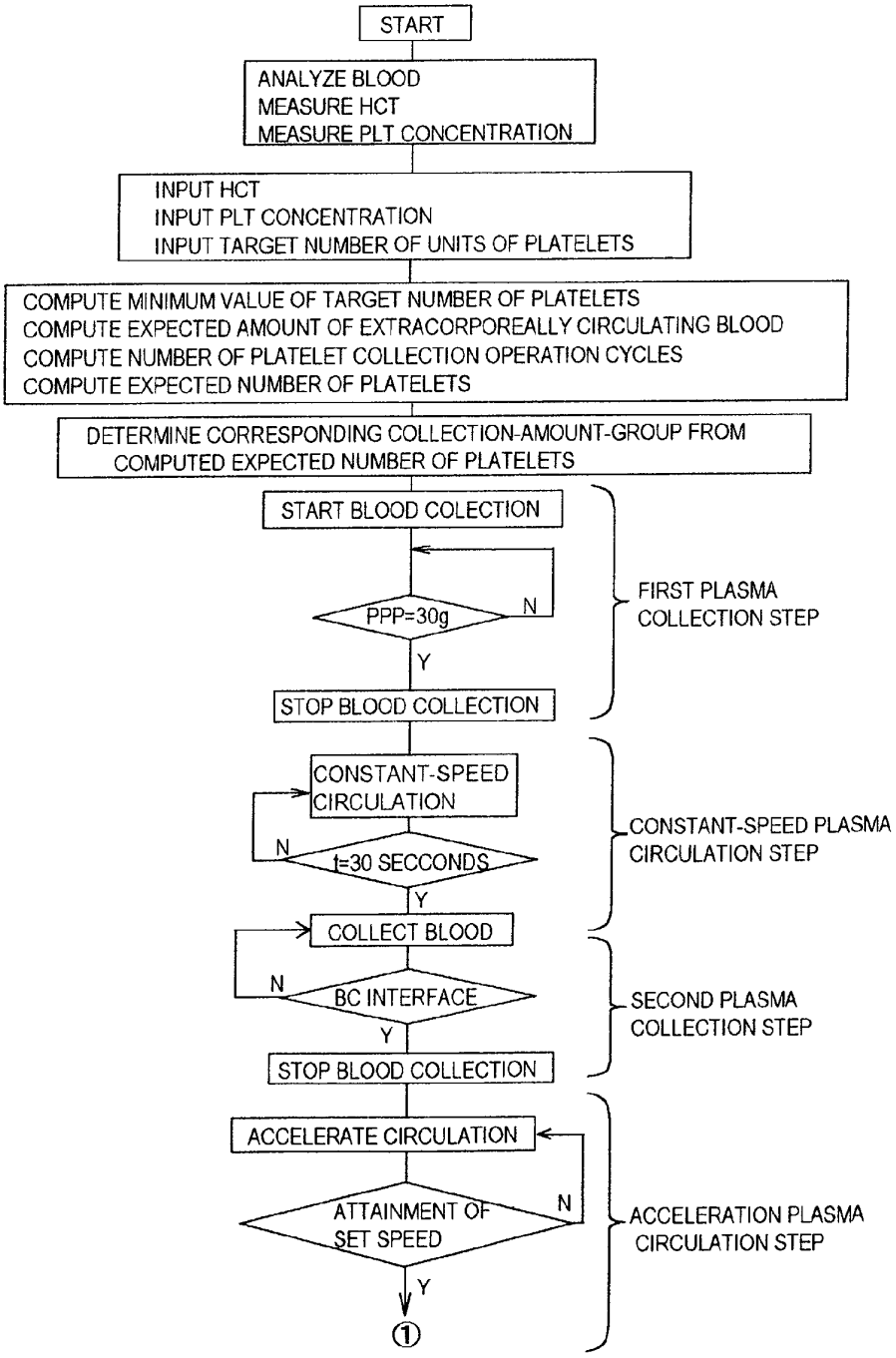
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FIG. 4



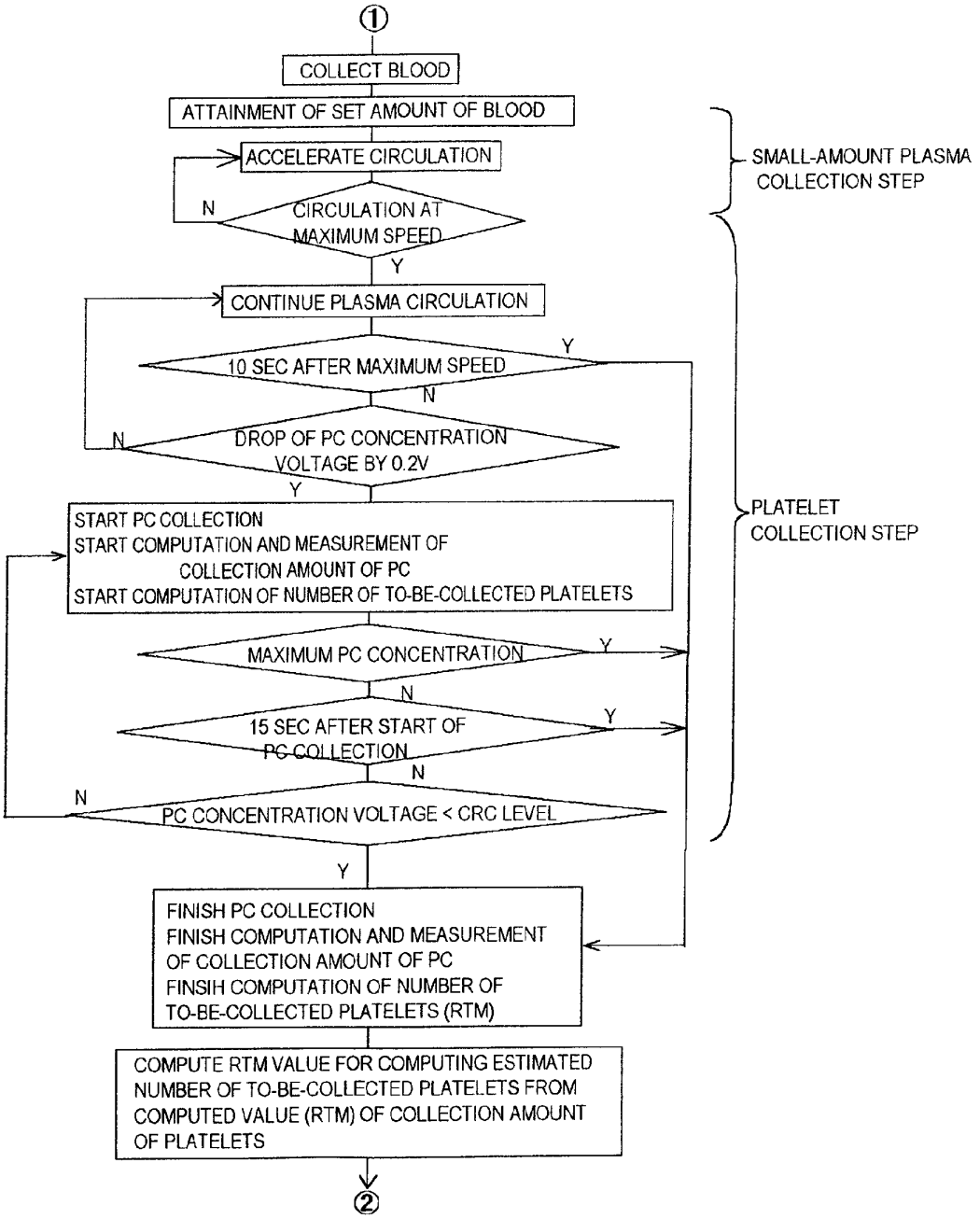
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FIG. 5



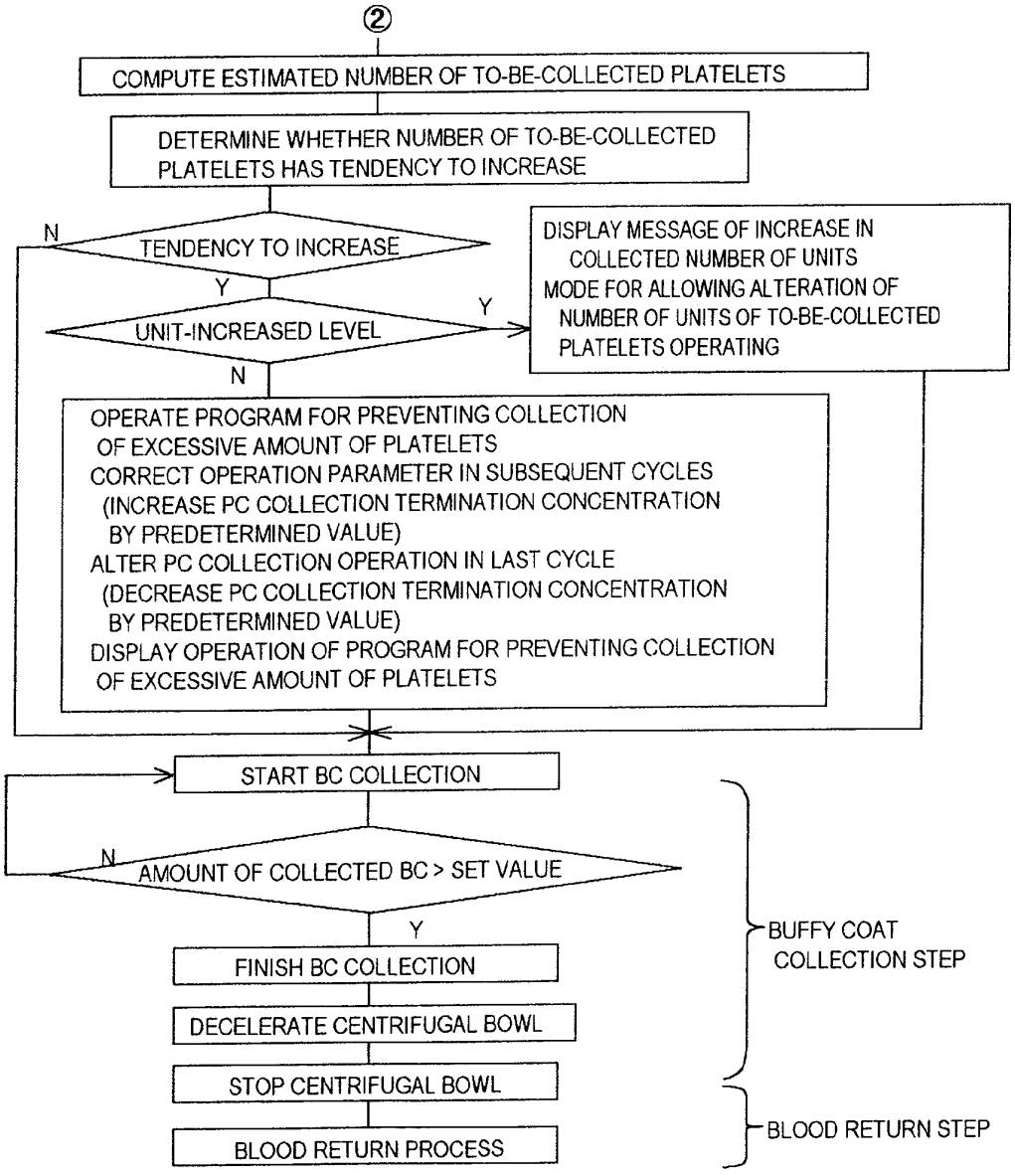
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FIG. 6



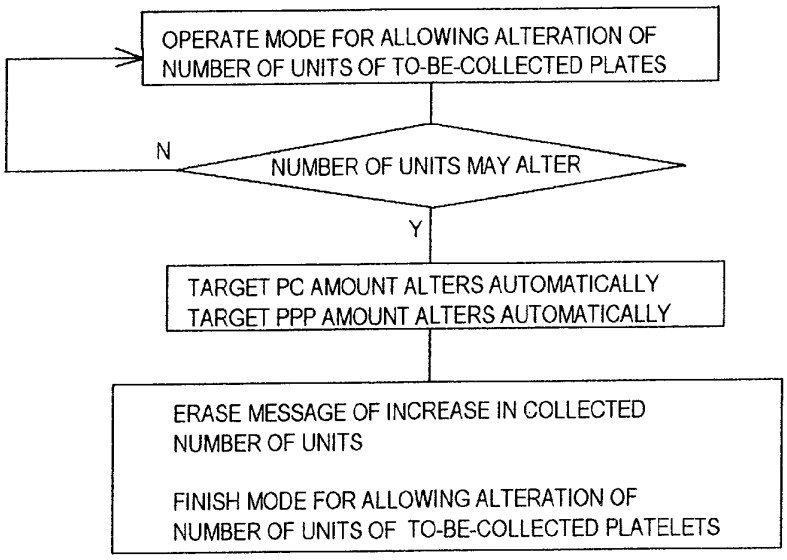
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FIG. 7



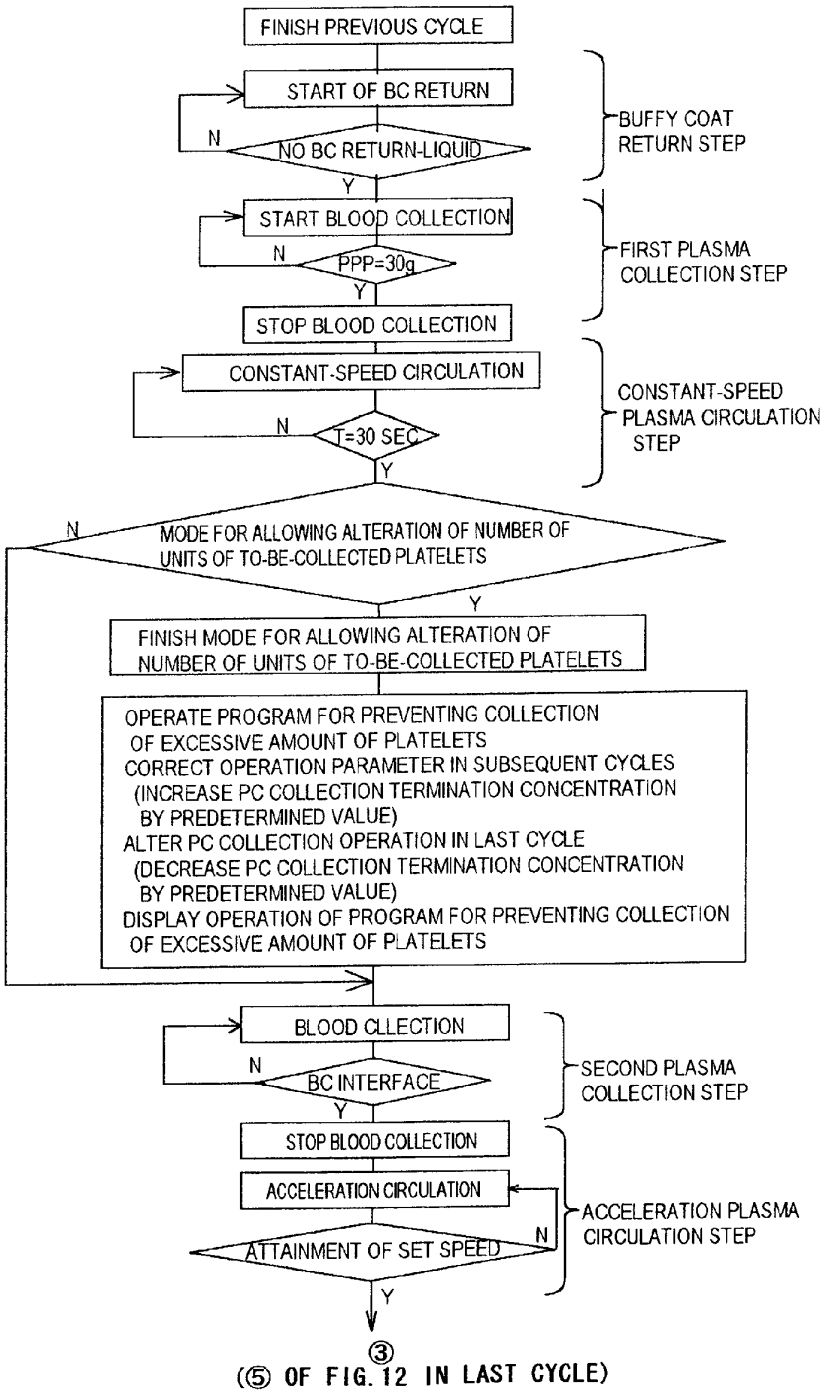
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FIG. 8



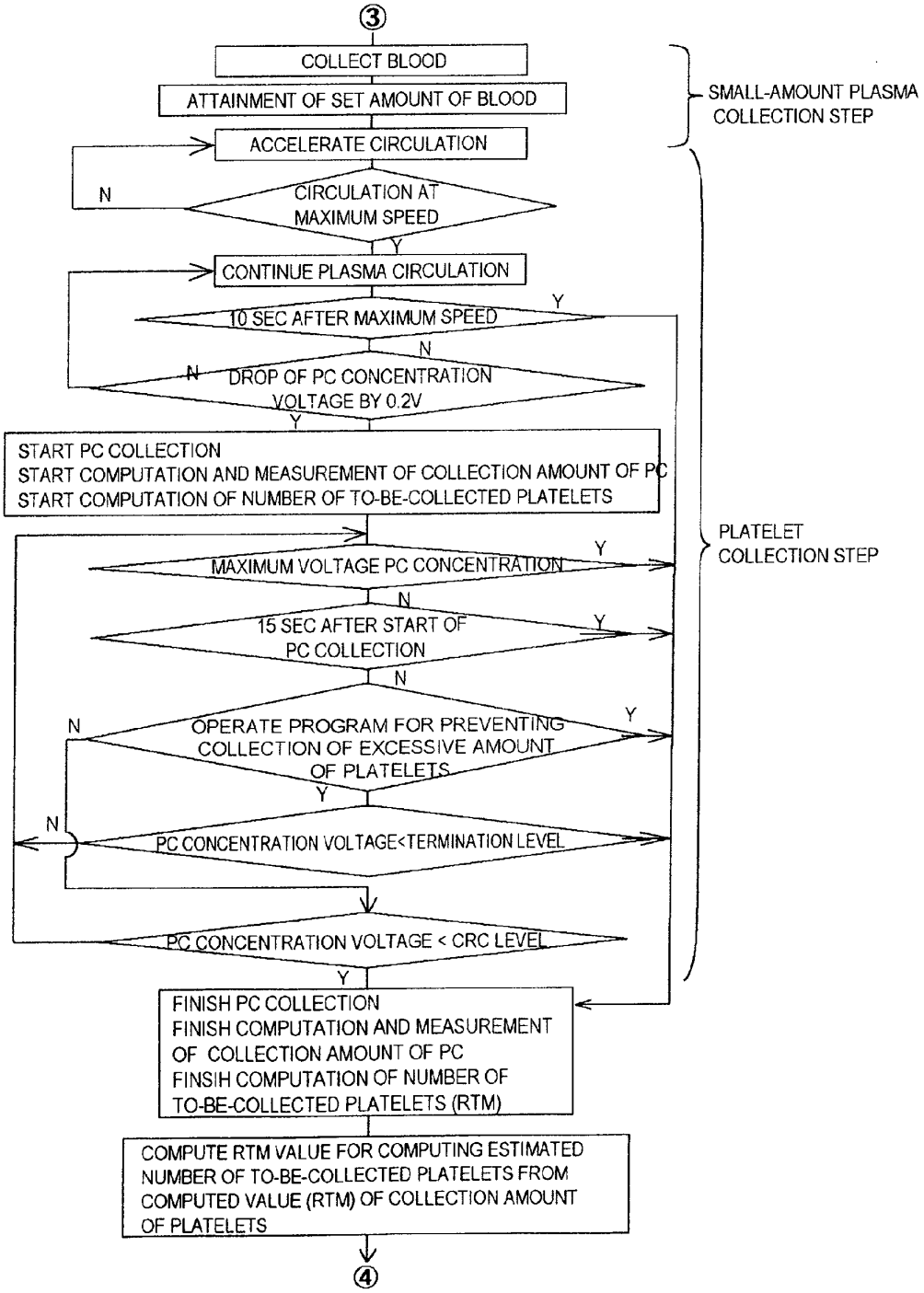
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FIG. 9



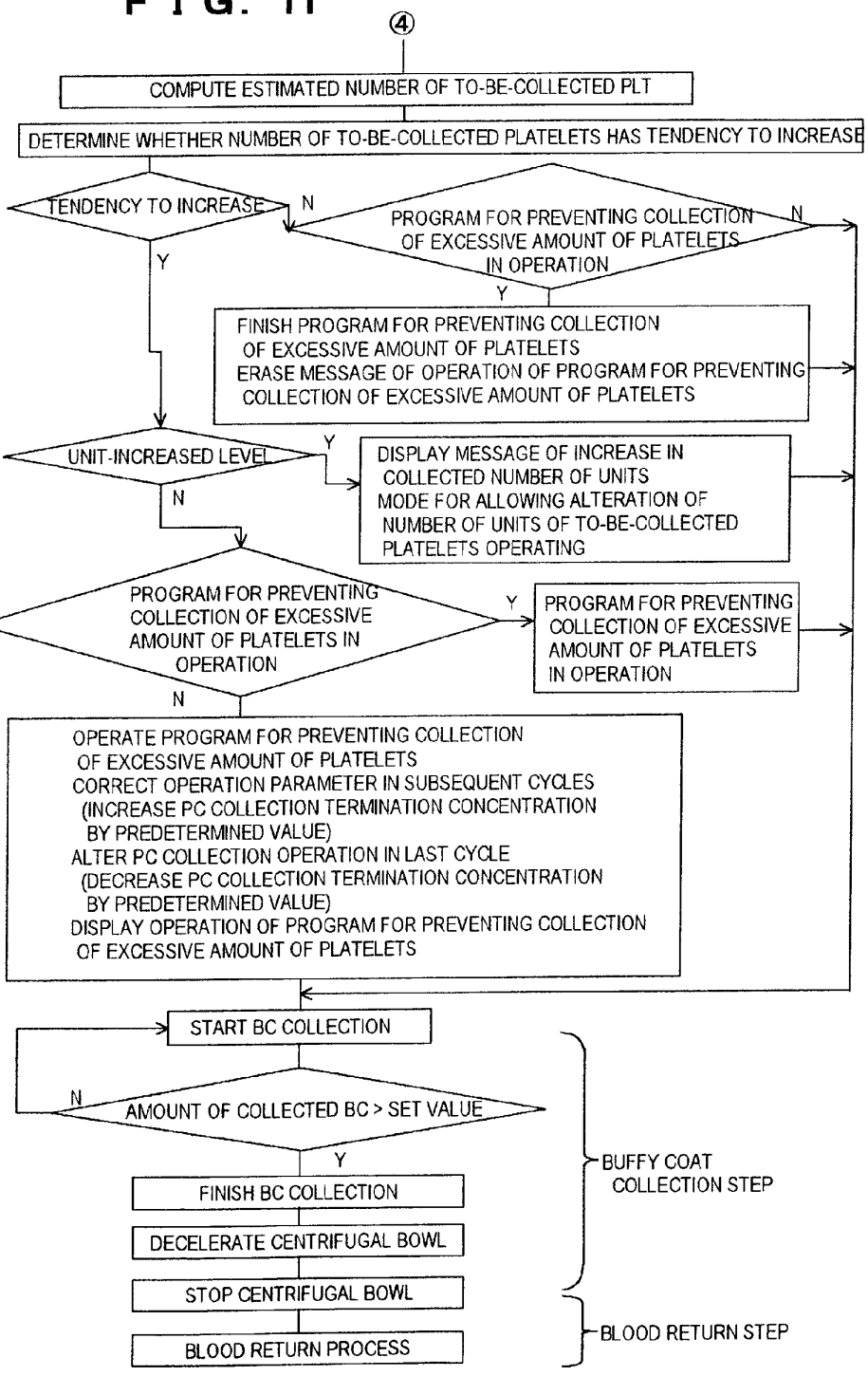
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FIG. 10



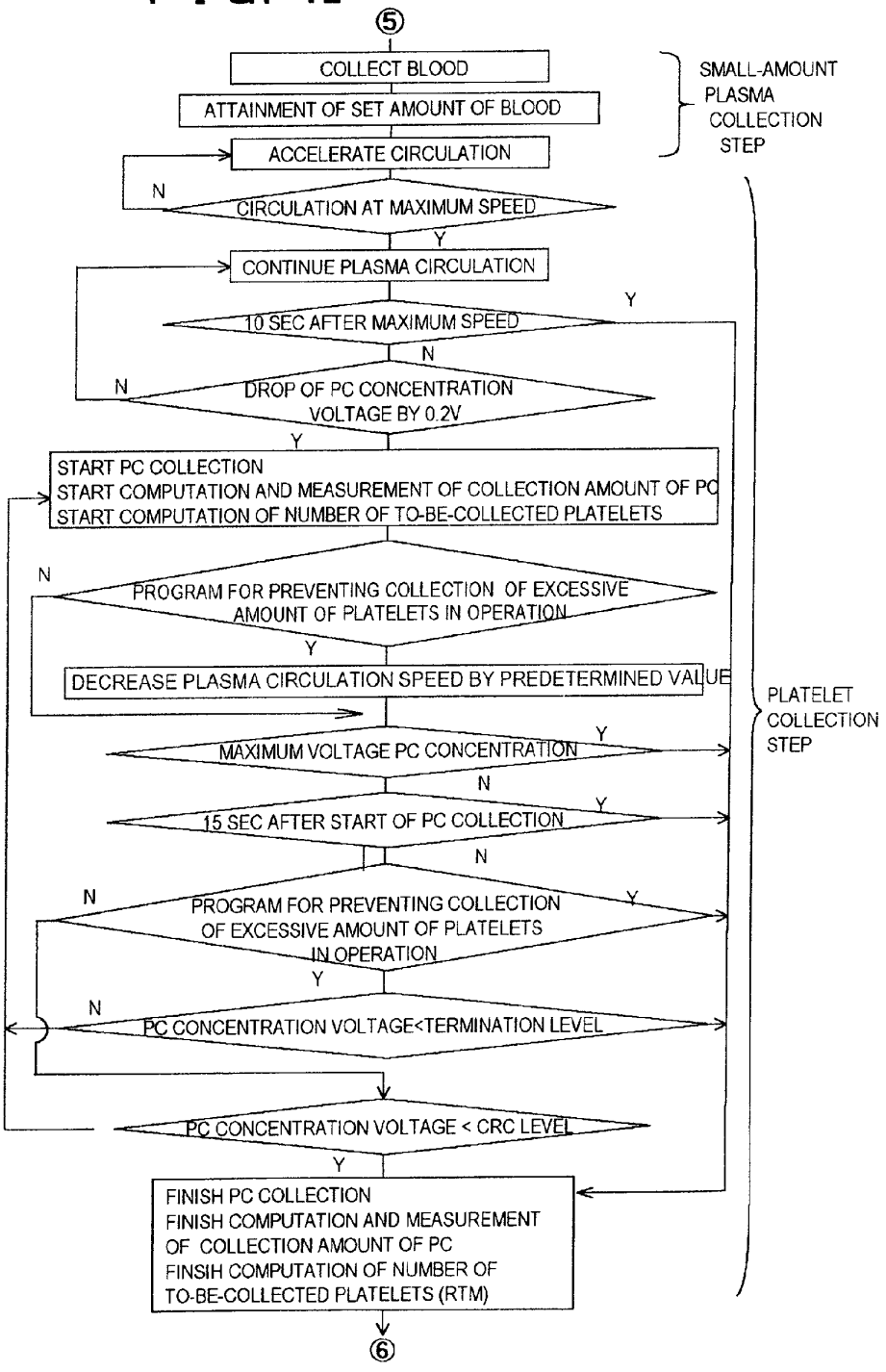
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FIG. 11



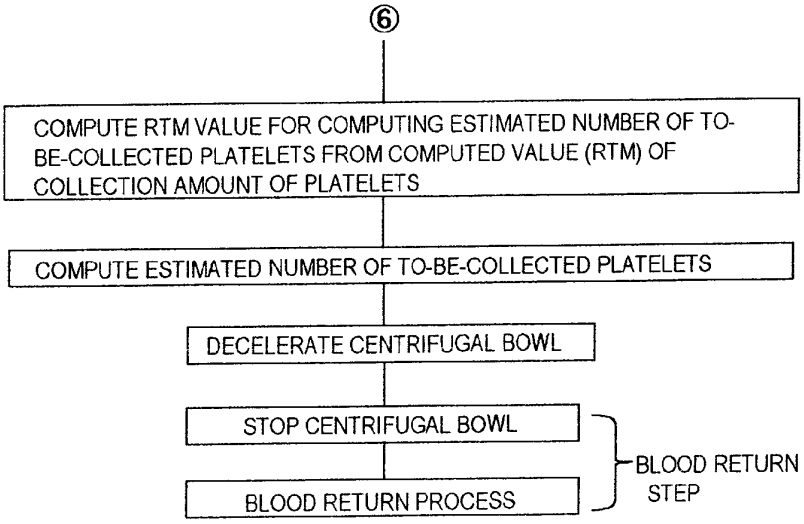
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FIG. 12



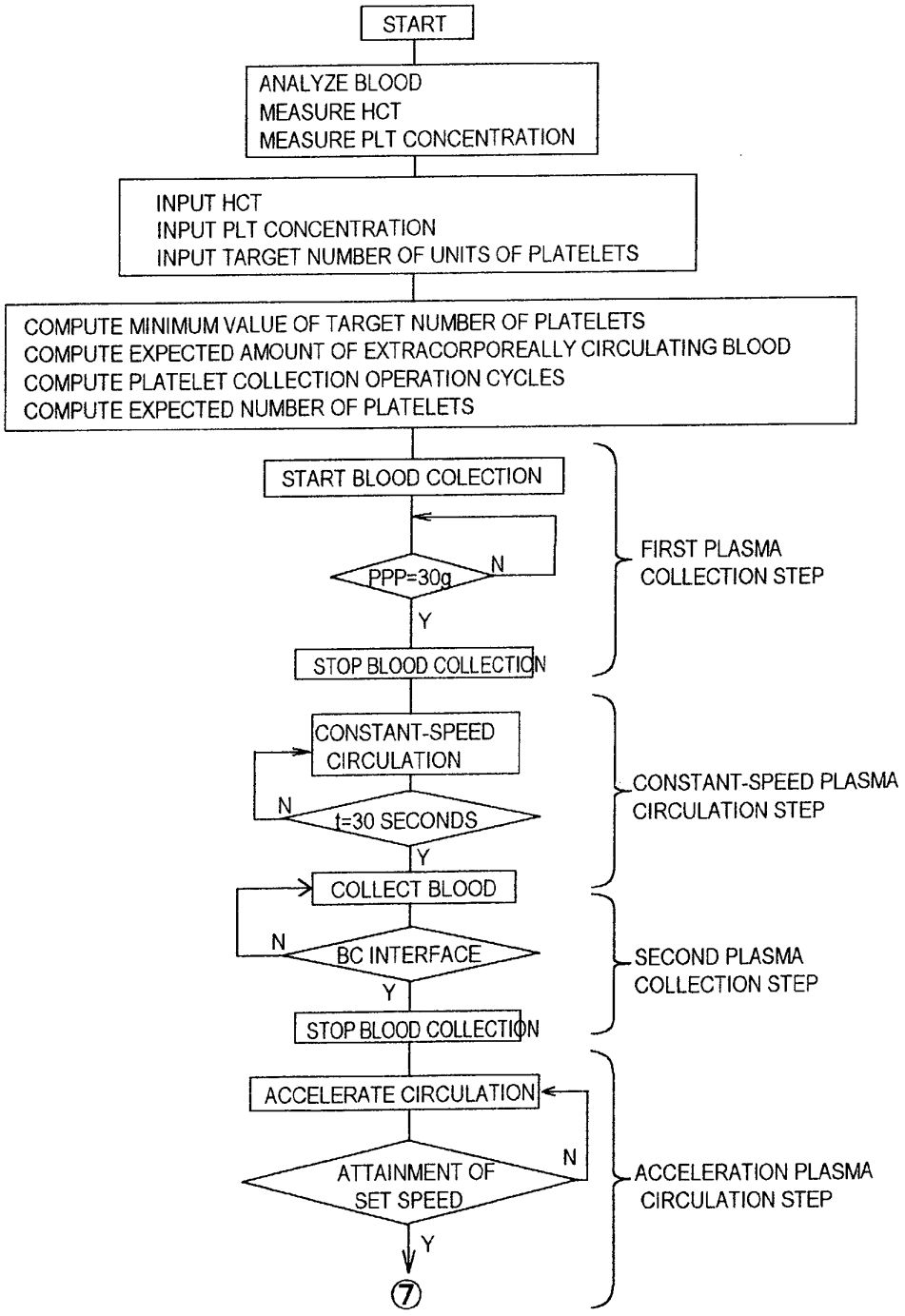
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FIG. 13



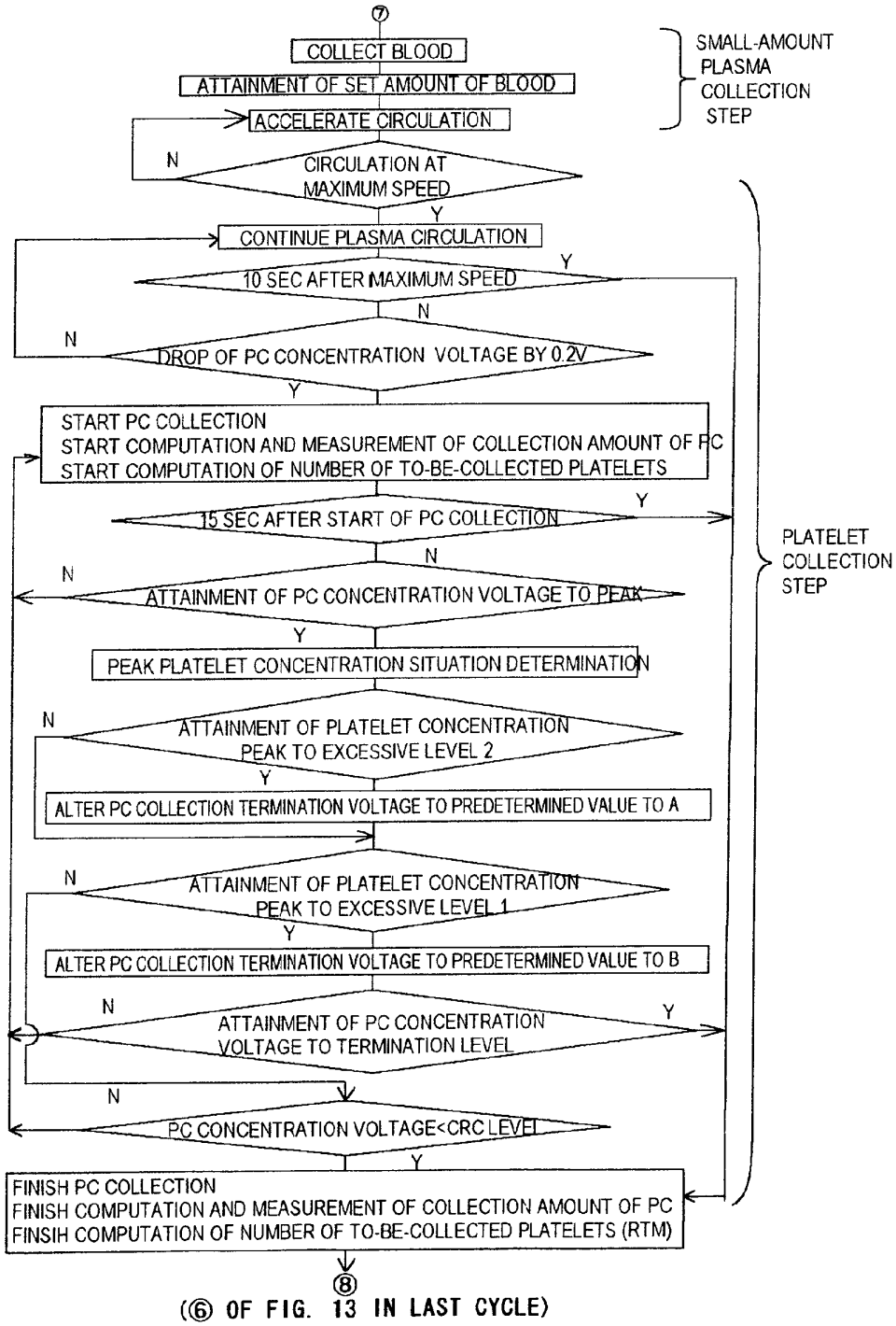
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FIG. 14



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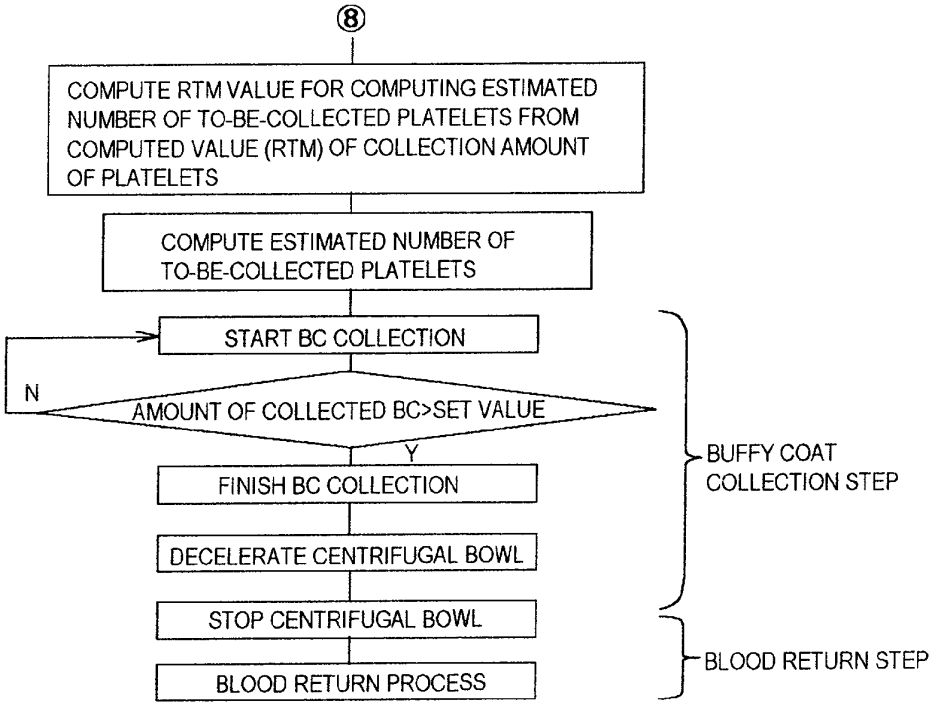
FIG. 15



(⑥ OF FIG. 13 IN LAST CYCLE)

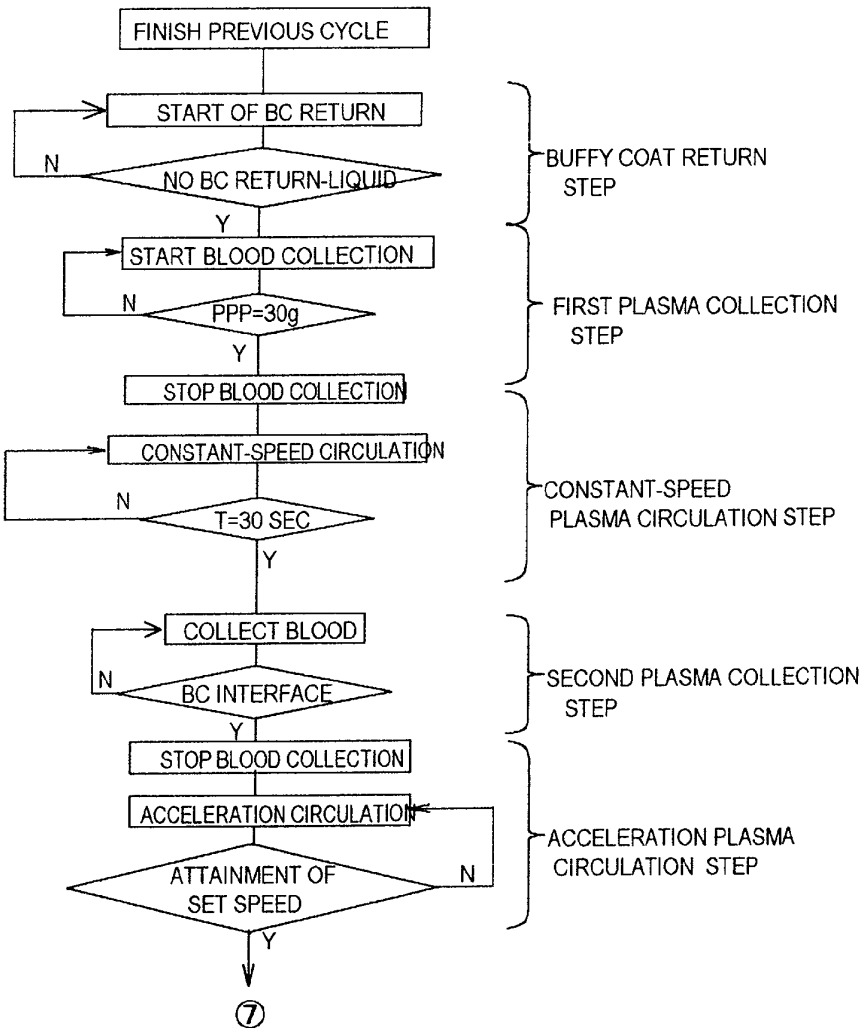
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FIG. 16



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FIG. 17



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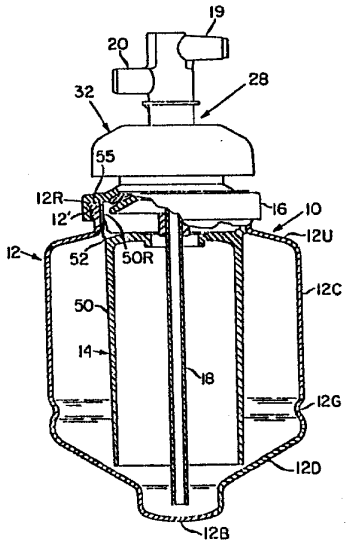
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(54) Centrifuge bowl or rotor for plasmapheresis.

(57) A disposable plasmapheresis centrifuge bowl (10) has a header and rotary seal assembly (28) enclosing an aperture (12R) in the of the bowl (10). The bowl (10) has a one-piece seamless bowl body (12), and various core members (14) may be inserted into the body (12) via the aperture (12R), to control flow of blood constituents inside the bowl (10) and affect the separation thereof.



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"CENTRIFUGE BOWL OR ROTOR FOR PLASMAPHERESIS"

This invention relates to blood processing and, more specifically, plasmapheresis. More especially, the invention relates to a centrifuge bowl or rotor for plasmapheresis.

Background Art

A plasmapheresis process is described in U. S. Patent 4,086,924 issued May 2, 1978 to Allen Latham, Jr. In this plasmapheresis process, whole blood is withdrawn from a donor using a phlebotomy needle and pressure cuff, is mixed with anticoagulant and is transported by a blood pump to a plasmapheresis centrifuge bowl 10 in which the whole blood is separated into a plasma and non-plasma component.

The centrifuge bowl 200 is described in connection with Figs. 4 and 5 of U. S. Patent 4,086, 924, which are reproduced herein as Figs. 1, 2 and 3 and labelled "Prior Art". As shown therein, the centrifuge generally comprises a multi-piece feed tube and seal assembly with a first transverse central input port 90 leading to a longitudinal feed tube stem 92 through which whole blood is introduced into the bottom 106 of the centrifuge bowl 200.

A second transverse peripheral port 94 is provided to allow separated plasma component to flow out of the centrifuge bowl 200. A channel leading to peripheral port 94 is formed between upper skirt 96 and lower skirt 98, which extend outwardly from a

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point approximately opposite where the central port 90 joins feed tube stem 92.

The outlet channel formed between upper and lower skirts 96 and 98, respectively, continues into an annular coaxial channel around the periphery of the longitudinal extension of central port 90 until it joins peripheral port 94.

An elastomeric bellows 128 forms a spring member which urges carbon ring seal 126 against skirt 96 forming a rotary seal therebetween.

Central port 90, feed tube stem 92, peripheral port 94 and skirts 96 and 98 are generally manufactured by molding or extrusion techniques using blood compatible plastic, such as styrene, ABS, polycarbonate, polyethylene, polyurethane, etc. The ports and skirts are part of a feed tube assembly which is coaxial to and remains stationary while the centrifuge bowl rotates about its longitudinal axis.

The centrifuge bowl body 200 is of two piece construction formed of two integrally molded pieces, an upper piece 202 and lower piece 204, which are joined at approximately the mid-point, where a raised joint 108 is provided so that the upper and lower halves of the bowl, which were separately injection-molded, may be joined by welding. A molded series of outer wall members comprising an inclined upper wall member, shown generally at 100, a substantially vertical central wall member 102, and a lower steeply inclined wall member 104, and a

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recessed bottom wall member 106 define the exterior walls of the centrifuge bowl chamber.

A tubular core 120 defines a separation channel 150 between the outer core wall 103 and the inner longitudinal walls of the bowl body wall. As shown in the planar view of Fig. 3, the core is provided with vanes 122 which have steps 124 at the extremities, which are used to accurately position the core coaxially by seating part of the upper housing 124 against the vanes. When they are seated, vanes 122 serve to provide a flow channel or opening from the sedimentation area along the longitudinal length of the core wall 103, leading to the outlet channel formed between skirts 96 and 98.

Weld lines X-X, Y-Y and Z-Z have been added to Figs. 1 and 2 of the drawings to show how the individual parts and assemblies of the prior art bowl body 200 are joined together and assembled. As may be seen therefrom, the lower portion and upper portion of the feed tube and seal assembly is welded at two places, Z-Z and Y-Y, after the lower portion is inserted through a first large intermediate opening 105 and a second smaller opening 107 in upper bowl body piece 202. Next, core 120 is snapped in place on upper piece 202 by means of vanes 122 which seat on the upper piece. Finally, lower piece 204 is placed over the core 120 abutting joint 108 at X-X and is welded in place.

Apart from the overall labor intensive complexity of the above procedure, several basic

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problems exist in the prior art bowl construction above described. First, the weld at 108 about the periphery of the bowl body is subjected to the greatest possible centrifugal forces when the bowl is in operation since it is located at the furthest radial point from the bowl axis. Rupture of the weld at this juncture is a chief cause of bowl failure. Secondly, the bowl construction does not permit testing of the seal and feed tube assembly until it is permanently integrated with the bowl. Thus, if a defect is found in the assembly, the complete assembly must be scrapped.

Accordingly, a need exists for a more reliable, easier to assemble, centrifuge bowl capable of mass production with a minimum amount of labor and in which the seal and feed tube assembly can be separately tested.

According to the present invention, there is provided a disposable centrifuge rotor comprising:

(a) an integral seamless, unitary bowl body adapted for rotation about an axis and having a single aperture therein through an outer wall of the bowl body; and

(b) a rotary seal assembly affixed to the bowl body and covering the said aperture.

Also according to the present invention, there is provided a disposable centrifuge rotor comprising:

(a) a seamless bowl body adapted to rotation about its longitudinal axis and having a single closeable aperture concentric with said axis at one end thereof;

(b) a core member concentric with said axis and having an open center extending within said bowl from said aperture about said axis; and

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(c) a rotary seal assembly having a cover for sealing the said seal assembly to the outer wall of the body about the periphery of the said aperture.

Further according to the present invention, there is provided a disposable centrifuge blood processing rotor comprising:

(a) an integral unitary bowl body adapted for rotation about its longitudinal axis and having a single aperture concentric with said axis at one end of the outer wall of the bowl body;

(b) a core member insertable in said aperture and having an internal central bore concentric with said bowl body axis; and

(c) a rotary seal assembly affixed to the outer wall about the periphery of the said aperture and having an effluent port and input port in fluid communication with the interior of said bowl body.

The invention is described in more detail in the five non-limitative paragraphs which follow.

The method and apparatus of the present invention comprises a disposable centrifuge rotor or bowl formed of two basic items. The first is a rotary seal and header assembly; the second, a unitary, integral, seamless, one peice bowl body. A third, optional element comprises a series of core member or members capable of being used in a standard bowl body for different separation processes. The seal and header assembly is capable of being assembled on an automatic machine. The bowl body is adapted to be manufactured by blow molding

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or injection blow molding and the core member, or members, by injection molding or other forming process.

The integral bowl body is adapted for rotation about its longitudinal axis. A single aperture is provided at one end of the bowl body concentric with the longitudinal axis of the bowl body. Core members of various configurations are adapted to be insertable through the aperture in the bowl body concentric with the longitudinal axis of the bowl.

The seal and header assembly has a first seal or crown member which mates with the outer body wall of the bowl member about the periphery of the bowl body aperture to affix the seal and header assembly to the bowl body. The seal and header assembly is formed of a header with input and output ports, and a feed tube coupled to the inlet port which extends within the core member concentric with the longitudinal axis of the bowl body and terminating a short distance from the lower wall of the bowl body.

An effluent tube is formed about the inner feed tube assembly with a narrow channel provided therebetween for flow of effluent, for example, plasma, to the outlet port. A second seal member is formed about the periphery of the effluent tube to form a rotary seal over the first seal member which permits the inner and outlet ports to remain stationary while the bowl rotates about its central axis.

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The entire centrifuge rotor thus described can be assembled in a matter of seconds after the outside seal and header assembly has been assembled by automated assembly techniques. A selected core member is inserted into the aperture in the unitary bowl body. Next, the seal and header assembly is placed over the aperture and the feed tube inserted into a concentric opening in the core until the first seal or crown is mateably engaged with the outer wall of the aperture and a seal is formed therebetween.

The invention and preferred embodiments thereof will now be explained in further detail, by way of example only, in the following description to be read in conjunction with the accompanying drawings, in which:

Figs. 1 and 2 are respectively front and side cross-sectional views of the centrifuge bowl described in U. S. Patent 4,086,924 and labelled "Prior Art".

Fig. 3 is a transverse cross-sectional view along line 3-3 of Fig. 1 of the prior art.

Fig. 4 is a partial cutaway side cross-sectional view of the centrifuge bowl of the present invention.

Fig. 5 is a partial cut-away sectional view of a feed tube assembly of Fig. 4.

Fig. 6 is a sectional view of the top end of a core 14 seen in Fig. 4.

Fig. 6A is a perspective view of the core 14 showing the slots 52 in more detail.

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Fig. 7 is a partial cutaway side cross-sectional view of the centrifuge bowl of the invention showing an alternate embodiment of the core member.

Fig. 8 is a sectional view taken along lines 8-8 of Fig. 7.

Fig. 9 is a partial cross-sectional view of yet another embodiment of the invention showing a two-piece core construction.

Fig. 10 is a detailed view taken along line 9-9 of Fig. 9.

Referring now to Figs. 4-6, a preferred embodiment of the invention will now be described in connection therewith. As may be seen therein, the apparatus of the invention comprises a disposable centrifuge rotor, or bowl, 10. The bowl comprises: a seal and header assembly, shown generally at 28 (Fig. 5), a one-piece, seamless, integral bowl body shown generally at 12 (Fig. 4) and a core member 14 (Fig. 6 and Fig. 4).

The seal and header assembly 28 is capable of being assembled utilizing automatic machine techniques. The seal and header assembly is comprised of a header 30, an effluent tube 25, a feed tube assembly 24, and a rotary seal 35 formed of a seal ring 22, and a flexible member 27 and an outside seal member or crown 16.

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The header 30 comprises an integral formed member having a transverse inlet bore 19 extending into a longitudinal passageway 19a coupled to the inner bore 61 of feed tube assembly 24 and, in turn, to feed tube stem 18, thus forming an inlet path for anticoagulated whole blood to enter the interior of centrifuge bowl body 12.

Header 30 also includes an outlet port, or bore 20, which extends transversely into a peripheral channel 20a extending in parallel relationship with the feed tube assembly 24 and into an outlet passageway 62. A shield portion 32 formed on header 30 extends over the rotary seal 35.

Feed tube assembly 24 is formed with an integral skirt 24' disposed adjacent a complimentary effluent tube skirt 25' formed on effluent tube 25.

The rotary seal 35, as mentioned above, is formed of a two-piece secondary seal ring which consists of flexible outside sealing member 27, which is affixed about its outer periphery to the periphery of molded ring seal 22. A seal crown 16 having internal screw threads 16', about the internal periphery thereof, is provided with a central opening through which effluent tube 25 extends. The inner periphery of flexible member 22 is joined to the effluent tube.

The header and seal assembly 28, as thus described, is formed and assembled as an individual entity and is inserted through an upper central opening in bowl body 12, as shown in Fig. 4 and mated with external threads 12' formed on the

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periphery of bowl body 12 after core member 14 has been inserted through said opening and fixed in place within the bowl body 12, as will be subsequently described.

The bowl body 12 is an integral body adapted to be manufactured by blow molding or injection blow molding and may be formed of a suitable plastic, such as transparent styrene or equivalent.

The bowl body is formed of an upper ring portion 12R, an upper diagonal portion 12U, a middle central portion 12C, a lower diagonal portion 12D and a bottom cross portion 12B. Screw threads 12' are formed on the outer surface of ring portion 12R and an opening extends longitudinally from the inner surface of the ring portion 12R into the main portion of the bowl body 12. A groove is formed about the periphery of the bowl at 12G to form a holding surface for a centrifuge rotor chuck (not shown).

An O-Ring gasket 55 is disposed on an inner peripheral shoulder of crown member 16 adjacent screw threads 16'. When member 16 is threaded onto bowl body 12, gasket 55 is compressed against the upper wall of ring 12R forming a liquid tight seal.

A cylindrical walled core 14 is adapted to be inserted into the upper opening in bowl body 12 through the opening in ring portion 12R. Core 14 is an integral member having a cylindrical outer wall 50 extending longitudinally and coaxial to the axis of bowl body 12. An upper ring portion 50R of core

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14 is adapted to abut the inner wall of the ring portion 12R of bowl body 12 when the core is inserted into the upper opening of the bowl body 12.

Four L-shaped reinforcing tabs 56 are formed on the top wall 50T of core 14 to reinforce the ring portion 50R. Four peripheral slots extend along the periphery of the core 14 at the juncture between the ring portion 50R and the cylindrical wall 50, as shown more clearly in Fig. 6A. These slots 52 provide a passageway for the exit of effluent, such as plasma, which has been separated from the whole blood by the operation of the centrifuge plasmapheresis process within the bowl body 12.

This operation may be described generally as follows: Whole blood is coupled from inlet port 19 through the longitudinal passageway in feed tube assembly 24 to the bottom of the spinning centrifuge bowl. The heavier red blood cells are forced radially outwardly from the central axis and are retained on the inner bowl wall along the main or central body portion 12C of the bowl. The lighter, less dense plasma is captured on the outer surface of cylindrical wall 50 and allowed to exit through the slots 52 at the top wall 50T of core 14 whereupon they pass through the channel between skirts 24' and 25' into the passageway 62 and out the outlet port 20 of header 30.

As mentioned previously, one of the advantages of the present invention is that the outside seal and header assembly 28 may be separately tested. For example, the assembly may be fastened to a test

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bowl body and checked under pressure for leaks, etc. Similarly, the bowl body 12 may be separately checked for leaks while attached to a test fixture. After testing of each, they may be assembled manually or with the use of automatic machinery.

In the alternate embodiment shown in Fig. 7, the bowl body 12A and header and seal assembly 28 are substantially similar to that previously described. However, the core labelled 14' is flared at the lower extremity and is formed of semi-rigid plastic material, such as polyvinylchloride (PVC) to allow the flared core to be inserted through the upper opening in the bowl body by deflecting the longitudinal wall 50'. This results in a core body having skirts 50S extending parallel to the diagonal walls 50D of the bowl body. This skirted core configuration is similar to that shown in U. S. Patent 4,300,717 and enables different blood flow patterns to be formed within the bowl.

Fig. 8 shows the lower bowl body details of the alternate embodiment of Fig. 7 in which channels 80 are formed in the bowl body 12' during the molding process to facilitate flow of blood from the center of the bowl to the sides in a predetermined pattern.

Figs. 9 and 10 depict an alternate two-piece core embodiment in which the core member 14'' is comprised of a generally cylindrical hollow walled core, as in Fig. 4, but includes a disc-like member 90 which provides a flared wall portion 98 adjacent diagonal bowl wall 12D. Member 90 is made of semi-rigid plastic which can be compressed to allow

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it to pass through the top opening in the bowl body. Circular grooves formed around protrusions 96 on member 90 permit cylindrical core wall 50'' to mate with member 90 after the core is inserted into the bowl body. The grooves 92 form a press-fit holding the two pieces 90 and 50'' together during rotation of the bowl 10. Aperture 97 permits whole blood from feed tube stem 18 to enter the bottom of the bowl body 12B.

Equivalents

Those skilled in the art will recognize that there are many equivalents to the specific embodiments described herein. Such equivalents are intended to be encompassed within the scope of the following claims.

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CLAIMS:

1. A disposable centrifuge rotor comprising:
(a) an integral seamless, unitary bowl body (12) adapted for rotation about an axis and having a single aperture (12R) therein through an outer wall of the bowl body; and
(b) a rotary seal assembly (28) affixed to the bowl body (12) and covering the said aperture.

2. The rotor according to claim 1, including a core member (14, 14', 14") adapted to be inserted through the said aperture prior to its being covered by the seal assembly (28).

3. The rotor according to claim 2, wherein the core member (14') is semi-rigid and flared at one end.

4. The rotor according to claim 2, wherein the core member (14") comprises a rigid member (50") having an outer diameter small enough to enable passage through the said aperture and a flexible member (90) having a greater diameter which is compressed to pass through the said aperture and thereafter expanded and affixed to the rigid member.

5. The rotor according to claim 1, 2, 3 or 4, wherein the rotary seal assembly (28) is provided with a threaded cover (32) which is screwed onto complementary threads (12') on the bowl body (12) to cover the aperture thereof.

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6. The rotor according to claim 5, wherein a seal ring (55) is disposed between the seal assembly (28) and bowl body (12) about the periphery of the aperture.

7. The rotor according to any of claims 1 to 6, for use in processing blood components, wherein the bowl body has shaped portions thereon, as formed, which affect the flow of blood components.

8. A disposable centrifuge rotor comprising:
(a) a seamless bowl body (12) adapted to rotation about its longitudinal axis and having a single closeable aperture (12R) concentric with said axis at one end thereof;
(b) a core member (14, 14', 14") concentric with said axis and having an open center extending within said bowl from said aperture about said axis; and
(c) a rotary seal assembly (28) having a cover (32), for sealing the said seal assembly to the outer wall of the body (12) about the periphery of the said aperture.

9. The rotor according to claim 8, wherein the core member (14', 14") is at least partly flexible at portions thereof having an outer diameter greater than the bowl body aperture.

10. A disposable centrifuge blood processing rotor comprising:
(a) an integral unitary bowl body (12) adapted for rotation about its longitudinal axis and having a single aperture (12R) concentric with said axis at one end of the outer wall of the bowl body;

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(b) a core member (14, 14', 14") insertable in said aperture and having an internal central bore concentric with said bowl body axis; and

(c) a rotary seal assembly (28) affixed to the outer wall about the periphery of the said aperture and having an effluent port (20) and input port (19) in fluid communication with the interior of said bowl body (12).

11. The disposable centrifuge rotor according to claim 10 including a peripheral slit extending at least partially about the periphery of said core member for permitting exit of separated whole blood constituents from said bowl body to said effluent port.

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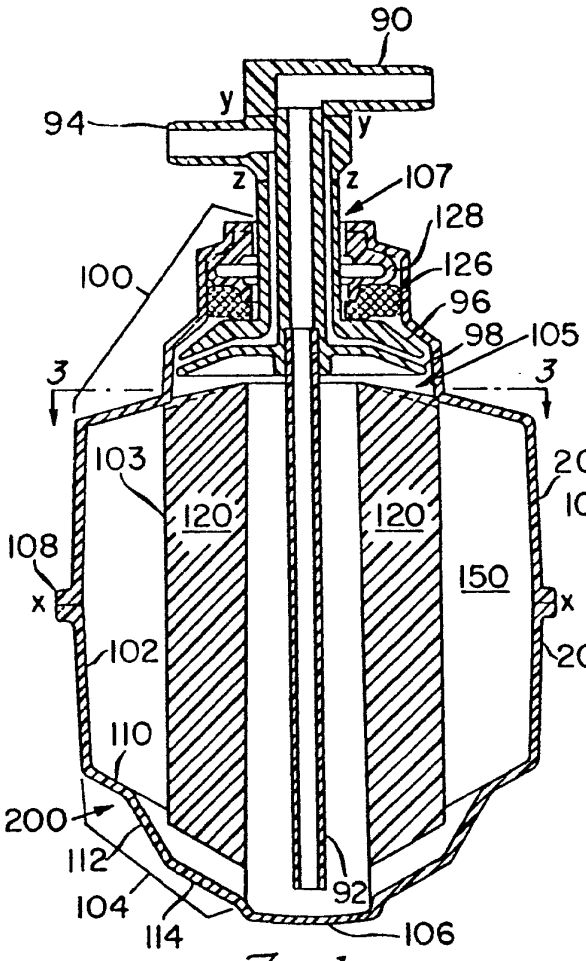


Fig. 1

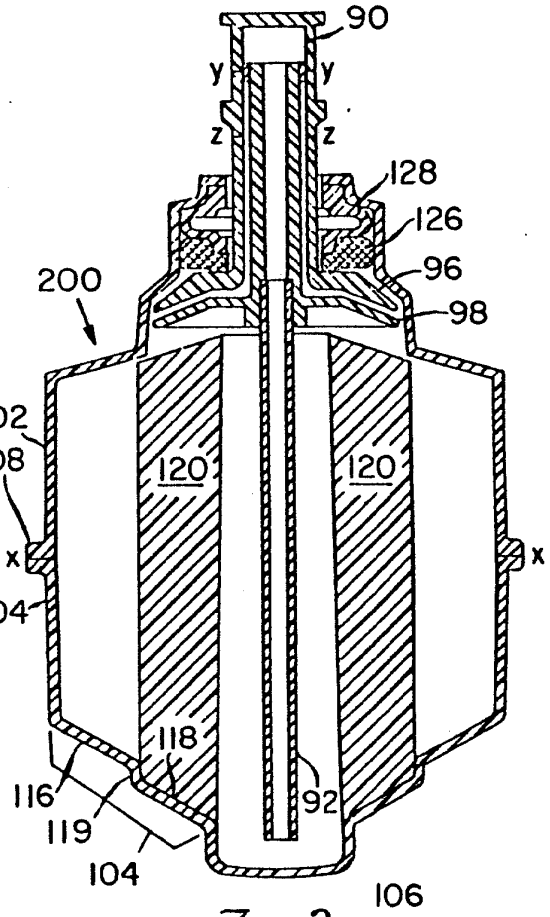


Fig. 2

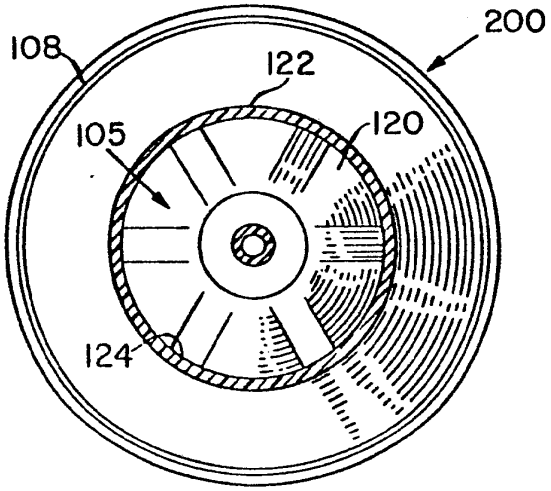


Fig. 3

PRIOR ART

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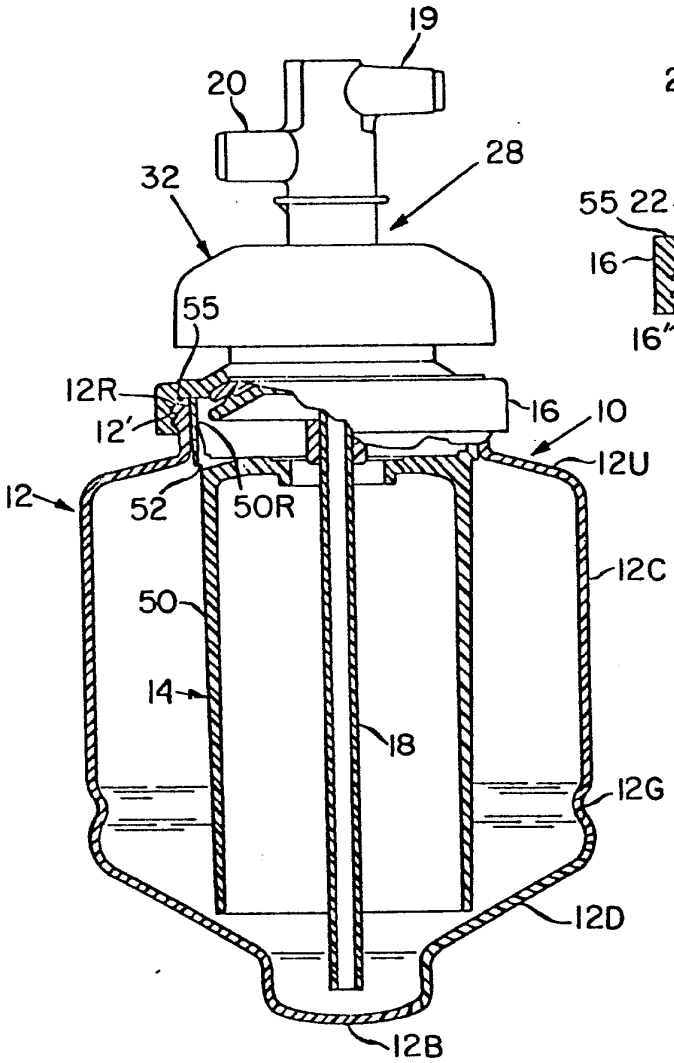


Fig. 4

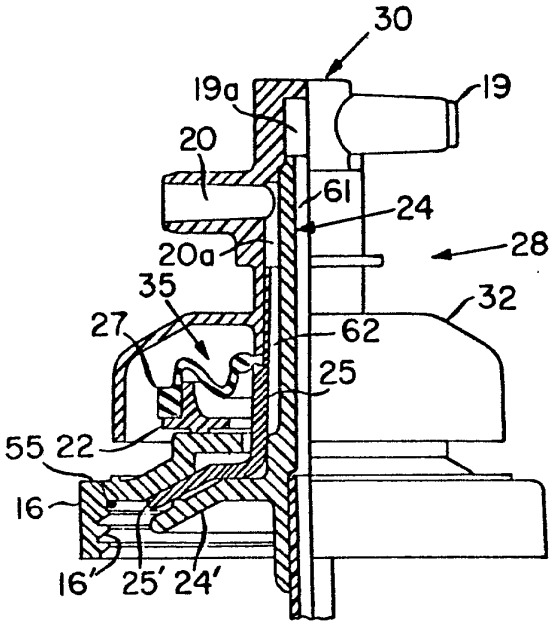


Fig. 5

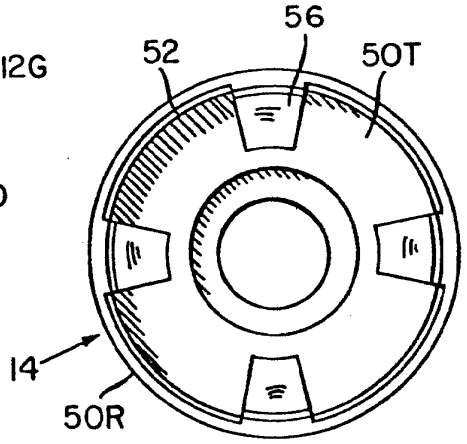


Fig. 6

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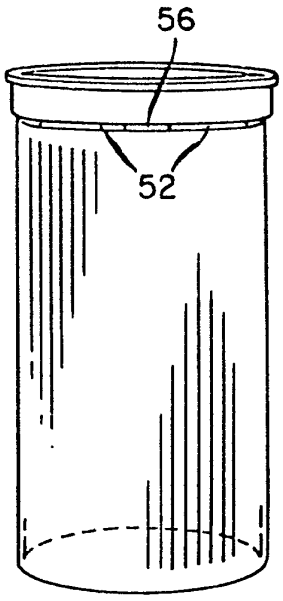


Fig. 6A

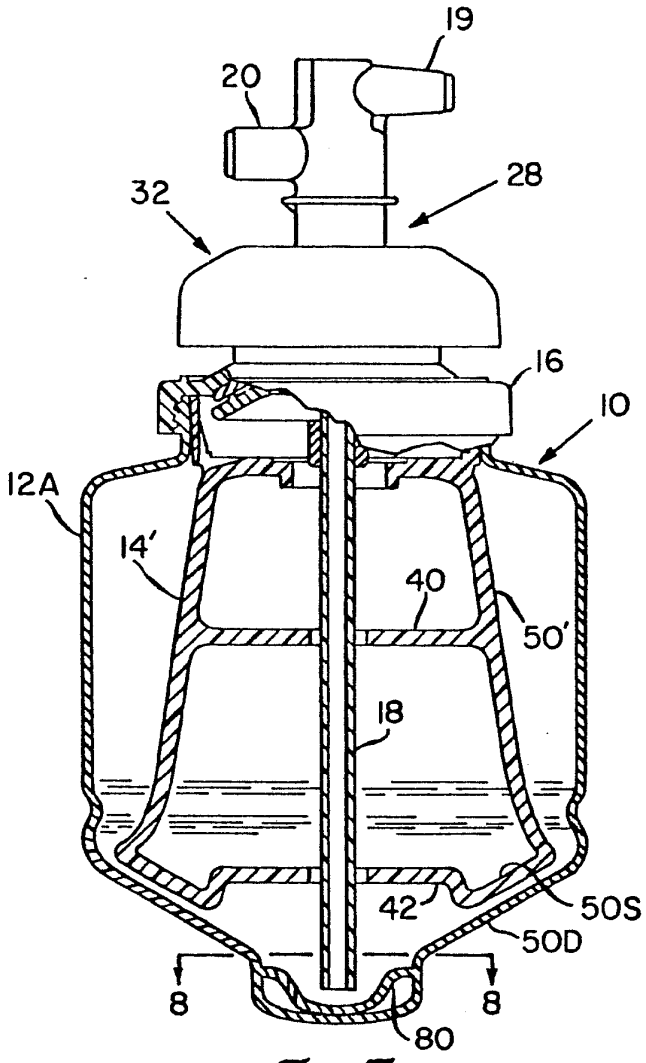


Fig. 7

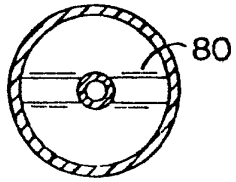


Fig. 8

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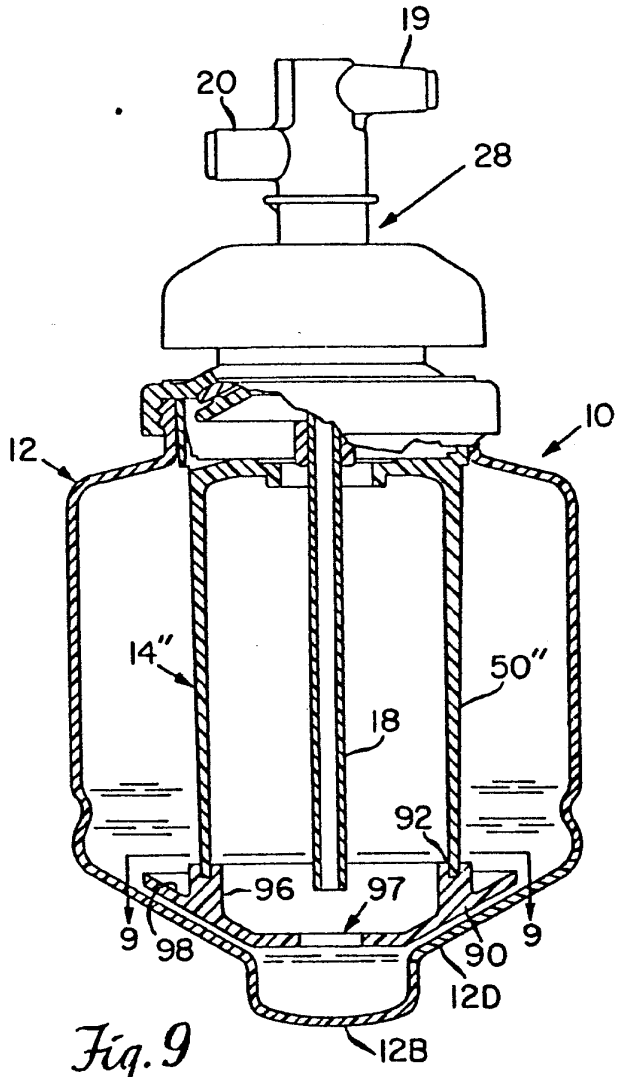


Fig. 9

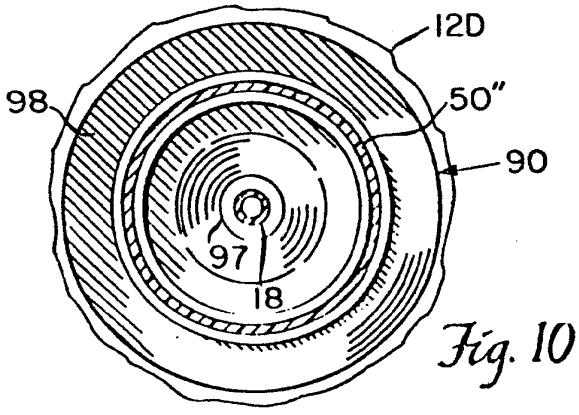


Fig. 10

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Petitioner Terumo Exhibit 1021-0410

0257755

European Patent Office

EUROPEAN SEARCH REPORT

Application number EP 87306082.6

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,A	US - A - 4 300 717 (A. LATHAM JR.) * Totality, especially fig. 1,6 *	1,8,10	A 61 M 1/36 B 04 B 7/02
D,A	US - A - 4 086 924 (A. LATHAM JR.) * Totality, especially fig. 4,5 *	1,8,10	
A	US - A - 4 140 268 (A. LA COUR) * Totality, especially fig. 1 *	1,8,10	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 M 1/00
B 04 B 1/00
B 04 B 7/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	23-11-1987	LUDWIG

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1503 03 82

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Petitioner Terumo Exhibit 1021-0411

Espacenet

Bibliographic data: EP0619145 (A2) — 1994-10-12

Rotary seal for centrifuge.

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Applicant(s): ELECTROMEDICS INC [US] ± (ELECTROMEDICS, INC, ; ELECTROMEDICS INC)

Classification: **- international:** ***A61M1/02; B04B1/02; B04B15/02; B04B5/04; B04B9/12;*** (IPC1-7): B04B15/02; B04B9/12
- cooperative: **B04B15/02; B04B5/0442; B04B9/12;** B04B2005/0464

Application number: EP19940630019 19940331 Global Dossier

Priority number (s): US19930043436 19930405

Also published as: EP0619145 (A3) JPH0775746 (A)

Abstract of EP0619145 (A2)

The rotary seal, embodying a rotary seal ring (11) and a stationary seal ring (42), for a centrifugal separator (14) including an imperforate bowl (12) has a seal ring hub (10) for supporting the rotary seal ring (11). The seal ring hub (10) is formed by an annular hub plate (50) defining a central shaft receiving opening (51). The plate (50) includes an axially extending annular lip (52) on its periphery and an axially extending annular rib (54) in spaced juxtaposition with the opening (51). A plurality of spaced apart chordally extending vanes (56) extend between the rib (54) and the lip (52) for stabilizing the plate (50) during rotation of the seal and providing a flow of cooling air around the rotary seal.

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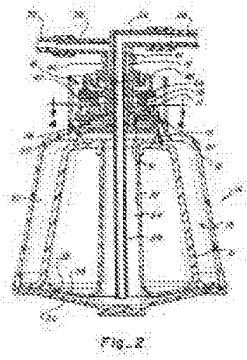


Fig. 2

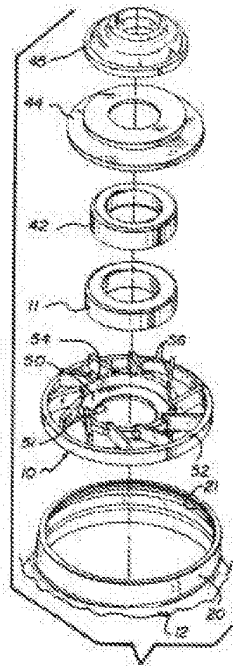


Fig. 5

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Office européen des brevets

(11) Publication number : **0 619 145 A2**

(12) EUROPEAN PATENT APPLICATION

(21) Application number : **94630019.1**

(51) Int. Cl.[5] : **B04B 9/12,** B04B 15/02

(22) Date of filing : **31.03.94**

(30) Priority : **05.04.93 US 43436**

(43) Date of publication of application :
12.10.94 Bulletin 94/41

(84) Designated Contracting States :
DE FR IT

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(54) Rotary seal for centrifuge.

(57) The rotary seal, embodying a rotary seal ring (11) and a stationary seal ring (42), for a centrifugal separator (14) including an imperforate bowl (12) has a seal ring hub (10) for supporting the rotary seal ring (11). The seal ring hub (10) is formed by an annular hub plate (50) defining a central shaft receiving opening (51). The plate (50) includes an axially extending annular lip (52) on its periphery and an axially extending annular rib (54) in spaced juxtaposition with the opening (51). A plurality of spaced apart chordally extending vanes (56) extend between the rib (54) and the lip (52) for stabilizing the plate (50) during rotation of the seal and providing a flow of cooling air around the rotary seal.

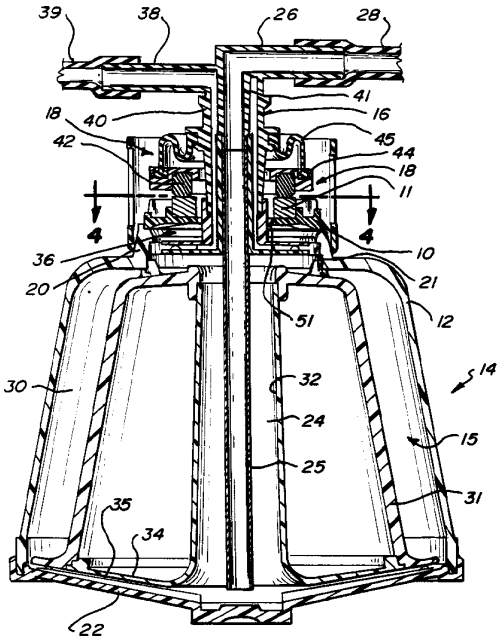


Fig_2

EP 0 619 145 A2

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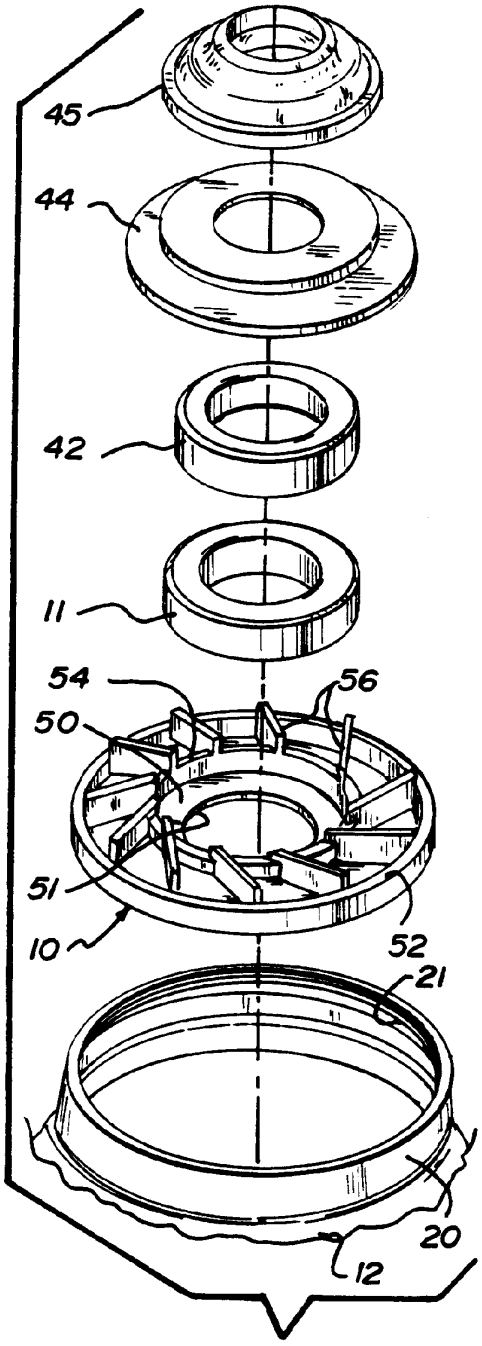


Fig_5

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BACKGROUND OF THE INVENTION

Field of the Invention.

The present invention relates to rotary seals for an imperforate bowl centrifuge. More specifically, the present invention relates to a rotary seal for a blood processing centrifuge separator bowl.

Description of the Prior Art.

Centrifuge bowls with rotary seals are old and well known in the art of processing blood. In this art, blood is separated into its red cell component and plasma component by a centrifuge utilizing an imperforate bowl which is rotated about a stationary tubular shaft through which whole blood is introduced into the bowl and blood fractions, particularly plasma and red blood cells are sequentially discharged from the bowl. An important part of the centrifuge apparatus is the rotary seal between the stationary shaft and rotating bowl to prevent the leakage of blood components as the bowl rotates.

U.S. Pat. No. 4,668,214, issued May 26, 1987, to G. Reeder, for Method of Washing Red Blood Cells, discloses a blood processing centrifuge which includes a rotating bowl and a rotary seal between the bowl and a stationary shaft. The rotary seal includes a rotating seal ring mounted in an annular metal plate or hub. The metal plate serves as a heat sink to cool the rotating seal ring. U.S. Pat. No. 4,300,717, issued November 17, 1981, to A. Latham, for Rotary Centrifuge Seal, discloses a centrifuge bowl and a rotary seal between the bowl and a stationary shaft. The rotary seal comprises an upper stationary seal ring supported in a metal adaptor ring secured to the stationary shaft and a lower ceramic rotary seal ring supported in a metallic adaptor ring secured to the rotatable imperforate centrifuge bowl. In order to conduct heat from the seal rings, the patent describes a rotary seal ring construction formed of a good heat conducting material such as metal which conducts heat away from the area of contact between the stationary and rotary rings. The use of ports in an outer shield to dissipate air currents for cooling is described. This patent also discloses the use of vanes on the upper external surface of the imperforate centrifuge bowl for purposes of dissipating heat generated by the seal.

Some commercial blood pheresis centrifuge bowls and seals utilize a metallic heat sink ring with the seal ring, both of which are supported on a plastic plate or hub secured to the centrifuge bowl.

The principal problems with the foregoing prior art devices are a lack of efficient cooling, the rotary seal rings tend to chatter, and the supporting hubs utilize expensive metals.

OBJECTS OF THE INVENTION

It is the principal object of the present invention to provide an improved rotary seal for a blood processing centrifuge bowl.

A more specific object is to provide an improved rotary seal of the foregoing character which is stable, does not chatter or rattle, and which provides an enhanced cooling effect for the rotary seal.

Another object of the present invention is to provide a rotary seal of the foregoing characteristics which is less expensive than present devices, and is lightweight, rugged, efficient in operation, and maintains a lower operating temperature.

SUMMARY OF THE INVENTION

In accordance with the foregoing objects, the present invention is embodied in an improved seal ring hub for supporting a rotary seal ring of a rotary seal. The rotary seal includes a rotary seal ring and a stationary seal ring for a centrifugal separator which has an imperforate bowl as a part thereof. The seal ring hub comprises an annular hub plate defining a central shaft receiving opening, an axially extending annular lip on its periphery, and an axially extending annular rib in spaced juxtaposition with the annular opening. The rib extends parallel to the lip and defines with the plate a seal ring supporting seat adjacent the opening. A plurality of spaced apart chordally extending vanes extend between the rib and the lip. The vanes extend axially beyond the lip and the rib and terminate adjacent the lip and overlie the rib. The vanes serve to stabilize the plate during rotation of the seal, and provide a flow of cooling air around the rotary seal.

DESCRIPTION OF THE DRAWINGS

Fig. 1 is a perspective view, partially cut away, of a blood treating centrifuge including an imperforate bowl and a rotating seal construction embodying the present invention.

Fig. 2 is an enlarged cross-section view of the centrifuge bowl, seal and shaft construction taken substantially in the plane of line 2-2 on Fig. 1.

Fig. 3 is an enlarged portion of the construction shown in Fig. 2 specifically showing the seal construction embodying the present invention.

Fig. 4 is a section view taken substantially in the plane of line 4-4 on Fig. 2.

Fig. 5 is a perspective exploded view of the seal construction shown in Fig. 3.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention is embodied in a support-

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ing plate or hub 10 mounting a rotary seal ring 11 and adapted to be secured to an imperforate outer bowl 12 of a centrifuge 14 suitable for the processing and separation of blood and blood components. The centrifuge 14 includes a bowl assembly 15 rotatably mounted on a stationary shaft assembly 16 and utilizing a rotary seal assembly 18 for preventing leakage of the blood and blood components between the rotary bowl assembly 15 and stationary shaft assembly 16.

The centrifuge assembly 14, as shown in Figs. 1 and 2 embodies a generally bell-shaped outer imperforate bowl 12 having an upper sleeve portion 20 defining an upper opening 21. The bottom of the bowl 12 is closed by a bottom plate 22 adapted to be operatively connected to a centrifuge motor (not shown). The bowl 12 and bottom plate 22 define a central cavity 24 into which an inlet tube 25 forming a part of the stationary shaft assembly 16 extends. The tube opens at the lowermost end of the cavity 24 and at its upper end is provided with an inlet tube 26 connected to an inlet line 28 extending to a pump (not shown) which serves to pump whole blood into the separator bowl.

For forming an outer circumferential separating chamber 30, a central conical-shaped bowl or core 31 is mounted within the outer shell 12. The central core 31 includes a central passage 32 through which the inlet tube 25 extends. The central core 31 is provided with a bottom plate 34 positioned adjacent but spaced from the bottom plate 22 to define a separating passage 35 therebetween which opens into the outer circumferential separating chamber 30.

For discharge of separated blood components, the separating chamber 30 opens at the upper end of the centrifuge bowl assembly 14 into an outlet chamber 36 defined between the sleeve portion 20 of the outer bowl 12 and the seal ring hub or plate 10.

For exhausting blood components to an outlet conduit 38 connected to an outlet tube 39, a stationary sleeve 40 defines with the inlet tube 25 an annular outlet passage 41. The stationary tube 40 and inlet tube 25 define a stationary shaft which is supported on the centrifuge mounting apparatus (not shown).

For providing a seal between the stationary shaft assembly 16 and the rotating centrifuge bowl assembly 15 the rotating seal assembly 18 includes a stationary seal ring 42 which is rotatingly engaged by the rotary seal ring 11. The stationary seal ring 42 is supported in a stationary hub 44 mounted on the shaft assembly 16 and sealed thereto by a flexible diaphragm 45.

Because the contacting faces of the stationary and rotary seal rings respectively generate heat during operation of the centrifuge, the present invention provides an improved heat dissipation and seal ring stabilizing structure. To this end, the seal ring mounting hub or plate comprises an annular plate 50 adapted to be secured adjacent its outer peripheral edge to the upstanding sleeve portion 20 of the outer centrifuge housing 12. The annular hub plate 50 defines a central shaft receiving opening 51 surrounding the stationary shaft assembly 16. On its upper surface, the seal ring hub 50 defines an axially extending annular lip 52 adjacent its outer peripheral edge and an intermediate axially extending annular rib 54 parallel and concentric with the lip 52 and being positioned in spaced juxtaposition with the central annular opening 51. The rib 54 and upper surface 55 of the annular plate defines a seat for supporting the rotary seal ring 11 in position for rotating engagement with the stationary seal ring 42 secured to the stationary shaft assembly 16. For purposes of cooling the rotary seal formed by the seal rings 11, 42, a plurality of equally circumferentially spaced chordally arranged vanes 56 are mounted integrally with the mounting plate or hub 50 and extend between the outer lip 52 and the seat defining rib 54. In the modification shown, the vanes overlie the inner annular rib 54 but terminate short of the outer annular lip 52.

The vanes provide both a cooling effect on the rotary seal as well as a stabilizing effect on the seal ring supporting plate 50 preventing chatter or rattling of the seal rings.

While a certain illustrative embodiment of the present invention has been shown in the drawings and described above in detail, it should be understood that there is no intention to limit the invention to the specific form disclosed. On the contrary, the intention is to cover all modifications, alternative constructions, equivalents, and uses falling within the spirit and scope of the invention as expressed in the appended claims.

Claims

1. In a rotary seal for a centrifugal separator including an imperforate bowl rotatable about a central shaft, said rotary seal embodying a rotary seal ring and a stationary seal ring, a seal ring hub for supporting said rotary seal ring comprising an annular hub plate defining a central shaft receiving opening, an axially extending annular rib on said plate in spaced juxtaposition with said opening, said rib defining with said plate a seal ring supporting seat adjacent said opening, and a plurality of spaced apart vanes extending outwardly from said rib for stabilizing said plate during rotation of said seal and providing a flow of cooling air around said rotary seal.

2. In a rotary seal for a centrifugal separator including an imperforate bowl rotatable about a central shaft, said rotary seal embodying a rotary seal ring and a stationary seal ring, a seal ring hub for

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supporting said rotary seal ring comprising an annular hub plate defining a central shaft receiving opening, an axially extending annular lip on the periphery of said plate, an axially extending annular rib on said plate in spaced juxtaposition with said opening, said rib extending parallel to said lip and defining with said plate a seal ring supporting seat adjacent said opening, and a plurality of spaced apart vanes extending between said rib and said lip for stabilizing said plate during rotation of said seal and providing a flow of cooling air around said rotary seal.

3. In a rotary seal ring of a rotary seal for a centrifugal separator including an imperforate bowl rotatable about a central shaft, said rotary seal embodying a rotary seal ring and a stationary seal ring, a seal ring hub for supporting said rotary seal ring comprising an annular hub plate defining a central shaft receiving opening, an axially extending annular lip on the periphery of said plate, an axially extending annular rib on said plate in spaced juxtaposition with said opening, said rib extending parallel to said lip and defining with said plate a seal ring supporting seat adjacent said opening, and a plurality of spaced apart chordal vanes extending between said rib and said lip, said vanes extending axially beyond said lip and said rib for stabilizing said plate during rotation of said seal and providing a flow of cooling air around said rotary seal.

4. In a rotary seal for a centrifugal separator including an imperforate bowl rotatable about a central stationary shaft, said rotary seal embodying a rotary seal ring and a stationary seal ring, a seal ring hub for supporting said rotary seal ring comprising an annular hub plate defining a central shaft receiving opening, an axially extending annular lip on the periphery of said plate, an axially extending annular rib on said plate in spaced juxtaposition with said opening, said rib extending parallel to said lip and defining with said plate a seal ring supporting seat adjacent said opening, and a plurality of spaced apart chordal vanes extending between said rib and said lip, said vanes extending axially beyond said lip and said rib and terminating adjacent said lip and overlying said rib for stabilizing said plate during rotation of said seal and providing a flow of cooling air around said rotary seal.

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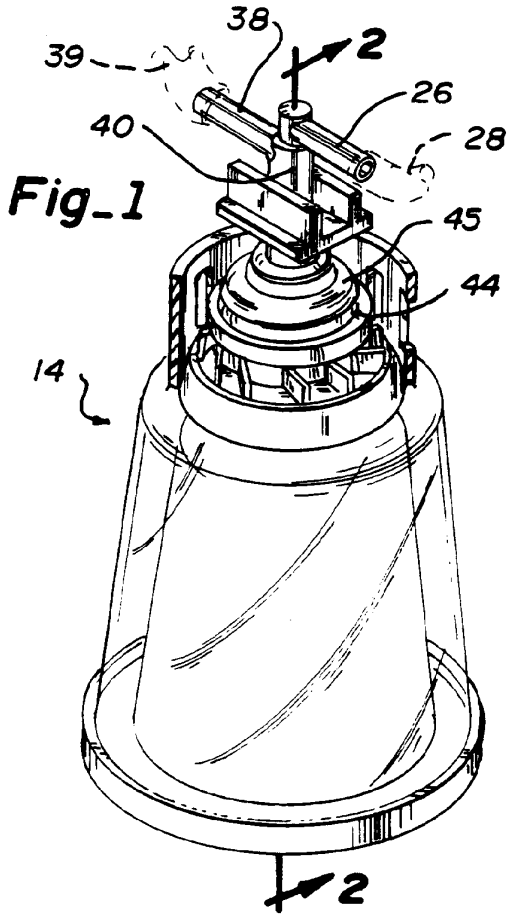


Fig_1

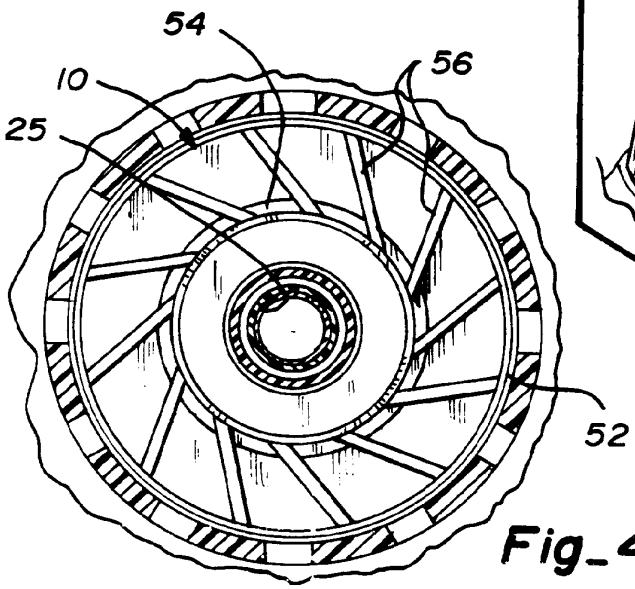


Fig_4

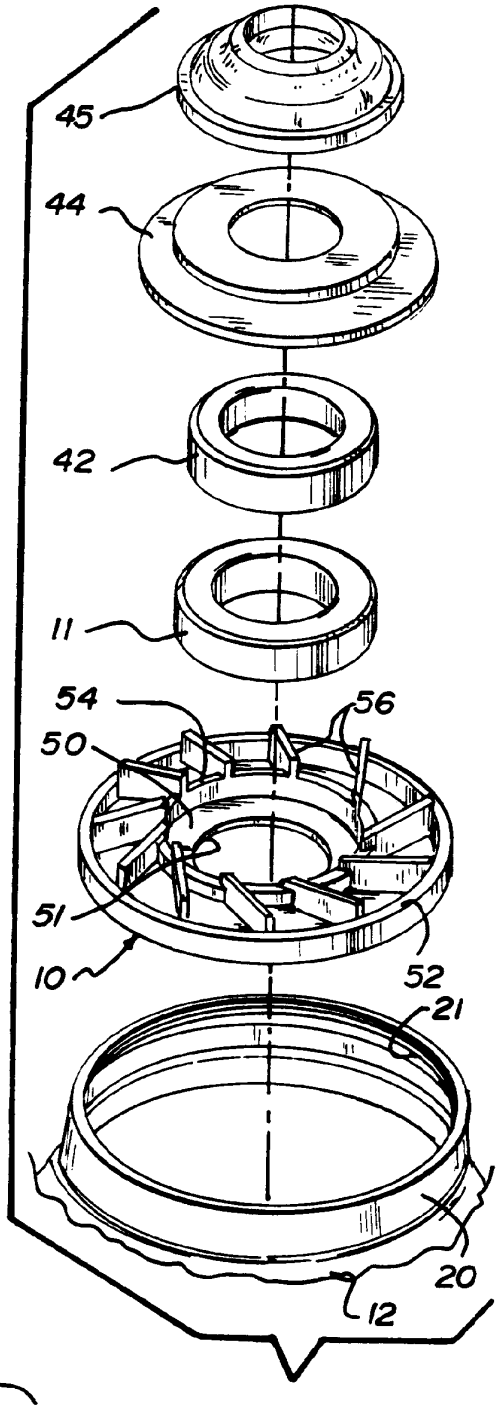


Fig_5

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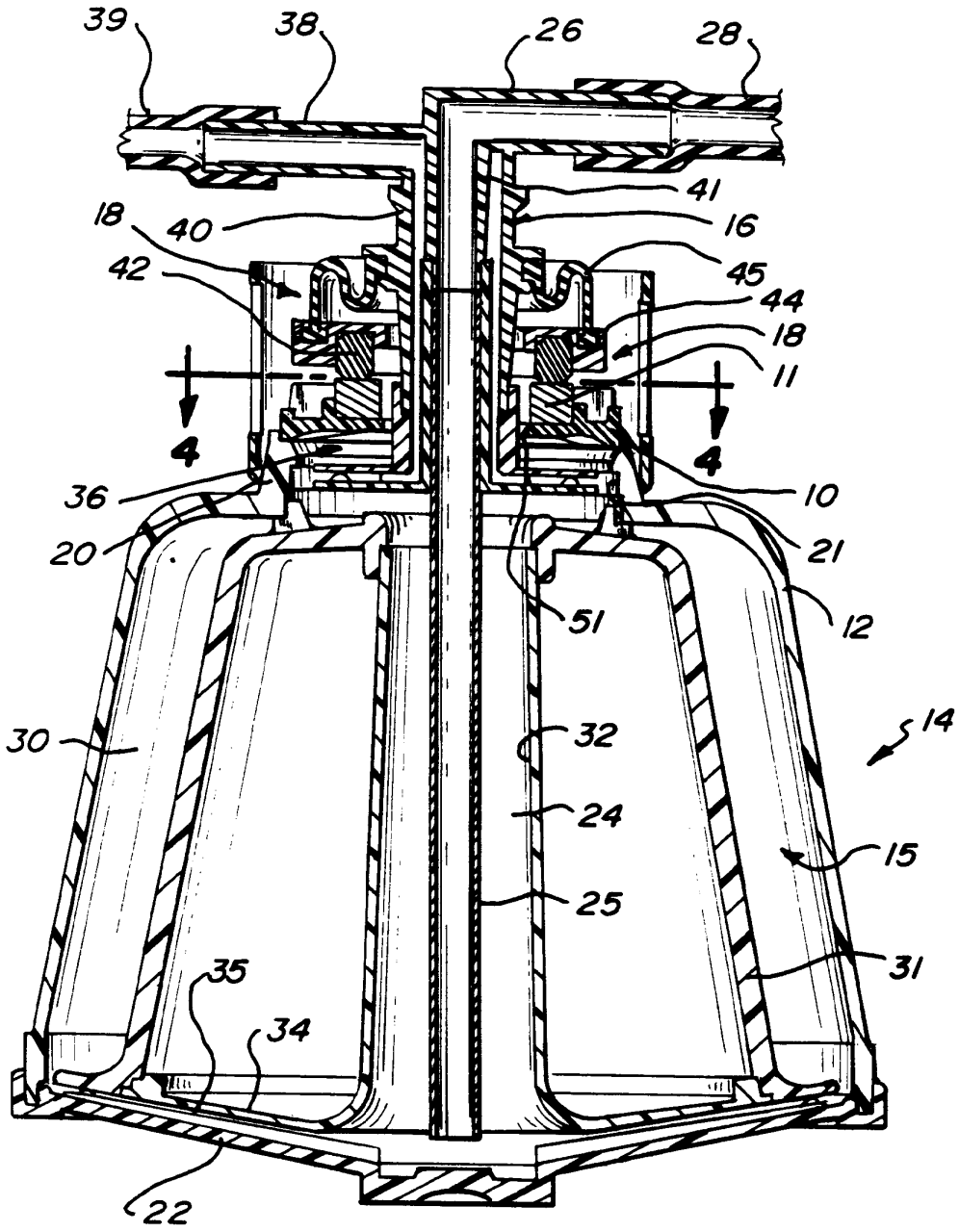


Fig_2

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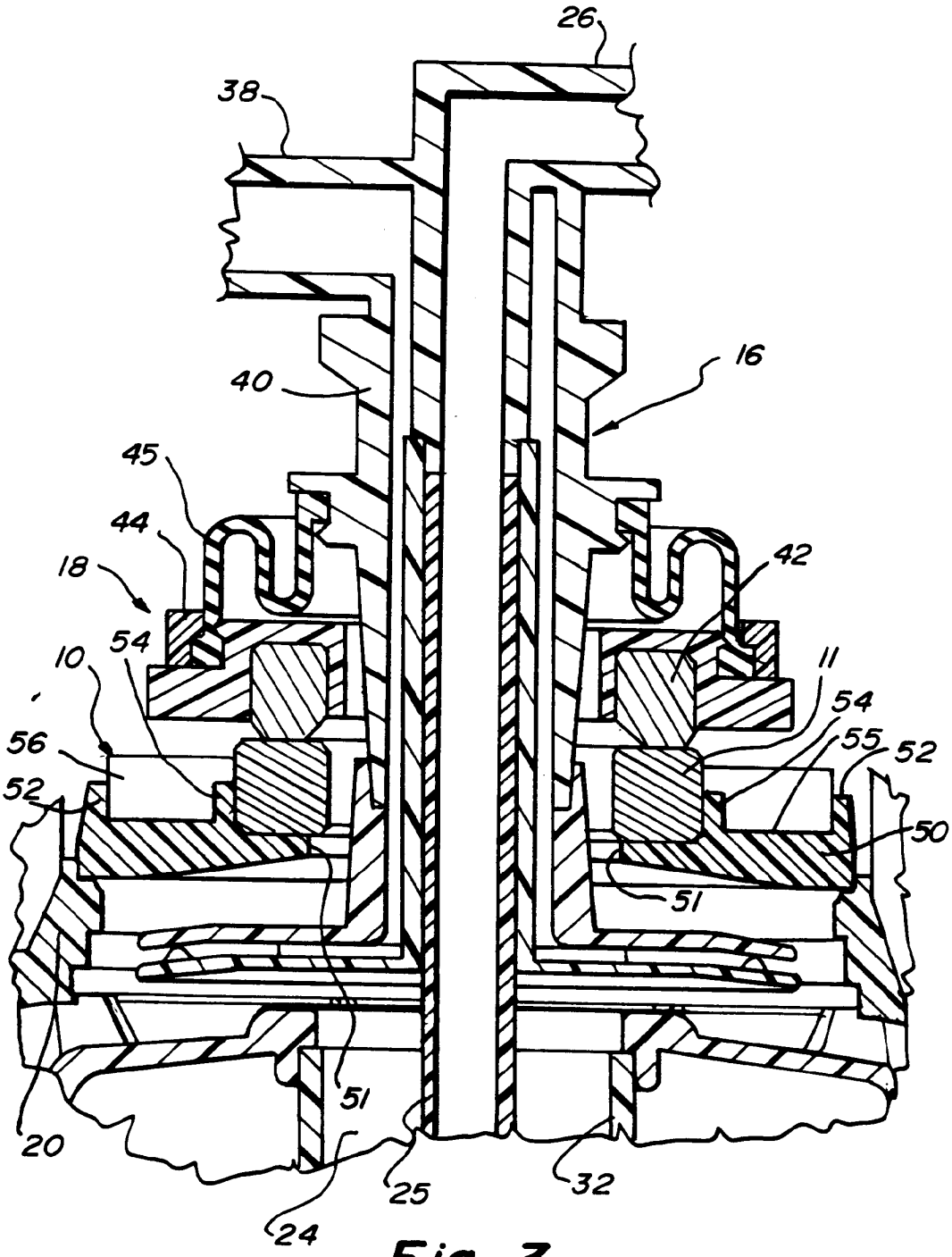


Fig_3

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Petitioner Terumo Exhibit 1021-0421

Espacenet

Bibliographic data: EP0664159 (A1) — 1995-07-26

Plural collector centrifuge bowl for blood processing.

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Applicant(s): HAEMONETICS CORP [US] ± (HAEMONETICS CORPORATION)

Classification: **- international:** ***A61M1/02; B04B1/02; B04B5/04; B04B7/08;*** (IPC1-7): B04B5/04; B04B7/08
- cooperative: **A61M1/3693**; **A61M1/3696**; **B04B5/0442**; **B04B7/08**; B04B2005/0464

Application number: EP19940309334 19941214 Global Dossier

Priority number (s): US19940184677 19940121

Also published as: JPH07284529 (A) US5514070 (A)

Abstract of EP0664159 (A1)

A centrifuge bowl (10) and process for separating whole blood into less dense components (plasma, platelets, etc.), and more dense components (RBC), and collecting both less dense and more dense components without stopping bowl rotation. This is accomplished by having upper and lower radially extending passageways (P1, P2) with equal radial extensions which permit reversal of fluid flow direction without spillage.

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Petitioner Terumo Exhibit 1021-0422

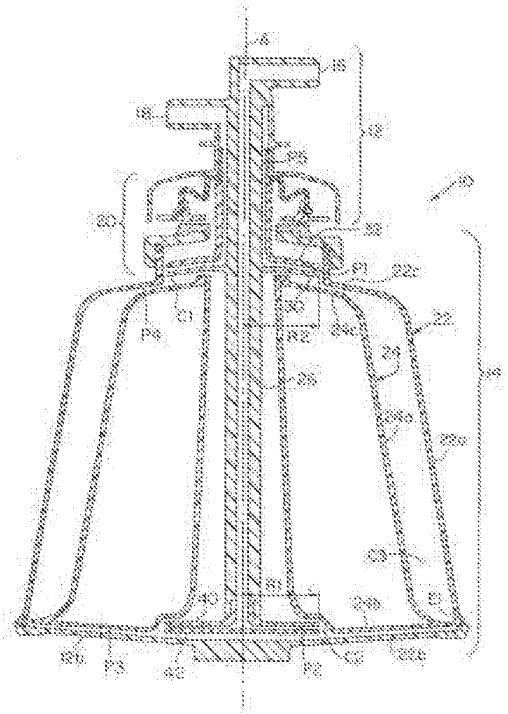


Fig 1

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0423

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 664 159 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **94309334.4**

(51) Int. Cl.6: **B04B 5/04**, B04B 7/08

(22) Date of filing: **14.12.94**

(30) Priority: **21.01.94 US 184677**

(43) Date of publication of application:
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(84) Designated Contracting States:
DE FR GB IT

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(54) Plural collector centrifuge bowl for blood processing.

(57) A centrifuge bowl (10) and process for separating whole blood into less dense components (plasma, platelets, etc.), and more dense components (RBC), and collecting both less dense and more dense components without stopping bowl rotation. This is accomplished by having upper and lower radially extending passageways (P1, P2) with equal radial extensions which permit reversal of fluid flow direction without spillage.

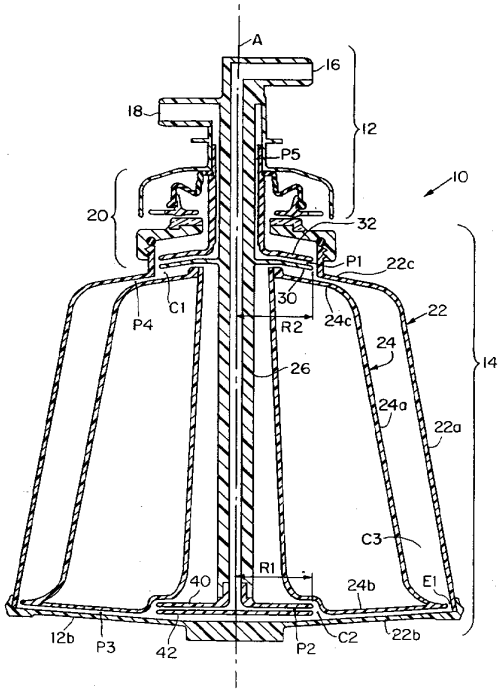


Fig. 1

EP 0 664 159 A1

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Background of the Invention

In 1968 a disposable blood processing bowl was introduced by the inventor, Allen Latham, Jr., in a paper entitled "A New Approach to Automated Centrifugal Processing of Blood" at the 21st Annual Meeting of the American Association of Blood Banks. Mr. Latham described a system for processing blood using an expendable, or disposable, centrifuge rotor in the form of a relatively inexpensive bowl. The system was proposed for use in a number of pheresis procedures, such as plasmapheresis and plateletpheresis. In these processes, whole blood is taken from a donor and various blood components are separated from the whole blood and harvested while some components are returned to the donor. The system was also suggested for use in cell washing, such as in deglycerization, in which thawed deglycerized red cells are washed to remove the glycerine preservative before being infused in a patient.

In operation, the bowl is held in a chuck which is attached to a spindle and driven by a motor. The bowl consists of a rotor, or bowl body portion in which blood component is separated and a stator portion consisting of an input and output port. A rotary seal couples the stator to the rotor. One side of the input port is connected through a first peristaltic pump to a source of whole blood from a donor and the other side is in fluid communication with a fractionation volume in the rotor. Anticoagulant is mixed with the whole blood prior to entry into the centrifuge bowl.

The rotor is rotated at a fixed speed and various blood fractions are collected at the output port and directed into appropriate containers, such as plastic bags, by diverting the flow through plastic tubing in accordance with the setting of three-way clamp/switches.

Fractionation within the centrifuge is determined by the relative densities of the different cell components being separated and collected. The various cell fractions pass through the outlet port of the centrifuge bowl by progressive displacement from the lower portion of the bowl.

The bowl consists of two major components. One is a rotatable bowl body with an inner core mounted coaxial to a central longitudinal axis through the bowl body. The other is a rotary seal and header assembly, which is provided on top of the bowl body.

The bowl body is divided into two chambers, the first is an upper collection chamber adjacent an upper radially extending collection passageway leading to the output port. The second is a separation chamber formed between the longitudinally extending cylindrical wall of the core and the side wall of the bowl body.

Anticoagulated whole blood introduced to the bowl body via the fixed input port is coupled to the bottom of the bowl body by a fixed inlet tube coupled to the input port and extending longitudinally therefrom along a central longitudinal axis to the bottom wall of the bowl body. Whole blood is coupled to the separation chamber via one or more radially extending introduction passageways formed between an inner surface of the lower bowl body wall and a lower radially extending wall of the core which extends in parallel to the lower bowl body wall leaving a narrow entrance at the extended outer diameter of the bowl for introduction of whole blood from the introduction chamber into the separation chamber. Separated less dense whole blood component in the separation chamber is coupled to the collection chamber via a passageway formed between radially inwardly extending wall portions of the core and bowl body leading to the upper collector passageway and through the output port. The upper collector passageway is formed by a pair of opposed radially outwardly extending members which lead to a longitudinally extending coaxial passageway coupled to the outlet port. The header assembly must remain fixed, since the inlet and outlet tubing to, or from, a donor or patient, is coupled to it. The rotary seal provides an appropriate interface between the fixed header and the rotating bowl body. The system, including the bowl, interconnecting tubing and receptacles, are connected together and sterilized in advance of use, so that they arrive in sterile form ready for immediate use. All parts, other than the rotary seal assembly, are generally made from blood-compatible plastic, such as polycarbonate (for the bowl), or polyethylene (for the tubing and receptacles). One of the disadvantages of the centrifuge bowls described above is that, when the last of the less dense components, i.e. plasma, platelets, etc., are being displaced by passage through the outlet port, the supply of an anticoagulated whole blood must be interrupted to prevent the outflow of the more dense components, i.e., red blood cells (RBC). The centrifuge is stopped leaving concentrated RBC in the bowl which are then collected by suctioning out through the inlet port prior to commencing another separation cycle. As noted by Panzani in U.S. 4,859,333 this interruption is particularly disadvantageous in the case of intraoperative autotransfusion where whole blood is washed and RBC separated for rapid reinfusion. Panzoni's solution to this problem is to add a third port 12(a) connected to an additional central conduit 12 which extends to the bottom of the bowl and which is sealed from the conventional inlet tubing by a gasket 13. (U.S. 4,859,333 Col. 4, lines 9-20). A vacuum or negative pressure is applied to the third port where it is desired to collect RBC which are drawn up the

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additional conduit 12 which is in communication with bottom passage 16, which is in the peripheral communication with outer passage 7 where the concentrated RBC are located (U.S. 4,859,333, Col. 4, lines 42-54).

Summary of the Invention

In accordance with the present invention an additional passageway is provided at the bottom of the centrifuge bowl to enable collection of the denser fraction (e.g. RBC) of whole blood component separated in the bowl.

This additional passageway is formed by providing a radially outwardly extending communication channel or passageway at the distal end of the fixed inlet tube. This radial extension is formed by upper and lower planar disc-like members which depend from the distal end of the inlet tube and extend outwardly to an introduction chamber formed at the bottom of the bowl. The members extend radially outwardly the same distance as the upper collector passageways in the conventional prior art centrifuge bowl described above. When desired, more dense blood component can be collected while the bowl is rotating by introducing less dense component fluid or a physiological solution fluid, such as, saline into the conventional output port. Fluid entering the outlet port travels in a reverse direction to the separation chamber which forces more dense component out the separation chamber to the introduction chamber, out the additional passageway at the distal end of the input tube, and from there out the input port for collection or harvesting.

Brief description of the Drawing

Figure 1 is a front elevational view in section illustrating the structure of a first embodiment of the invention:

Figure 2 is a front elevational view of a second embodiment of the invention.

Detailed Description of the Invention

A first embodiment of the invention will now be described in connection with Figure 1.

The centrifuge bowl is held in a chuck (not shown) which is attached to a spindle and driven by a motor (also not shown). The bowl consists of a rotor, or bowl body portion 14 in which blood component is separated and a stator portion 12 consisting of an input port 16 and output port 18. A rotary seal 20 couples the stator 12 to the rotor 14. One side of the input port is connected through a first peristaltic pump (not shown) to a source of whole blood from a donor and the other side is in fluid communication with a fractionation volume in the rotor 14. Anticoagulant is mixed with the whole blood prior to entry into the centrifuge bowl.

The rotor 14 is rotated at a fixed speed and various blood fractions are collected at the output port 18 and directed into appropriate containers (not shown), such as plastic bags, by diverting the flow through plastic tubing in accordance with the setting of three-way clamp/switches (not shown).

Fractionation within the centrifuge bowl is determined by the relative densities and sizes of the different cell components being separated and collected. The various cell fractions pass through the outlet port 18 of the centrifuge bowl by progressive displacement from the lower portion of the bowl.

The bowl 10 consists of two major components. One is the rotatable bowl body, per se, 22 with an inner conical core 24 mounted coaxial to a central longitudinal axis A through the bowl body. The other is a rotary seal and header assembly 12, which is provided on top of the bowl body 14.

The bowl body 14 is divided into three chambers Cl, C2 and C3. The first chamber, Cl, is an annular upper collection chamber adjacent an upper radially extending collection passageway Pl leading to the output port 18. The second chamber, C2, is a lower annular introduction chamber adjacent a lower radially extending collector passageway P2 at the distal end of an inlet tube 26 at the bottom of the bowl. The third chamber, C3, is a separation chamber formed between a tapered longitudinally extending cylindrical wall 24a of the core and a side wall 22a of the bowl body.

Chambers C1 and C2 are interconnected to Chamber C3 by passageways P4 and P3, respectively, formed between bowl body walls and core walls. Anticoagulated whole blood introduced to the bowl body 14 via the fixed input port 16 is coupled to the bottom of the bowl body by the fixed inlet tube 26 which extend along central longitudinal axis A to the lower introduction chamber C2.

Whole blood in the introduction chamber C2 is coupled to the separation chamber C3 via one or more radially extending introduction passageways P5 formed between an inner surface of the lower bowl body wall 22b and a lower radially extending wall 24b of the core which extends in parallel with the lower bowl body wall 22b leaving a narrow entrance E1 at the extended outer diameter of the bowl for introduction of whole blood from the introduction chamber C2 into the separation chamber C3.

Separated less dense whole blood component in the separation chamber C3 is coupled to the collection chamber Cl via passageway P4 formed between radially inwardly extending wall portions 24C and 22C, respectively, of the core and bowl body leading toward the upper collector passage-

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way PI and thence through the output port 18. The upper collector passageway PI is formed by a pair of opposed radially outwardly extending and inclined members 30, 32 which lead to a longitudinally extending coaxial passageway P5 coupled to the outlet port 18.

Preferably, the centrifuge system, including the bowl 10, interconnecting tubing and receptacles, are connected together and sterilized in advance of use, so that they arrive in sterile form ready for immediate use. All parts, other than the rotary seal assembly, are generally made from blood-compatible plastic, such as polycarbonate (for the bowl), or polyethylene (for the tubing and receptacles).

In accordance with the present invention passageway P2 provided at the bottom of the centrifuge bowl, in conjunction with the adjacent introduction chamber C2, enables collection of the denser fraction (e.g. RBC) of whole blood component separated in chamber C3.

This additional passageway P2 is formed by providing a radially outwardly extended communication channel or extension 38 at the distal end of the fixed inlet tube. This radial extension 38 is formed by upper and lower planar disc-like members 40 and 42 which depend from the distal end of the inlet tube 26 and extend outwardly the same radial distance R1' as the radial extension R2' of the upper collector passageway P1 in the conventional prior art centrifuge bowl described above.

When desired, the more dense blood component, such as RBC, can be collected while the bowl is rotating by introducing the less dense component fluid, such as, plasma or a physiological solution fluid, such as, saline into the conventional output port 18. Fluid entering the outlet port 18 travels in a reverse direction down coaxial passageway P5, through radial passageway P1, through collection chamber CI, radial passageway P4 and into the separation chamber C3; which forces the more dense component out of separation chamber C3 through radial passageway P5 to the introduction chamber C2. From C2, the fluid passes out the additional passageway P2 at the distal end of the input tube 26 and from there out the input port 16 for collection or harvesting.

In the alternate embodiment of Fig. 2 like parts carry the same reference numbers with a prime suffix. In view of the general similarity between Figs. 1 and 2 only the differences will be described in detail.

The general bowl configuration in Fig. 2 is similar to the bowl shown in U.S. Patent 4,943,273 issued July 24, 1990 (and incorporated herein by reference). Whereas the Fig. 1 bell-shaped bowl configuration is similar to that described in U.S. Patent 5,045,048 issued September 3, 1991 (also incorporated herein by reference).

The main differences are as follows:

In the Fig. 2 bowl, the core 24' is formed of a thick molded cylindrical longitudinally extending side wall 24a' and upper and lower radially extending walls 24c'and 24b', respectively.

Lower wall 24b' extends radially outwardly from wall 24a' and upper wall 24c' extends radially inwardly from wall 24a'. The lower collective chamber C2' is located at the outlet of passageway P2' and is coupled to separation chamber C3' via passageway P5' formed between core wall 24b' and radially outward inclined bowl wall 22d.

Separation chamber C3' is coupled to collection chamber C1' by passageway P4' formed in upwardly extending circular core wall 24e.

As in Fig. 1, the radial extensions R1 and R2 of passageways P2' and P1', respectively, are made equal to allow reverse flow of fluid through the chambers while the bowl is spinning.

This completes the description of preferred embodiments of the invention.

Possible applications for the invention include:

a) Plasma collection, in which the extra corporeal volume (ECV) is minimized along with platelet contamination.

When the prior art bowls are used for plasmaphereses, several centrifuge collection cycles are required to collect about 600 ml. of plasma. This is because the bowl volume is less than the volume of RBC's associated with 600 ml. of plasma. As a consequence the "buffy coat," which is composed of platelets and white cells, reaches the collection chamber CI several times, thereby contaminating the plasma exiting the bowl.

By way of contrast, in the present invention RBC's can be removed before the layer of platelets reaches the collection chamber C1, thereby minimizing contamination of the plasma and allowing a smaller bowl to be used without multiplying the number of centrifuge braking collection cycles.

b) Platelet or leukocyte collection in which ECV is minimized while allowing Buffy Coat growth.

With the prior art bowl operated in a "surge" protocol and the platelet collection is the result of two steps: the "buffy coat" grows while the bowl is filling, and this buffy coat is elutriated by the surge process from its fixed position in the bowl to the effluent line through the collection chamber. The limitations of the platelet collection (White blood cell contamination, platelet efficiency) is in the buffy coat size at the moment of the surge. This buffy coat size is itself limited by the volume processed per cycle.

The new bowl allows one to process more whole blood, even with a smaller bowl volume, to grow a single "buffy coat".

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c) Cell saving in which high hematocrit washed RBC can be pumped out, whatever the volume processed, so that one bowl volume design can be used for all cell washing applications.

d) RBC collection, in which the contamination with platelets and white blood cells could be minimized. After the plasma collection has been done, the RBC's could be collected without disturbing the "buffy coat" by introducing preservative solution into the bowl.

Equivalents

Those skilled in the art will know, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention. For example, the difference between the so called cell collection and the introduction chambers C1 and C2 respectively is not in the function of collecting or introducing blood product from or into the separation chamber. The difference is in the fact that the collection chamber C1 allows the collection of separated components from the less dense to the more dense, and that the introduction chamber C2 allows the converse.

Another way to differentiate the collection chamber C1 from the introduction chamber C2 is that the entrance/exit E1 from/to passageway P5 is at the maximum radius of the separation chamber C3 while the entrance/exit from/to passageway P4 is at the minimum radius of the separation chamber C3.

Also note that the volumes of the C1 and C2 chambers should be small (an order of 1/10) compared to the volume of the separation chamber C3.

These and all other equivalents are intended to be encompassed by the following claims.

Claims

1. A blood processing centrifuge bowl for separating whole blood into more dense and less dense components comprising:

(a) a bowl body rotatable about a longitudinal axis and having:

(i) an upper wall radially extending from said axis;

(ii) a lower wall radially extending from said axis; and

(iii) a side wall connected to the upper and lower side walls and an aperture formed through the upper wall;

(b) a rotary seal assembly covering said aperture with a stator side and a rotor side, wherein the rotor side is attached to the bowl body;

(c) an inlet port and an outlet port each attached to the stator side of the seal assembly;

(d) a core, within the bowl body, having a side wall which extends longitudinally to a distal end and upper and lower radially extending walls;

(e) a separation chamber defined by the side wall of the bowl body and the side wall of the core;

(f) an inlet tube extending longitudinally from the inlet port to a distal end adjacent the lower wall of the bowl body;

(g) an introduction chamber formed adjacent the upper wall of the core and the upper walls of the bowl body;

(h) a collection chamber formed adjacent the distal end of the core side walls and a portion of the lower wall of the bowl body;

(i) an upper radially extending collection passageway fluidly coupling the separation chamber to the outlet port;

(j) a lower radially extending collection passageway fluidly coupling the introduction chamber to the distal end of the inlet tube; and

(k) a lower radially extending separation passageway fluidly coupling the lower collection chamber to the separation chamber.

2. The centrifuge bowl of Claim 1 wherein the radial extension of the upper and lower collection passageways have the same radius.

3. The centrifuge bowl of Claim 2 wherein the upper and lower passageways are each formed of two planar annular opposed upper and lower members.

4. The centrifuge bowl of Claim 3 wherein the upper member of the lower passageway is affixed to the distal end of the inlet tube transverse thereto with an aperture formed in the upper member into which said tube extends in fluid communication.

5. The centrifuge bowl of Claim 1 wherein the core depends from the bowl body upper wall concentric with the aperture and includes, in addition to said longitudinally extending cylindrical side wall, a radially inner wall which extends longitudinally and concentric to said inlet tube.

6. The centrifuge bowl of Claim 5 wherein the lower wall of the core connects the distal ends of the inner core wall with the cylindrical side wall of the core.

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7. The centrifuge bowl of Claim 1 wherein the lower radially extending core wall extends outwardly from the distal end of the core side wall to a location proximal to the bowl body side wall.

8. The centrifuge bowl of Claim 7 wherein the bowl body includes lower inclined walls connecting the lower bowl body walls to the bowl body side wall.

9. The centrifuge bowl of Claim 8 wherein the lower collection passageway is disposed at a region of the bowl body proximal to the connection between the lower bowl body wall and the bowl body side walls.

10. The centrifuge bowl of Claim 1 wherein the side wall of the bowl body is bell-shaped.

11. A method of processing whole blood to separate the whole blood into more dense and less dense components comprising the steps of:

a) introducing the whole blood into a centrifuge bowl which is rotatable about a central longitudinal axis, via an input port extending to an input tube disposed coaxial to said axis to couple said whole blood to a lower radially outwardly extending collection passageway;

b) coupling the whole blood from said lower collection passageway to a radially adjacent introduction chamber;

c) coupling the whole blood from said introduction chamber to a radially outward separation chamber where said whole blood is separated into less dense and more dense components;

d) coupling less dense components to an upper collection chamber:

e) coupling less dense components from the upper collection chamber to an outlet port via an upper radially inwardly extending collection passageway leading to said outlet port, and;

f) when desired, reversing the flow of components through said bowl by introducing less dense fluid into said outlet port while terminating step (a) and collecting more dense component at the input port.

12. The method of Claim 11 wherein the more dense component is red blood cells.

13. The method of Claim 11 wherein the radial length of the extensions of said upper and lower collection passageway is equal.

14. The method of Claim 11 wherein the upper and lower collection passageways are each formed of two planar annular opposed upper and lower members.

15. The method of Claim 11 including joining the upper member of the lower passageway to the distal end of the input tube transverse thereto and forming an aperture in the upper member into which said tube extends in fluid communication.

16. The bowl of Claim 1 wherein the core side wall is conical or cylindrical.

17. The bowl of Claim 1 wherein the introduction chamber and the collection chamber is much smaller in volume than the separation chamber.

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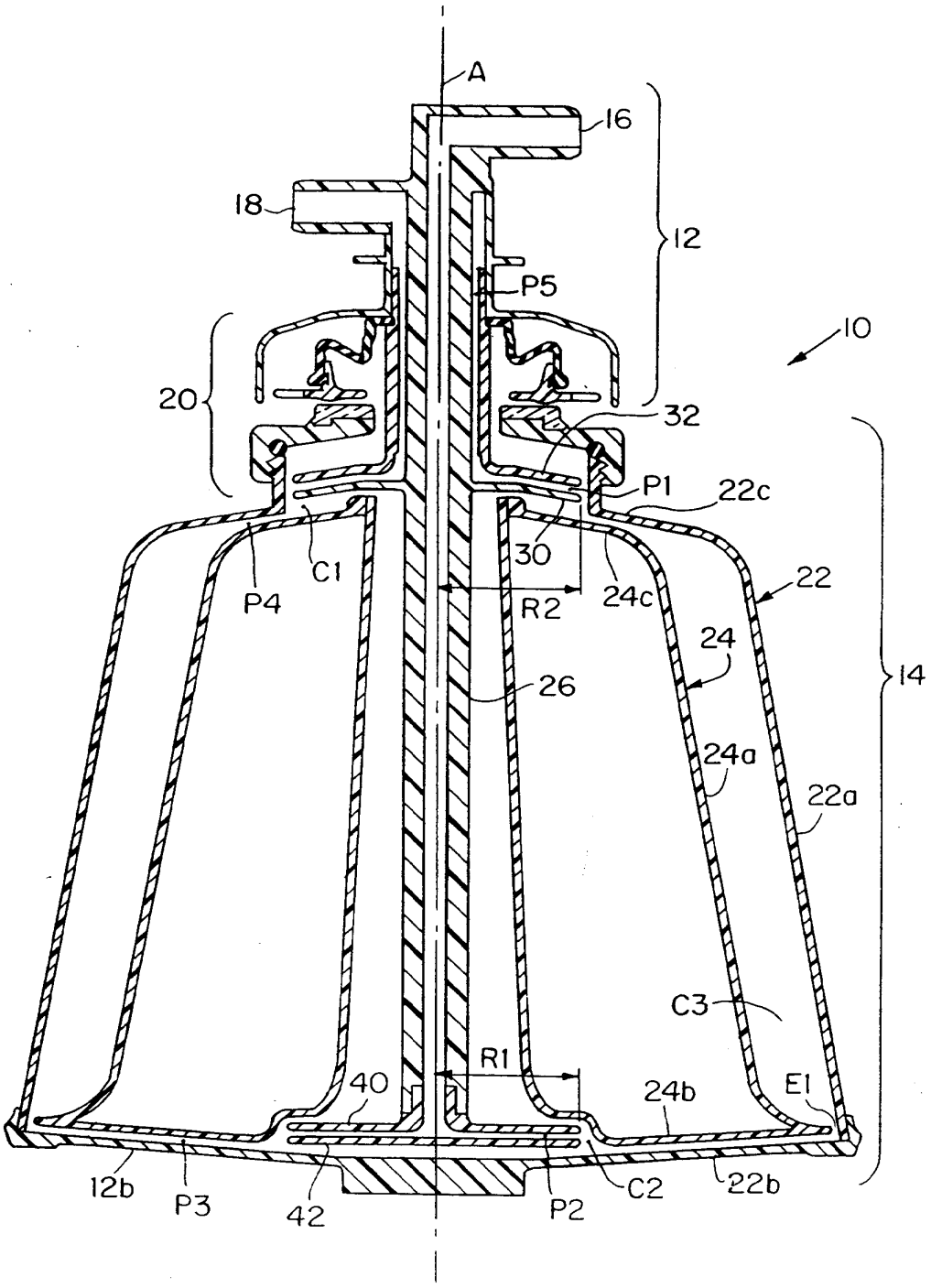


Fig. 1

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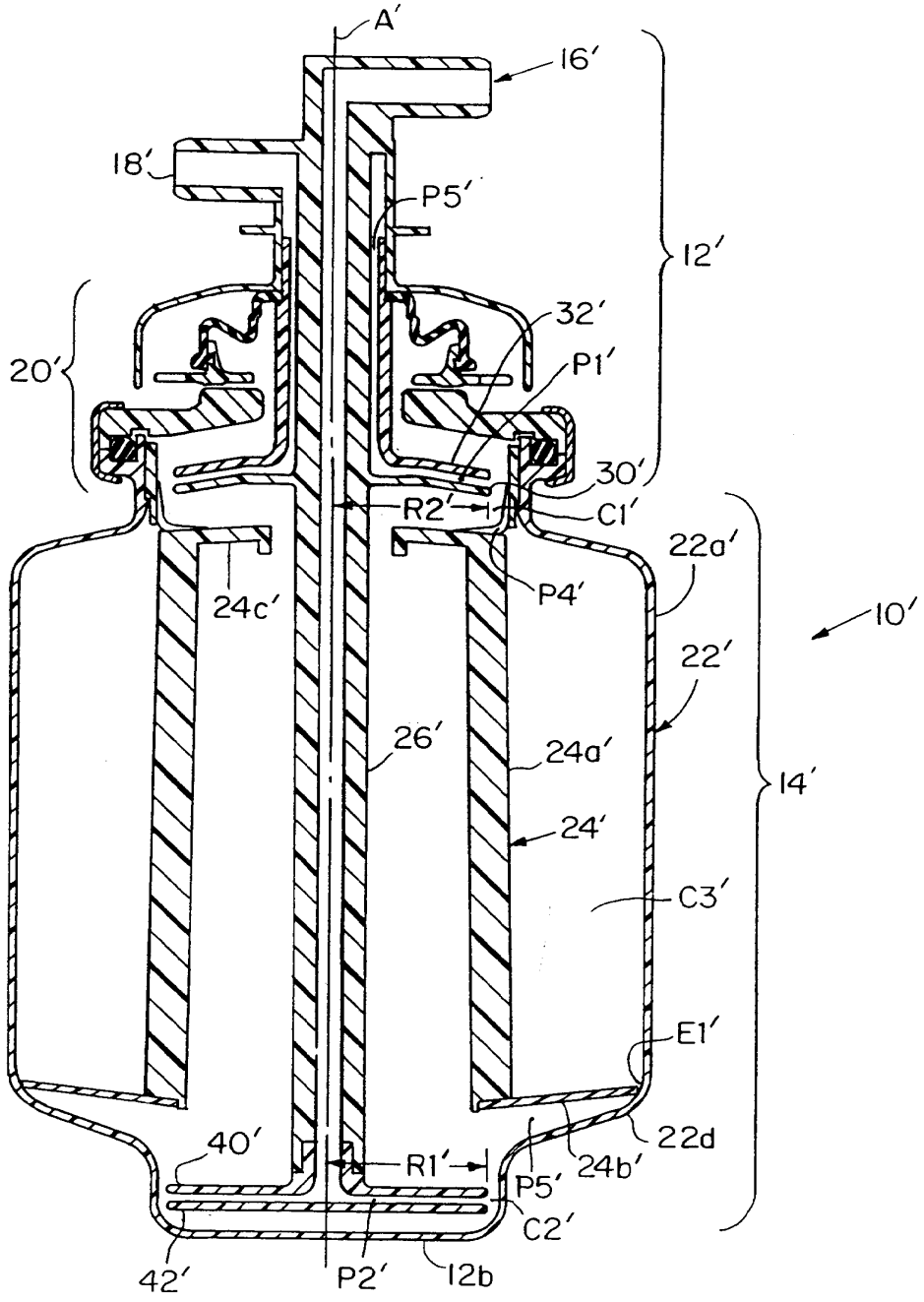


Fig. 2

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 9334

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	EP-A-0 285 891 (DIDECO) * the whole document * ---	1,11	B04B5/04 B04B7/08
A,D	US-A-4 943 273 (E. PAGES) * figure 1 * -----	1,11	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

B04B

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	24 April 1995	Leitner, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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Centrifuge bowl for blood processing

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Classification: **- international:** ***A61M1/02; B04B5/04; B04B7/08;*** (IPC1-7): B04B5/04; B04B7/08
- cooperative: **A61M1/3693**; **A61M1/3696**; **B04B5/0442**; **B04B7/08**; B04B2005/0464

Application number: EP19970302266 19970402 Global Dossier

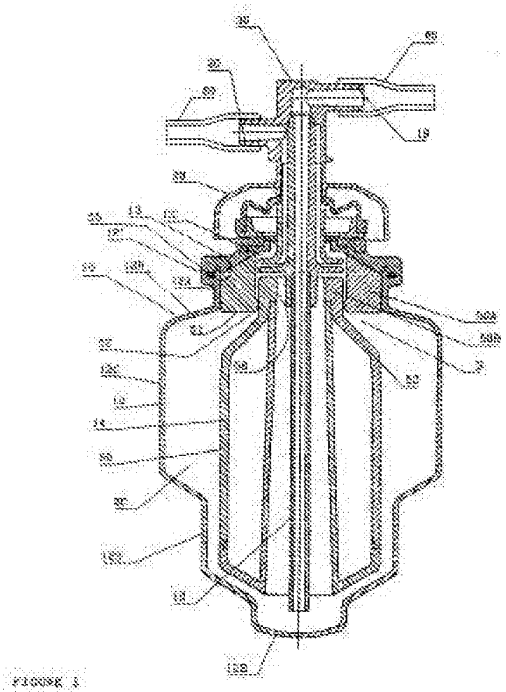
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Abstract of EP0799645 (A1)

A centrifuge bowl suitable for separating blood components, in particular concentrated red blood cells. A centrifuge bowl 10 comprises a core 14 having an annular portion 50A and a cylindrical outer wall 50. Annular portion 50A has a thick wall for minimizing the holdup volume of blood components within a collection chamber CC and the radially inner wall of the annular portion is disposed radially closely adjacent to the opening defined by skirts 24a, 25a. The outer wall 50 defines a separation chamber SC with bowl body 12 and its upper tapered portion defines a separation region S. Three slit-like openings 52 are formed at the junction between outer wall 50 and annular portion 50A, thereby prevent back flow while permitting flow of blood components from separation chamber SC to collection chamber CC. The upper end of outer wall 50 is formed with a cylindrical hub 50B extending toward the skirt member, which hub 50B serves to prevent fluid in collection chamber CC from flowing to the interior of bowl body 12 through central opening 56.

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(54) Centrifuge bowl for blood processing

(57) A centrifuge bowl suitable for separating blood components, in particular concentrated red blood cells. A centrifuge bowl 10 comprises a core 14 having an annular portion 50A and a cylindrical outer wall 50. Annular portion 50A has a thick wall for minimizing the holdup volume of blood components within a collection chamber CC and the radially inner wall of the annular portion is disposed radially closely adjacent to the opening defined by skirts 24a, 25a. The outer wall 50 defines a separation chamber SC with bowl body 12 and its upper tapered portion defines a separation region S. Three slit-like openings 52 are formed at the junction between outer wall 50 and annular portion 50A, thereby prevent back flow while permitting flow of blood components from separation chamber SC to collection chamber CC. The upper end of outer wall 50 is formed with a cylindrical hub 50B extending toward the skirt member, which hub 50B serves to prevent fluid in collection chamber CC from flowing to the interior of bowl body 12 through central opening 56.

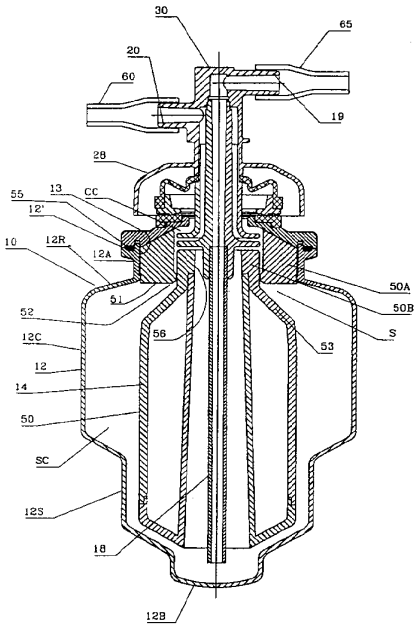


FIGURE 1

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Description

TECHNICAL FIELD

The present invention relates to the field of blood processing, in particular to centrifuge bowls for separating blood components by centrifugation and cores therefor.

BACKGROUND ART

Whole human blood includes blood cells such as red blood cells, white blood cells and platelets and these cells are suspended in plasma, an aqueous solution of proteins and other chemicals. Blood transfusions were used to made using whole blood. Recently, however, blood transfusions are widely given by transfusing only those blood components required by a particular patient instead of using a transfusion of whole blood. Transfusing only those blood components necessary saves the available supply of blood, and in many cases, is convenient for the patient.

Centrifugation has been widely accepted as a technique for separating blood components such as plasma and platelets from whole blood, wherein blood components are separated depending upon the specific gravities. Disposable centrifuge rotors or bowls have been developed for separating blood components by such centrifugation and for washing blood cell components collected from a surgical site.

Typical examples include a centrifuge bowl of the type disclosed in U.S. Patent No. 4,300,717 ("Latham" bowl) and a centrifuge bowl of the type disclosed in U.S. Patent No. 4,086,924 ("Grenade" bowl). The bowl in each case comprises a rotor portion in which blood components are separated and a stator portion having an inlet port and an outlet port, and a rotary seal combines these portions together. Anticoagulated whole blood and/or wash solution is introduced to the interior of the rotor portion through the inlet port. The rotor portion rotates at a fixed or variable speed and blood components within the rotor portion are separated by centrifugation in accordance with the specific gravities. With blood continuously entering the bowl through the inlet port, the separated various blood components are progressively displaced inwardly from the radially outward portion of the bowl and successively reach at a skirt portion which opens radially outwardly and communicates with the outlet port. Blood components exiting through the outlet port are retained and stored, while components remaining in the bowl after collection is complete are then returned to the patient or donor through the outlet port, or deposited in an appropriate container for preservation. The rotor portion comprises a generally frustoconical or cylindrical bowl body and a generally cylindrical core is coaxially disposed therein as the stator portion. Separation by centrifugation is achieved in the space between the core and the bowl body, i.e., a separation chamber. The rotary seal is constructed as a rotary seal assembly including the inlet port and the outlet port and a collection chamber, which is a space for guiding the separated blood components to the outlet port, is formed between the seal and the top of the core. Openings are provided about the core periphery for communication between the separation chamber and the collection chamber. A central opening is formed in the core and a stem for guiding fluid from the inlet port to the lower portion of the bowl is inserted through the central opening.

In addition to the bowls of the above constructions, U.S. Patent Nos. 4,983,158 and 4,943,273 disclose another types of bowls which are herein referred to as "BM bowl". These bowls include an integral bowl body formed by blow molding and cores of various shapes can be coaxially inserted into the bowl through an aperture formed in one axial end of the bowl body. The bowl of U.S. Patent No. 4,943,273 features a diverter member, which can be fitted into the bowl by insertion, is provided below the core so that the bowl would be suitable for washing blood cell components collected from a surgical site.

Further, U.S. Patent No. 5,100,372 discloses an improved core adapted for insertion into a BM bowl, wherein it is taught to provide the core with small size openings for communication between the separation chamber and the collection chamber, so that any blood components remaining on the upper portion of the core can be effectively removed by "splash back".

Moreover, International Publication WO94/08721 pamphlet (PCT/US93/09276) discloses a core for a Grenade bowl for use in blood cell separation or washing, in which the core is provided with a plurality of radially outwardly extending projections for minimizing formation of Coriolis waves which would otherwise cause undesirable turbulence in the separation chamber. Furthermore, a bowl of the BM type for washing or concentrating red blood cells and having only the upper core portion without a body that coaxially extends with the bowl body, is disclosed in International Publication WO89/01792 pamphlet (PCT/US88/02963). Furthermore, U.S. Patent No. 5,045,048 discloses another type of Latham type bowl. In Fig. 1 of this U.S. Patent, the radially outward periphery of skirt portions 24a and 25a communicating the outlet port is shown closely adjacent to the inner wall of the bowl body. However, no detailed explanation is given.

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OBJECT OF THE INVENTION

Conventionally, when blood components are separated using the bowls as described above, plasma and platelets are the components of interest and red blood cells, which eventually remain in the bowl after the separation, are usually returned to the patient or donor. However, there are occasions where red blood cells are separately needed for treatment of diseases, just like plasma and platelets, and a need exists in the medical field for concentrated red blood cells (plasma depleted whole blood). Concentrated red blood cells are about the half the volume of whole blood when the number of red blood cells and the amount of hemoglobin per unit are the same, thus offer an advantage that influences upon transfusion to patients, in particular to aged and infants, are smaller.

Conventional bowls of the types described above suffer from a disadvantage in that, when used for separating concentrated red blood cells from whole blood, the collected concentrated red blood cells are of poor quality. In particular, while BM type bowls are suitable for the purpose of red blood cells separation due to economic reasons, one of the problems associated with the conventional BM type bowls is that white blood cells cannot be separated properly and remain in the concentrated red blood cells. As has been widely known, when concentrated red blood cells contaminated with white blood cells are used for transfusion, there are dangers such as FNHTR (Febril Non-Hemolytic Transfusion Reaction), production of white blood cell antibodies, virus infection carried by white blood cells. Further, in each of Latham and BM type bowl, even if one attempted to remove white blood cells by continuing the process until red blood cells, the component of the heaviest specific gravity, start to elute from the separation chamber, the problem of contamination with white blood cells is still a plague and, moreover, this approach has been found to give rise to another problem, contamination with free hemoglobin.

Accordingly, it has been conventional to resort to so-called dual bag system or quaternary bag system when it is desired to collect from whole blood concentrated red blood cells substantially free from white blood cells. In the dual bag system, anticoagulated whole blood in a plastic bag is subjected to centrifugation for separating the blood components and the plasma is squeezed out from the bag to obtain concentrated red blood cells, which are then diluted, filtered through a filter for removing white blood cells by adsorption, thereby removing 99% or more of the white blood cells (Shoni Naika 26, 6 (1994)). In the quaternary Or four bag system, on the other hand, four bags including a bag containing red blood cell preservant (MAP) are used. By centrifugation after blood collection, blood components are separated as layers in one of the bags in accordance with the specific gravities, and external force is applied to the bag to discharge out from the top portion of the bag to the other bags, in turn, platelet poor plasma, buffy coat, and a top portion of concentrated red blood cells that contains a substantial amount of granulocytes, thereby removing approximately 90% of lymphocytes and approximately 40% of granulocytes (Kiso to Rinsho 29 (12) 3295 (1995)). However, these systems suffer from disadvantages that a high-volume centrifuge apparatus is required and that the operations for separating blood components after centrifugation are complicated.

Accordingly, an object of the present invention is to improve conventional Latham type and BM type bowls such that they would be suitable for collecting concentrated red blood cells depleted of white blood cells.

Another object of the present invention is to improve conventional Latham type and BM type bowls such that separation of blood components such as platelet poor plasma can be achieved more satisfactory. The improved bowls are provided with novel cores.

As in the case of concentrated red blood cells collection, it is required that white blood cells be removed as much as possible when collection of concentrated platelets is desired. White blood cells are sometimes separated and transfused in aid of immunotherapy. However, these components were not conveniently available in conventional BM type bowls. A further object of the present invention, accordingly, is to provide a BM type bowl which is improved for achieving better separation of components such as platelet concentrate, buffy coat and white blood cells.

A further object of the present invention is to provide a core suitable for such BM type bowl.

DISCLOSURE OF THE INVENTION

A centrifuge bowl for blood processing provided in accordance with the present invention comprises a bowl body adapted for rotation about its axis and having an aperture at one axial end thereof, a rotary seal assembly affixed to the bowl body to cover the aperture and having an inlet port and outlet port in fluid communication with the interior of the bowl body and a core disposed within the bowl body. The core includes a first portion defining a collection chamber that is in fluid communication with the outlet port, and a second portion defining a separation chamber in fluid communication with the inlet port between the core and the inner wall of the bowl body. The core further includes means for defining fluid passages communicating the collection chamber and the separation chamber and a central opening formed concentric about the axis. The means for defining fluid passages may, in Latham type bowls, for example, be projections or recesses formed around the central opening of the generally frustoconical core, which projections or recesses define fluid passages between the outer surface of the core and the inner surface of the bowl when the core engages the bowl body. Alternatively, such projections or recesses may be formed about the inner surface of bowl

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body which engages the core. In the case of cores for use in BM type bowls, the fluid defining means may, for example, be a plurality of openings formed about the periphery of the core, the core which can be inserted into the bowl body.

According to one aspect of the present invention, in a centrifuge bowl of the type described above, the collection chamber is adapted to minimize the holdup volume of blood components therein, the core is provided with a barrier member for preventing flow from the collection chamber into the central opening, and each of the fluid passages has a minimal size for restricting back flow while permitting flow of blood components from the separation chamber to the collection chamber. The term "holdup volume" refers to a maximum possible volume or amount of blood or separated blood components resident in the collection chamber. Such construction enables to prevent rupture of red blood cells in the collection chamber, thereby preventing hemoglobins from flowing out to become free hemoglobins (FHgbs) which are a source of contamination for concentrated red blood cells. Contamination of concentrated red blood cells due to back flow of white blood cells and liberated hemoglobins from the collection chamber to the interior of the bowl can also be prevented.

The outlet port communicates with the collection chamber through a skirt member. The skirt member has a radially outward opening, which is disposed preferably radially inwardly of the fluid passages, and has a small diameter. Typically, the diameter is equal to or less than 33mm, preferably equal to or less than 28mm and most preferably equal to or less than 25mm. The small diameter of the skirt member enables to decrease shear force between the outer periphery of the skirt member and the opposing surface of the core or bowl body, thereby minimizing rupture of blood cell components in the collection chamber. The outer periphery of the small skirt is preferably disposed closely adjacent to the upper portion, or the first portion of the core or the inner wall of the bowl body, thereby decreasing the shear force and minimizing the holdup volume in the collection chamber. The radial spacing between the skirt periphery, or the skirt opening, and the surface closely adjacent thereto is preferably equal to or less than 2mm and more preferably equal to or less than 1mm. The skirt portion usually extends straight in the axial direction. However, so long as its diameter is maintained small, the skirt can assume other shapes such as an axially flared shape.

The fluid passages or openings are 2 or more in number, for example 2 to 8, and are formed equidistantly in the circumferential direction. The total area of the fluid passages or openings is preferably equal to or less than 80mm^2, so as to prevent back flow when blood components are displaced from the separation chamber to the collection chamber. More preferably, the total area is equal to or less than 40mm^2 and most preferably in the range of 20 to 40mm^2.

The barrier member may be a cylindrical hub surrounding the central core opening and extending axially to a position axially closely adjacent to the skirt member. Flow from the collection chamber into the bowl body through the central opening is thereby prevented, thus preventing contamination of concentrated red blood cells with white blood cells and FHgbs. The axial distance between the axial end of the cylindrical hub and the skirt member is typically 2mm or less and preferably 1mm or less.

According to another aspect of the present invention, a core for use in a centrifuge bowl of the described character, in particular of the BM type, defines a separation region between the fluid passages or openings and the separation chamber, the axial length of which decreases progressively radially inwardly. For the separation of buffy coat or white blood cells from red blood cells, it is necessary that a phase or layer of white blood cells be grown and led from the outlet port to the exterior of the bowl. Conventional cores for use in BM type bowls assumed a substantially cylindrical shape as a whole, thus no area or region was available for the growth of such white blood cell phase. In the present invention, provision of the separation region having radially inwardly decreasing axial- length between the fluid passages or openings of the core and the separation chamber allows easy separation of white blood cells in BM type bowls. Such a separation region enables to separate platelets and white blood cells from each other, the components which do not differ substantially from each other in specific gravity and thus forming together a buffy coat layer (including platelets and white blood cells, i.e., lymphocytes, monocytes and granulocytes) rather than forming separate individual layers. Thus, it becomes possible to collect each of platelet concentrate depleted of white blood cells and white blood cells separately. Preferably, such separation region is formed between the upper and lower cylindrical core portions, by the lower axial end of the upper cylindrical portion and a radially inward conical taper portion of the lower cylindrical portion.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is an axial sectional view of one embodiment of BM type centrifuge bowl of the present invention.

Fig. 2 is a partial cutaway elevational view illustrating the rotary seal assembly used for the centrifuge bowl of Fig. 1.

Fig. 3 is a diagrammatic front elevational view of the core of the centrifuge bowl of Fig. 1.

Fig. 4A is a plan view of the core of Fig. 3 and Fig. 4B is a plan view of a prior art centrifuge bowl core of Fig. 8.

Fig. 5 is an axial sectional view of one embodiment of Latham type centrifuge bowl of the present invention.

Figs. 6A and 6B are diagrammatic plan and front elevational views, respectively, of the core of the centrifuge bowl of Fig. 5.

Fig. 7 is a diagrammatic partial cutaway sectional view showing another core of the present invention for use in

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BM type centrifuge bowl.

Fig. 8 is an axial sectional view of a prior art BM type centrifuge bowl.

Fig. 9 is an axial sectional view of a prior art Latham type centrifuge bowl.

Fig. 10 is a plan view of a core for use in the centrifuge bowl of Fig. 9.

DESCRIPTION OF PREFERRED EMBODIMENTS

Referring now to Figs. 1-4, a preferred embodiment according to BM type of the invention will be described. As shown in Fig. 1, the centrifuge bowl of BM type according to the present invention comprises a disposable centrifuge rotor, or bowl 10, which is used for processing whole blood from a patient or donor, in particular for obtaining concentrated red blood cells substantially free from white blood cells. The bowl 10 comprises a rotary seal assembly, or seal and header assembly, shown generally at 28 (Fig. 2), a seamless one-piece bowl body shown generally at 12 and a core 14 (Figs. 3 and 4).

The seal and header assembly 28 provides a rotary seal and fluid communication pathway between the interior of the rotatable bowl body 12 and stationary conduits 65 and 60 connected respectively to an inlet port 19 and an outlet port 20. The assembly 28 is comprised of a stationary header, shown generally at 30, an effluent tube 25, a feed tube assembly, shown generally at 24, and a rotary seal, shown generally at 35. Rotary seal 35 comprises a seal ring 22, a flexible member 27 and an outside seal member, or crown 16.

The header 30 is comprised of an integrally formed member having an inlet bore, or inlet port 19, extending radially into an axial passageway 19a. The passageway 19a is coupled to an inner, axially extending bore 61 of feed tube assembly 24 and, in turn, to a feed tube stem 18, thereby forming a non-rotating inlet path for anticoagulated whole blood to enter the interior of centrifuge bowl body 12.

The header 30 also includes an outlet bore, or outlet port 20, which extends radially into a channel 20a extending about feed tube assembly 24 in coaxial relationship. The channel 20a then couples to an outlet passageway 62. An outer shield member 32 is formed on header 30 and extends over rotary seal 35.

The feed tube assembly 24 is formed with a lower skirt 24a integral therewith and a corresponding, complimentary upper skirt 25a is integrally formed on effluent tube 25, thereby forming a radially outwardly opening skirt member in the collection chamber. The skirt member is of a reduced diameter, relative to prior art skirt member of this type of bowl structure as shown in Fig. 8.

As mentioned above, rotary seal 35 is formed of a flexible member 27, a seal ring 22 and a crown 16. Flexible member 27 is affixed about its outer periphery to the periphery of seal ring 22. Crown 16 includes an axially open groove 16a on its periphery and is provided with a central opening 23, through which effluent tube 25 extends. The inner periphery of flexible member 27 is joined to effluent tube 25.

The header and seal assembly 28, as thus described, is formed and assembled as on individual unit and, after the core 14 has been inserted through an aperture 13 formed in one axial end of bowl body 12 and disposed within the bowl body 12 as shown in Fig. 1, inserted through the opening of bowl body 12 and fixed thereto by appropriate means such as welding or threading.

The bowl body 12 is preferably an integral body adapted to be manufactured by blow molding or injection blow molding and may be formed of a suitable plastic, such as transparent styrene resin or the like.

The bowl body 12 comprises an upper annular portion 12A, an upper radial portion 12R, a cylindrically extending middle portion 12C, a lower stepped portion 12S and a bottom closure portion 12B. A groove 12' corresponding to the groove 16a of crown 16 is formed on annular portion 12A and an O-ring 55 is disposed between the grooves. When the crown 16 is fixed onto bowl body by threading, welding or the like, O-ring 55 is compressed to form a liquid tight seal.

The core 14 is generally cylindrical and is adapted to be disposed within bowl body 12 by insertion through said aperture 13 formed in annular portion 12A of bowl body 12. The core 14 includes a cylindrical portion, or generally cylindrical outer wall 50, extending coaxially with bowl body 12. An upper cylindrical portion, or annular portion 50A of core 14 is adapted to be snugly received in aperture 13 of bowl body 12 when core 14 is inserted into bowl body 12, thereby defining a collection chamber CC between crown 16 and annular portion 50A of core 14 for collecting separated blood components through the skirt member. The annular portion 50A is formed to have a relatively thick wall and the inner wall thereof is disposed radially closely adjacent to the opening of the skirt member, i.e., the periphery of upper and lower skirts 25a and 24a.

Outer wall 50 of core 14 has a diameter approximately equal to that of annular portion 50A and forms a separation chamber SC between outer wall 50 and middle and stepped portions 12C and 12S of bowl body 12. The axial ends of outer wall 50 are tapered and the upper tapered end is joined to the inner periphery of the lower end of annular portion 50A, at which junction four slit-like openings 52 are formed equidistantly at 90 degrees intervals about the periphery (Fig. 4A). These openings 52 serve to provide passages for blood components, such as plasma and platelets, separated from whole blood by centrifugation in separation chamber SC in bowl body 12, to flow into collection chamber CC. The tapered distal ends of outer wall 50 are connected with each other through an axially extending cylinder member and

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feed tube stem 18 extends through the interior of the cylinder member toward the bottom closure portion 12B of bowl body 12.

The lower axial end 51 of annular portion 50A and the upper tapered portion, or radially inward inclination 53 of outer wall 50, define a separation region S, which has radially inwardly progressively decreasing axial length, between openings 52 and separation chamber SC. The upper end of the upper tapered portion of outer wall 50 is integrally joined to a cylindrical hub 50B which extends axially to a position axially closely adjacent to the skirt member and a central opening 56 of core 14 is defined by the hub 50B. The cylindrical hub 50B serves as a barrier that prevents fluid in collection chamber CC from flowing to the interior of bowl body through central opening 56.

For better understanding of the function of the centrifuge bowl 10 shown in Figs. 1-4, in particular the novel core 14, it may be helpful to refer to the following illustrative two protocols. These processing protocols can be executed utilizing apheresis apparatus available from Haemonetics Corporation of 400 Wood Road, Braintree, MA 02184, U.S. A. under the tradenames MCS, MULTI and CCS.

WBC Depleted Concentrated Red Blood Cells Collection Protocol

1. Whole blood is drawn from a patient or donor, anticoagulated and guided into bowl 10 via inlet port 19 through conduit 65. This may be achieved by, for example, driving conduit 65 with a peristaltic pump (not shown). The anticoagulated whole blood is led from inlet port 19 to bottom closure portion 12B of rotatable bowl body 12 through axial passageway 19a, bore 61 and feed tube stem 18. The whole blood is forced radially outwardly from closure portion 12B to separation chamber SC and blood components are separated by the centrifugal force in accordance with the specific gravities. The most heavy fraction, red blood cells, form an outermost cylindrical layer along middle portion 12C of bowl body 12 and plasma layer and buffy coat (platelets and white blood cells) are formed inside thereof in the order of lighter to heavier specific gravities. Granulocytes, which are the most heavy fraction among white blood cells, are however partly distributed about the radially inner side of the layer of concentrated red blood cells. By continuing the withdrawal of whole blood and its introduction into bowl 10 via inlet port 19, the outermost red blood cells layer is grown and the separated blood components enter, in the order of lighter to heavier specific gravities, into collection chamber CC from stepped portion 12S via separation region S and openings 52, flow through the opening of the skirt member, i.e., between upper and lower skirt portions 25a and 24a, to outlet passageway 62, channel 20a and then to outlet port 20, and led to a blood component storage bag (not shown) through conduit 60.

2. The process is continued until it is detected that a part of the concentrated red blood cells, obtained by centrifugation, has started to flow out from outlet port 20, and rotation of bowl 10 is stopped when such detection is made. The detection can be made automatically by monitoring conduit 60 with an optical sensor.

3. The peristaltic pump driving conduit 65 is then reversed, discharging from inlet port 19 concentrated red blood cells remaining in bowl 10. The discharged concentrated red blood cells can be collected in a bag (not shown) coupled to a line branched from conduit 65 by cramping the line extending from conduit 65 to the patient or donor and by releasing a cramp in the line extending to the collection bag for concentrated red blood cells

4. After all the concentrated red blood cells in the bowl 10 are discharged, the process can be repeated again. Namely, by releasing the cramp in the line extending between the patient or donor and conduit 65, cramping the line between conduit 65 and the collection bag and forward-rotating the peristaltic pump, the blood separation process can be repeated again and concentrated red blood cells can be collected automatically. The cycle can be repeated as several times as desired.

WBC Depleted Platelet Concentrate Collection Protocol

1. Whole blood drawn from a patient or donor is guided into bowl 10 via inlet port 19 through conduit 65 with the use of a peristaltic pump (not shown) and an anticoagulant is continuously added thereto. The anticoagulated whole blood is led from inlet port 19 to bottom closure portion 12B of rotatable bowl body 12 through axial passageway 19a, bore 61 and feed tube stem 18. As in the case of the WBC depleted concentrated red blood cells collection protocol described above, the whole blood is separated by the centrifugal force into a layer of red blood cells, the radially outermost layer within the bowl, and the inner, buffy coat and plasma layers. By continuing the withdrawal of whole blood, the separated blood components enter, with the plasma layer first, into collection chamber CC via separation region S and openings 52, flow through the opening of the skirt member to outlet passageway 62, channel 20a and then to outlet port 20, and led to a blood component storage bag (not shown) through conduit 60.

2. When the front end of the buffy coat layer has approached the core openings 52, a surge step is started for separating platelets and white blood cells in the buffy coat layer. Collection of whole blood is stopped and a part of the collected plasma is introduced into the bowl. While the components in the buffy coat having close specific

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gravities cannot be separated from each other only by centrifugation, if plasma is introduced radially inwardly against the centrifugal force during spinning, platelets, which have a small diameter, are selectively carried out by the plasma. The white blood cells, on the other hand, are retained in the separation region S. The flow rate of plasma introduced can be adjusted, for example, to progressively increase at a predetermined increment. After most of the platelets have been carried out and before white blood cells start to flow out, the plasma introduction is stopped.

3. Uncollected white blood cells and concentrated red blood cells remaining in the bowl are returned to the patient or donor by stopping rotation of the bowl 10 and reversing the peristaltic pump that drives conduit 65. The process may be automatically repeated as desired until a sufficient quantity of platelets has been collected.

When it is desired to collect concentrated red blood cells with a bowl, it is necessary to clearly form a layer of white blood cells and to expel all of the layer out to the exterior of the bowl. In accordance with the bowl 10 in Fig. 1 of the present invention, separation region S, which has radially inwardly progressively decreasing axial length, is defined by lower axial end 51 of annular portion 50A of core 14 and radially inward inclination 53 in the upper part of outer wall 50, and separated white blood cells are collected, after leaving separation chamber SC and before entering into openings 52, in this separation region S in the form of a layer and thus efficiently expelled through collection chamber CC. In prior art, insertable cores for use in BM type bowls have not been provided with such a separation region S. Such a separation region S is also found to be useful for a conventional structure as shown in Fig. 8 which does not include any of the thick-wall annular portion 50A in the upper core part, the skirt member of a reduced diameter and the cylindrical hub axially extending toward the skirt member. An illustrative example of a core 14' having such useful structure is shown in Fig. 7. Openings 52' in this core 14' can have a slit-like form as in the case of Fig. 4A.

Further, when it is desired to collect concentrated red blood cells with a bowl, it is important to prevent contamination of the concentrated red blood cells remaining in the bowl by white blood cells and free hemoglobins. In a bowl comprising a core 14" of the conventional structure as shown in Figs. 4B and 8, blood components are radially displaced from outward to inward in the order of lighter to heavier specific gravities, enter collection chamber CC' from separation chamber SC' through openings 52" and guided to the outlet port via the opening in the skirt member (arrow A). However, collection chamber CC' is not constructed to control the behavior of fluid therein. Accordingly, the white blood cells entered into collection chamber CC' through openings 52" are allowed to return to the interior of bowl body 12 from central opening 56' while residing in collection chamber CC' (arrow B), thereby contaminating the concentrated red blood cells in the bowl. The area of openings 52" is relatively large and this allows back flow from collection chamber CC' to separation chamber SC' when the components flow into collection chamber CC' from separation chamber SC', also resulting in contamination of the concentrated red blood cells in the bowl with white blood cells.

In addition, when red blood cells are partly expelled from the bowl for complete expulsion of white blood cells and granulocytes from the bowl, the red blood cells residing in collection chamber CC', before being guided to the outlet port from the skirt member 24a', 25a', are ruptured between the relatively large-diameter skirt member and the upper core wall spinning therearound. The hemoglobins are thereby released from the cells and allowed to return to the interior of the bowl along the arrows B and/or C, thereby causing contamination.

In accordance with the present invention, the fluid-behavior uncontrolled collection chamber of the prior art is modified by the thick-wall annular portion 50A closely disposed adjacent to the opening of the skirt member so as to minimize the holdup volume of blood components within the collection chamber. In addition, the cylindrical hub 50B axially extending to a position closely adjacent to the skirt member prevents return of flow from collection chamber CC into central opening 56. The skirt member per se is of a reduced diameter for preventing rupture of blood cells and the openings 52 are of a size that prevents back flow while permitting flow from separation chamber SC and separation region S into collection chamber CC. The flow of separated blood components tending to return to the interior of the bowl from collection chamber CC through central opening 56 and/or openings 52 is thus inhibited, and contamination by free hemoglobins is also prevented because of the minimized holdup volume.

In addition, with regard to the barrier formed by the cylindrical hub 50B, when the front end of blood components displaced radially inwardly within the collection chamber reaches the skirt opening, air cannot escape from within the bowl and thus the collection chamber will not be overfilled with blood components. Further, blood components resident in the collection chamber are subjected to centrifugal force. Therefore, blood components in the collection chamber will not backflow from the central opening into the bowl through the axial spacing between the top of hub 50B and the bottom of lower skirt 24a, provided that the top of hub 50B is sufficiently close to the bottom of lower skirt 24a and the diameter of central opening 56 is sufficiently small. As the top end of hub 50B axially faces the lower skirt 24a, the diameter of hub 50B is equal to or smaller than the skirt diameter and the diameter of central opening defined by the hub is sufficiently small.

Turning now to Figs. 5 and 6, a preferred embodiment according to Latham type of the invention will be described. As shown in Fig. 5, the centrifuge bowl of Latham type also comprises a disposable centrifuge rotor, or bowl 110, which has an aperture 113 at one end and comprises a rotary seal assembly 128, a bowl body 112 and a core 114. The rotary

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seal assembly 128 is substantially of the same construction as the rotary seal assembly 28 described above with reference to Fig. 2, and thus is not detailed herein to avoid redundancy. It should be noted that in this case, too, a radially outwardly opening skirt member having a small diameter is provided by a lower skirt 124a formed integral with feed tube assembly 124 and a corresponding, complimentary upper skirt 125a integrally formed on effluent tube 125.

The bowl body 112 may be formed of a suitable plastic material such as transparent styrene resin or the like and comprises an upper annular portion 112A, an upper radial portion 112R, a middle portion 112C conically extending down from the radial portion 112R, and a separate, disc-like bottom portion 112B. The crown 116 of rotary seal assembly 128 is affixed onto annular portion 112A by threading, welding or the like.

The core 114 disposed within bowl body 112 has a profile corresponding to the bowl body 112 and comprises a radial portion 114R extending along radial portion 112R, a middle portion 114C extending conically down from the radial portion 114R and a bottom portion 114B corresponding to bottom portion 112B. A cylindrical hub 150 that extends axially to a position axially closely adjacent to the skirt portion is formed around the periphery of a central opening 156. Annular portion 112A of bowl body 112, the portion which defines a collection chamber CC for collecting separated blood components through the skirt member, is formed to have a relatively thick wall as shown, the radially inner wall of which is disposed radially closely adjacent to the opening of the skirt member, i.e., the periphery of upper and lower skirts 125a and 124a. The collection chamber CC is thus constructed to minimize the holdup volume of blood components.

A separation chamber SC is defined between middle portion 114C of core 114 and middle portion 112C of bowl body 112. About the periphery of the lower end of hub 150 abutting the lower inner periphery of annular portion 112A of bowl body 112, three recesses 152 are formed equidistantly at 120 degrees intervals as shown in Figs. 6A and 6B. These recesses 152 serve to provide passages for blood components separated within bowl body 112, such as plasma and platelets, between separation chamber SC and collection chamber CC. The lower end of cylindrical hub 150 and the inner periphery of the disc-like bottom portion 114B are connected with each other through an axially extending cylinder member, and feed tube stem 118 extends through the interior of the cylinder member toward the bottom portion 112B of bowl body 112. Instead of recesses 152, recesses can be formed about the lower inner periphery of annular portion 112A of bowl body 112 to provide the fluid passages.

A separation region S, which has radially inwardly progressively decreasing axial length, is defined between radial portion 112R of bowl body and radial portion 114R of core 114. While such a separation region S has been conventional in Latham type bowls as shown in Fig. 9, the region S is radially extended in accordance with the present invention, thereby enabling better separation of blood components, in particular buffy coat and white blood cells.

The centrifuge bowl 110 shown in Figs. 5 and 6 may be used in accordance with processing protocols similar to the protocol illustratively explained above in connection with the embodiment of Figs. 1-4, employing the same apheresis apparatus. And the same advantages as described above can be obtained in this case as well. Namely, in a bowl with a core of prior art structure as shown in Figs. 9 and 10, concentrated red blood cells in the bowl are contaminated by white blood cells due to return of flow from collection chamber CC' to the interior of bowl body 112 through central opening 156' (arrow B) and back flow through relatively large-area openings 152' (arrow C), when blood components are guided along the arrow A from separation chamber SC to collection chamber CC' through openings 152'. In addition, when red blood cells are partly expelled from the bowl for complete expulsion of white blood cells and granulocytes from the bowl, the red blood cells residing in collection chamber CC', before being guided to the outlet port from the skirt member, are ruptured between the relatively large-diameter skirt member and the upper annular wall of bowl body spinning therearound, thus releasing hemoglobins which are allowed to return to the interior of the bowl along the arrows B and/or C to cause contamination.

In contrast, in accordance with the present invention, the collection chamber CC is constructed to minimize the holdup volume of blood components therein, with the use of the thick-wall annular portion 112A disposed closely adjacent to the opening of the skirt member. The cylindrical hub 150 that extends axially to a position closely adjacent to the skirt member prevents return of flow from collection chamber CC into central opening 156. The skirt member per se is of a reduced diameter for preventing rupture of blood cells and the openings 152 are of a size that prevents back flow while permitting flow from separation chamber SC and separation region S into collection chamber CC. The flow of separated blood components tending to return to the interior of the bowl from collection chamber CC through central opening 156 and/or openings 152 is thus inhibited, and contamination by free hemoglobins is also prevented owing to the minimized holdup volume. In this case, the diameter of hub 150 is equal to or less than the skirt diameter and the diameter of central opening 156 is thereby sufficiently small, thus preventing, together with the minimal axial spacing between the top of hub 150 and the bottom of lower skirt 124a, backflow from collection chamber CC.

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EXAMPLES

Example 1

A centrifuge bowl of the construction shown in Fig. 1 was prepared. The bowl body 12 and seal and header assembly 28 had the same structure as those available from Haemonetics Corporation of 400 Wood Road, Braintree, MA 02184, U.S.A. under the tradenames Haemonetics Multicomponent Set (Product #751, #803) and Haemonetics Disposable Plasma Collection Set (Special) (Product #525, #525J), except that the skirt member of the seal and header assembly, i.e., upper skirt 25a and lower skirt 24a had a smaller diameter of about 25mm. The axial length of core 14 was about 100mm and included the upper cylindrical portion, annular portion 50A, a cylindrical outer wall 50 having radially inward inclinations at its axial ends and a cylindrical hub 50B axially extending from the junction between annular portion 50A and outer wall 50. Annular portion 50A was formed with the outer diameter of about 48mm and the inner diameter of about 27mm and the diameter of outer wall 50 was about 47mm. The angle contained between the generally radially extending lower end 51 of annular portion 50A and the upper inclination of outer wall 50 was about 45 degrees. The cylindrical hub 50B has the outer diameter of about 25mm and the inner diameter, or the central opening, of about 14mm. The diameter of the lower core opening opposite the central opening was about 20mm. Four slit-like openings 52 of about 0.7mm in the radial direction were provided equidistantly in the circumferential direction, the total area of opening was about 28mm^2. The radial distance between the skirt member and the inner wall of annular portion 50A was about 1mm and the axial distance between the lower surface of lower skirt 24a and the upper end of cylindrical hub 50B was about 1mm.

The above centrifuge bowl was placed on an apheresis machine available from Haemonetics Corporation under the tradename Haemonetics Multicomponent System (MCS3p). Whole blood was drawn from 23 donors and concentrated red blood cells were separated by centrifugation in one cycle, in accordance with the WBC depleted concentrated red blood cells collection protocol. The centrifugation was continued until red blood cells partly flew out from outlet port 20. The rotation speed was 7000rpm for 13 donors, 6000rpm for 4 donors and 5000rpm for 6 donors. Removal rates of white blood cells, granulocytes and lymphocytes, yield of red blood cells, and amount of free hemoglobins (FHgbs) per unit volume in were measured in the collected concentrated red blood cells and averaged. The results are shown in Table 1.

Comparative Example 1

A centrifuge bowl having the structure shown in Fig. 8 was prepared. The bowl was available from Haemonetics Corporation under the tradenames Haemonetics Multicomponent Set (Product #751, #803) and Haemonetics Disposable Plasma Collection Set (Special) (Product #525, #525J). The diameter of the skirt member of this bowl was about 41mm, the total area of four openings 52' of core 14" was about 150mm^2, the radial distance between the skirt member and the inner wall of upper core annular portion 50A' was about 3mm and the axial distance between the lowermost end of the skirt member and the disc-like portion 50B' of the core was about 9mm. With this bowl, concentrated red blood cells were obtained from 8 donors in the same manner as in Example 1, and the rotation speed was 7000rpm for all of the donors. The results are also shown in Table 1.

TABLE 1

	WBCs	Removal Rates (%)		RBCs yield (%)	FHgbs (mg/dl)
		Granulocytes	Lymphocytes		
Example 1	65.1	42.6	95.6	83.7	12.0
Comparative Example 1	33.6	24.5	49.2	86.9	67.1

Example 2

A centrifuge bowl of the construction shown in Fig. 5 was prepared. The centrifuge bowl differed from the centrifuge bowl of Fig. 9 available from Haemonetics Corporation under the tradenames Haemonetics Multicomponent Set (Product #890J, #895J, #870) and Haemonetics Disposable ESP Set (Product #790, #795J) in the following points: In the former, the skirt member, i.e., upper and lower skirts 125a and 124a, was of a reduced diameter of about 30mm, the upper annular portion 1 12A of bowl body 112 had an inner diameter of about 32mm and the radial spacing between the skirt member and the opposing inner wall of annular portion 112A was about 1mm. The cylindrical hub 150 extended axially to define about 1 mm of axial distance between its upper end and the lower surface of the lower skirt 124a. In addition, three recesses 152 were formed as shown in Fig. 6A about the periphery of the lower end of hub 150 abutting

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the lower inner periphery of annular portion 112A of bowl body 112, and fluid passages having the area of about 21mm^2 in total were defined thereby. In contrast, in the latter, currently available bowl, the radial spacing between the skirt member and the inner wall of annular bowl body portion was about 2mm, the axial distance between the skirt member and the upper core end was about 7mm and the total area of fluid passages was about 97mm^2.

The centrifuge bowl of the Fig. 5 construction was placed on an apheresis machine available from Haemonetics Corporation under the tradename Haemonetics Multicomponent System (MCS3p). Whole blood was drawn from 11 donors and concentrated red blood cells were separated and evaluated in the same manner as in Example 1. The centrifugation was conducted at 6000rpm for all of the donors. The results are shown in Table 2.

Comparative Example 2

A centrifuge bowl having the structure shown in Fig. 9 was used and concentrated red blood cells were obtained from 10 donors in the same manner as in Example 2. The centrifugation was conducted at 6000 for all of the donors. The results are also shown in Table 2.

TABLE 2

	WBCs	Removal Rates (%)		RBCs yield (%)	FHgbs (mg/dl)
		Granulocytes	Lymohocytes		
Example 2	80.8	69.1	97.2	73.2	15.5
Comparative Example 2	71.2	44.3	98.1	80.0	48.2

Example 3

A centrifuge bowl of the same type as used in Example 1 was placed on an apheresis machine available from Haemonetics Corporation under the tradename Haemonetics Multicomponent System (MCS3p). Platelet concentrate was collected in one cycle by centrifugation at 6000rpm in accordance with the WBC depleted platelet concentrate collection protocol. Yields were measured in the separated platelet concentrate and the results are shown in Table 3.

Comparative Example 3

A centrifuge bowl of the same type as used in Comparative Example 1 was employed and platelet concentrate was separated in the same manner as in Example 3, except that the bowl was rotated at 7000rpm. The results are also shown in Table 3.

TABLE 3

	Yield/Bag			Blood Measurements Before Collection (per μl)	
	Platelet Concentrate	WBCs	Volume (ml)	Platelets	WBCs
Example 3	1.6×10^{10}	2.5×10^{6}	61	3.6×10^{5}	8.2×10^{3}
Comparative Example 3	1.5×10^{10}	9.4×10^{7}	111	2.1×10^{5}	4.3×10^{3}

As explained above, novel centrifuge bowls have been provided, which are suitable for obtaining in an apheresis machine concentrated red blood cells depleted of white blood cells. The bowls are also useful in separating blood components such as platelet poor plasma, platelet concentrate depleted of white blood cells, buffy coat and white blood cells more efficiently.

Claims

1. A centrifuge bowl for processing blood by centrifugation comprising:

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a bowl body adapted for rotation about its axis and having an aperture at one axial end thereof;
a rotary seal assembly affixed to said bowl body to cover said aperture and having an inlet port and outlet port in fluid communication with the interior of said bowl body; and
a core disposed within said bowl body and having a first portion defining a collection chamber in fluid communication with said outlet port, a second portion defining a separation chamber in fluid communication with said inlet port between the core and the inner wall of said bowl body, means for defining fluid passages communicating said collection chamber and said separation chamber and a central opening formed concentric about said axis, characterized in that:

said collection chamber is adapted to minimize the holdup volume of blood components therein;
said core is provided with a barrier member for preventing flow from said collection chamber into said central opening; and
each of said fluid passages having a minimal size for restricting back flow while permitting flow of blood components from said separation chamber to said collection chamber.

2. The centrifuge bowl as in claim 1, wherein said outlet port communicates with said collection chamber through a skirt member which includes a radially outward opening disposed radially inwardly of said fluid passages, said skirt member is of a reduced diameter.

3. The centrifuge bowl as in claim 1 or claim 2, wherein said core defines a separation region between said fluid passages and said separation chamber, the axial length of said separation region gradually decreases radially inwardly.

4. The centrifuge bowl as in either of claims 2 or 3, wherein said first portion and/or the inner wall of said bowl body is disposed closely adjacent to said skirt member for reducing the volume of said collection chamber, thereby minimizing the holdup volume.

5. The centrifuge bowl as in any of claims 2 to 4, wherein said barrier member is a cylindrical hub which extends axially from said second portion to a position axially closely adjacent to said skirt member.

6. A centrifuge bowl for processing blood by centrifugation comprising:

a bowl body adapted for rotation about its axis and having an aperture at one axial end thereof;
a rotary seal assembly affixed to said bowl body to cover said aperture and having an inlet port and outlet port in fluid communication with the interior of said bowl body; and
a core inserted into said bowl body through said aperture and having a first cylindrical portion received in said aperture and defining a collection chamber in fluid communication with said outlet port, a second cylindrical portion axially extending from said first cylindrical portion and defining a separation chamber in fluid communication with said inlet port between the core and the inner wall of said bowl body, openings formed between said first cylindrical portion and said second cylindrical portion and communicating said collection chamber and said separation chamber and a central opening formed concentric about said axis, characterized in that:

said outlet port communicates with said collection chamber through a skirt member which is of a reduced diameter and including a radially outward opening;
the radial inner wall of said first cylindrical portion is disposed radially closely adjacent to said opening of said skirt member;
said second cylindrical portion is provided with a cylindrical hub which extends axially from the junction between said first and second portions to a position axially closely adjacent to said skirt member, said cylindrical hub defining said central opening; and
each of said openings having a minimal size for restricting back flow while permitting flow of blood components from said separation chamber to said collection chamber.

7. The centrifuge bowl as in claim 6, wherein the diameter of said skirt member is equal to or less than 33mm and said radially outward opening is disposed radially inwardly of said openings.

8. The centrifuge bowl as in any of claims 2 to 7, wherein said diameter is equal to or less than 28mm.

9. The centrifuge bowl as in any of claims 6 to 8, wherein said first cylindrical portion and said second cylindrical portion define together a separation region between said openings and said separation chamber, the axial length

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of said separation region gradually decreases radially inwardly.

10. The centrifuge bowl as in any of claims 6 to 9, wherein the axial spacing between said axial end of said cylindrical hub and said skirt portion is equal to or less than 4mm.

11. The centrifuge bowl as in claim 10, wherein said axial spacing is equal to or less than 2mm.

12. The centrifuge bowl as in any of claims 1 to 11, adapted for collecting from whole blood any of platelet concentrate, platelet poor plasma, white blood cells or buffy coat.

13. A core for use in a centrifuge bowl for processing blood by centrifugation, said centrifuge bowl comprising a bowl body adapted for rotation about its axis and having an aperture at one axial end thereof and a rotary seal assembly affixed to said bowl body to cover said aperture and having an inlet port and outlet port in fluid communication with the interior of said bowl body,

said core being insertable into said bowl body through said aperture and having a first cylindrical portion to be received in said aperture for defining a collection chamber in fluid communication with said outlet port, a second cylindrical portion axially extending from said first cylindrical portion for defining a separation chamber in fluid communication with said inlet port between the core and the inner wall of said bowl body, openings formed between said first cylindrical portion and said second cylindrical portion for communicating said collection chamber and said separation chamber and a central opening formed to be concentric about said axis, characterized in that:
said first cylindrical portion is adapted to minimize the holdup volume of blood components in said colleciton chamber;
said second cylindrical portion is provided with a cylindrical hub which extends axially from the junction between said first and second cylindrical portions for preventing flow from said collection chamber into said central opening, said cylindrical hub defining said central opening; and
each of said openings having a minimal size for restricting back flow while permitting flow of blood components from said separation chamber to said collection chamber.

14. The core as in claim 13, wherein said first cylindrical portion and said second cylindrical portion define together a separation region between said openings and said separation chamber, the axial length of said separation region gradually decreases radially inwardly.

15. The core as in either of claims 13 or 14, wherein the total area of said openings is equal to or less than 80mm^2.

16. The core as in of claim 15, wherein said total area is equal or less than 50mm^2.

17. The core as in any of claims 13 to 16, wherein said openings are 2 or more in number and are formed equidistantly in the circumferential direction.

18. A centrifuge bowl for processing blood by centrifugation comprising:

a bowl body adapted for rotation about its axis and having an aperture at one axial end thereof, said bowl body conically flaring from one axial end to the other;
a rotary seal assembly affixed to said bowl body to cover said aperture and having an inlet port and outlet port in fluid communication with the interior of said bowi body; and
a core disposed within said bowl body and having a first portion extending generally radially for defining a collection chamber in fluid communication with said outlet port, a second portion extending from said first portion generally radially and then conically for defining a separation chamber in fluid communication with said inlet port between the core and the inner wall of said bowl body and a central opening formed concentric about said axis,
means provided in said core and/or bowl body for defining fluid passages communicating said collection chamber and said separation chamber, characterized in that:
said outlet port communicates with said collection chamber through a skirt member which is of a reduced diameter and including a radially outward opening disposed radially inwardly of said fluid passages;
said aperture of said bowl body is formed cylindrically and the radial inner wall of the cylindrical aperture is disposed radially closely adjacent to said opening of said skirt member;

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said first portion is provided with a cylindrical hub which extends axially from the junction between said first and second portions to a position axially closely adjacent to said skirt member;
each of said fluid passages having a minimal size for restricting back flow while permitting flow of blood components from said separation chamber to said collection chamber; and
said section of said second portion extending generally radially from said first portion is adapted to define with the inner wall of said bowl body a separation region between said fluid passages and said separation chamber, the axial length of said separation region gradually decreases radially inwardly.

19. The centrifuge bowl as in any of claims 2 to 5 or claim 18, wherein the diameter of said skirt member is equal to or less than 33mm.

20. The centrifuge bowl as in any of claims 1 to 12 or 18 or 19, wherein the total area of said openings or fluid passages is equal to or less than 80mm^2.

21. The centrifuge bowl as in claim 20, when dependent on claims 18 or 19, wherein said total area is equal to or less than 30mm^2, or when dependent on claims 1 to 12 wherein said total area is equal to or less than 50mm^2.

22. The centrifuge bowl as in any of claims 1 to 12 or 18 to 21, wherein said fluid passages or openings are 2 or more in number and are formed equidistantly in the circumferential direction.

23. The centrifuge bowl as in any of claims 1 to 12 or any of claims 18 to 22, wherein the axial spacing between said axial end of said cylindrical hub and said skirt portion is equal to or less than 2mm.

24. The centrifuge bowl as in claim 23, wherein said axial spacing is equal to or less than 1mm.

25. The centrifuge bowl as in any of claims 6 to 12 or any of claims 18 to 24, wherein the radial spacing between said radial inner wall of said cylindrical aperture and said opening of said skirt member is equal to or less than 2mm.

26. The centrifuge bowl as in any of claims 1 to 11 or any of claims 18 to 25, adapted for collecting from whole blood concentrated red blood cells substantially free from white blood cells.

27. A centrifuge bowl for processing blood by centrifugation comprising:

a bowl body adapted for rotation about its axis and having an aperture at one axial end thereof;
a rotary seal assembly affixed to said bowl body to cover said aperture and having an inlet port and outlet port in fluid communication with the interior of said bowl body; and
a core inserted into said bowl body through said aperture and having a first cylindrical portion received in said aperture and defining a collection chamber in fluid communication with said outlet port through a skirt member having a radially outward opening, a second cylindrical portion axially extending from said first cylindrical portion and defining a separation chamber in fluid communication with said inlet port between the core and the inner wall of said bowl body, openings formed between said first cylindrical portion and said second cylindrical portion and communicating said collection chamber and said separation chamber and a central opening formed concentric about said axis, characterized in that:
said first cylindrical portion and said second cylindrical portion define together a separation region between said openings and said separation chamber, the axial length of said separation region gradually decreases radially inwardly.

28. A core for use in a centrifuge bowl for processing blood by centrifugation, said centrifuge bowl comprising a bowl body adapted for rotation about its axis and having an aperture at one axial end thereof and a rotary seal assembly affixed to said bowl body to cover said aperture and having an inlet port and outlet port in fluid communication with the interior of said bowl body,

said core being insertable into said bowl body through said aperture and having a first cylindrical portion to be received in said aperture for defining a collection chamber in fluid communication with said outlet port, a second cylindrical portion axially extending from said first cylindrical portion for defining a separation chamber in fluid communication with said inlet port between the core and the inner wall of said bowl body, openings formed between said first cylindrical portion and said second cylindrical portion for communicating said collection chamber and said separation chamber and a central opening formed to be concentric about said axis,

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characterized in that:
said first cylindrical portion and said second cylindrical portion define together a separation region between said openings and said separation chamber, the axial length of said separation region gradually decreases radially inwardly.

29. The centrifuge bowl as in any of claims 9 to 12 or claim 27, or the core as in any of claims 14 to 17 or 28, wherein said separation region is defined between said first cylindrical portion and said second cylindrical portion by the axial end of said first cylindrical portion and a radially inwardly deflecting portion of said second cylindrical portion.

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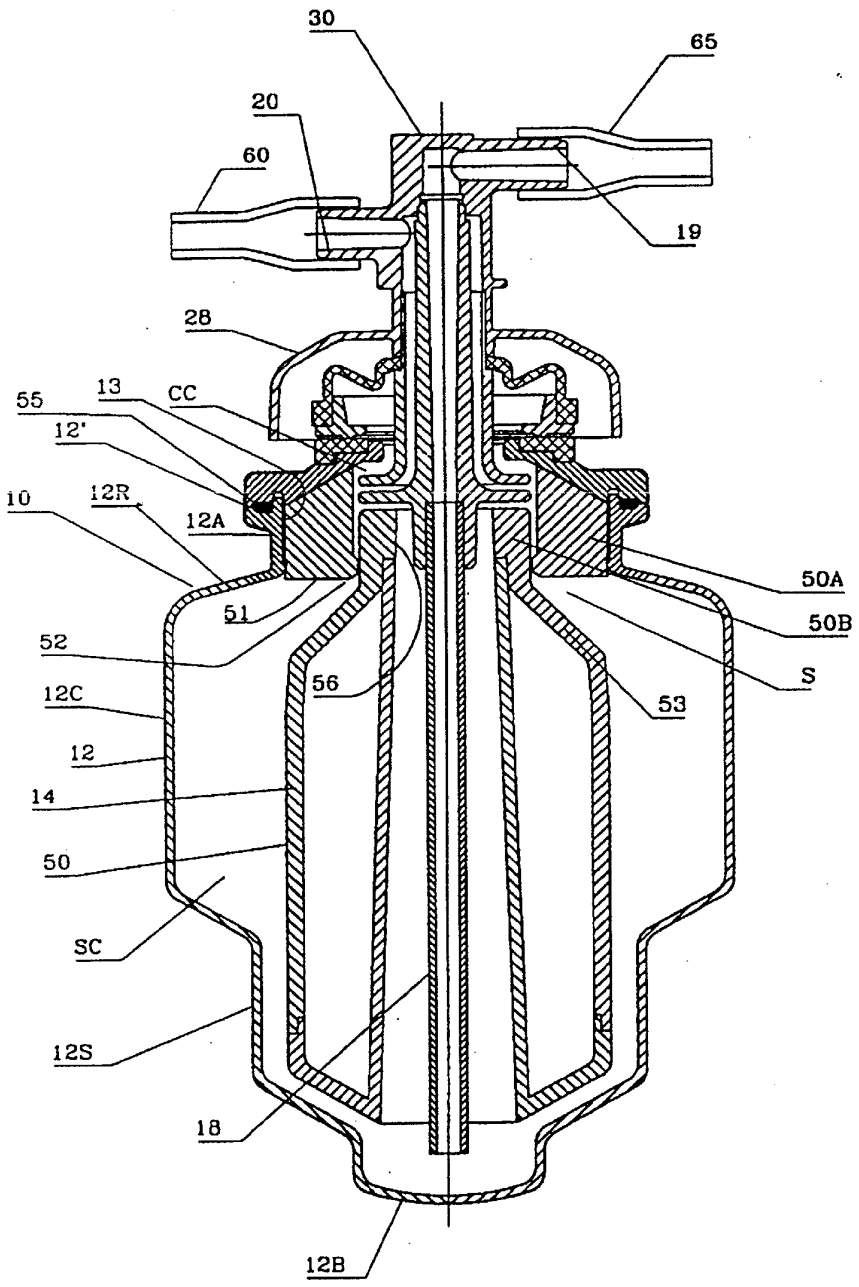


FIGURE 1

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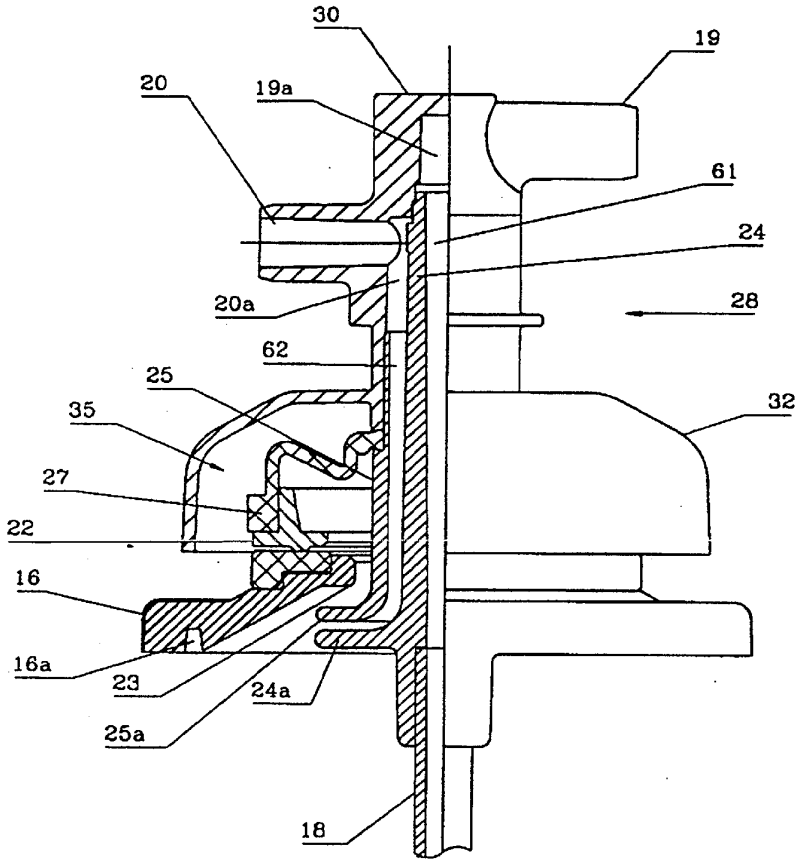


FIGURE 2

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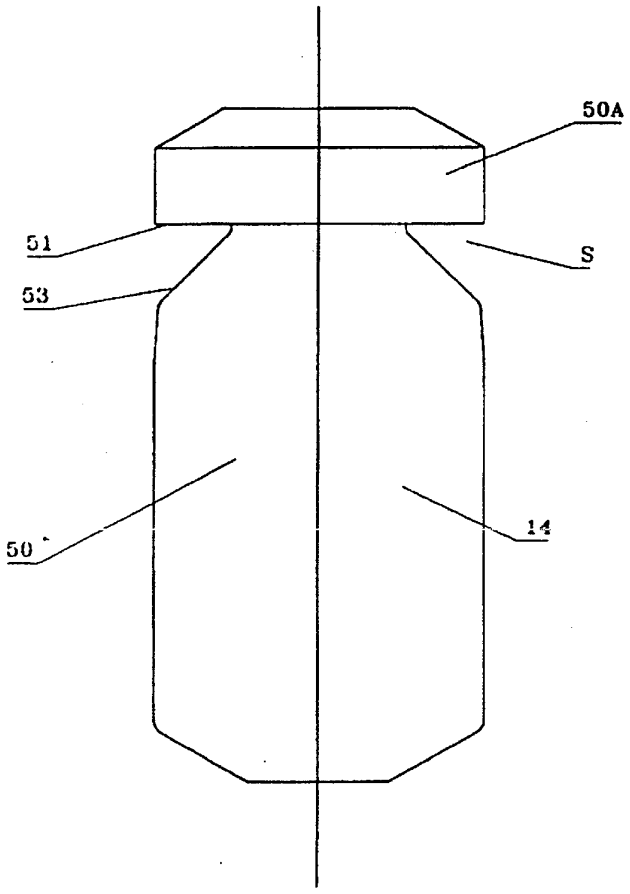


FIGURE 3

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FIGURE 4A

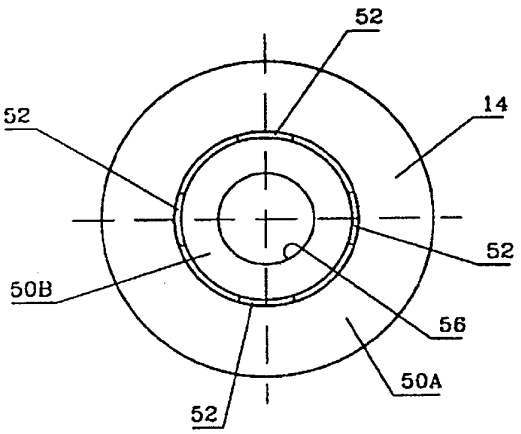
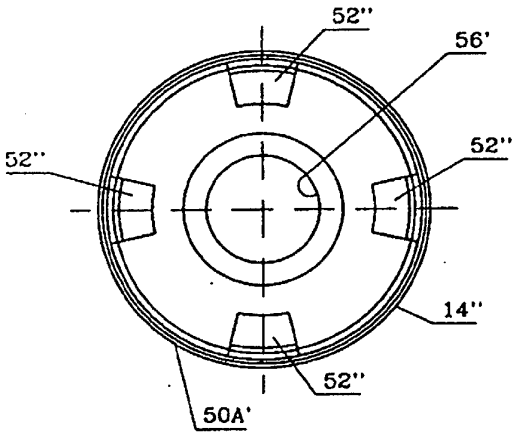


FIGURE 4B



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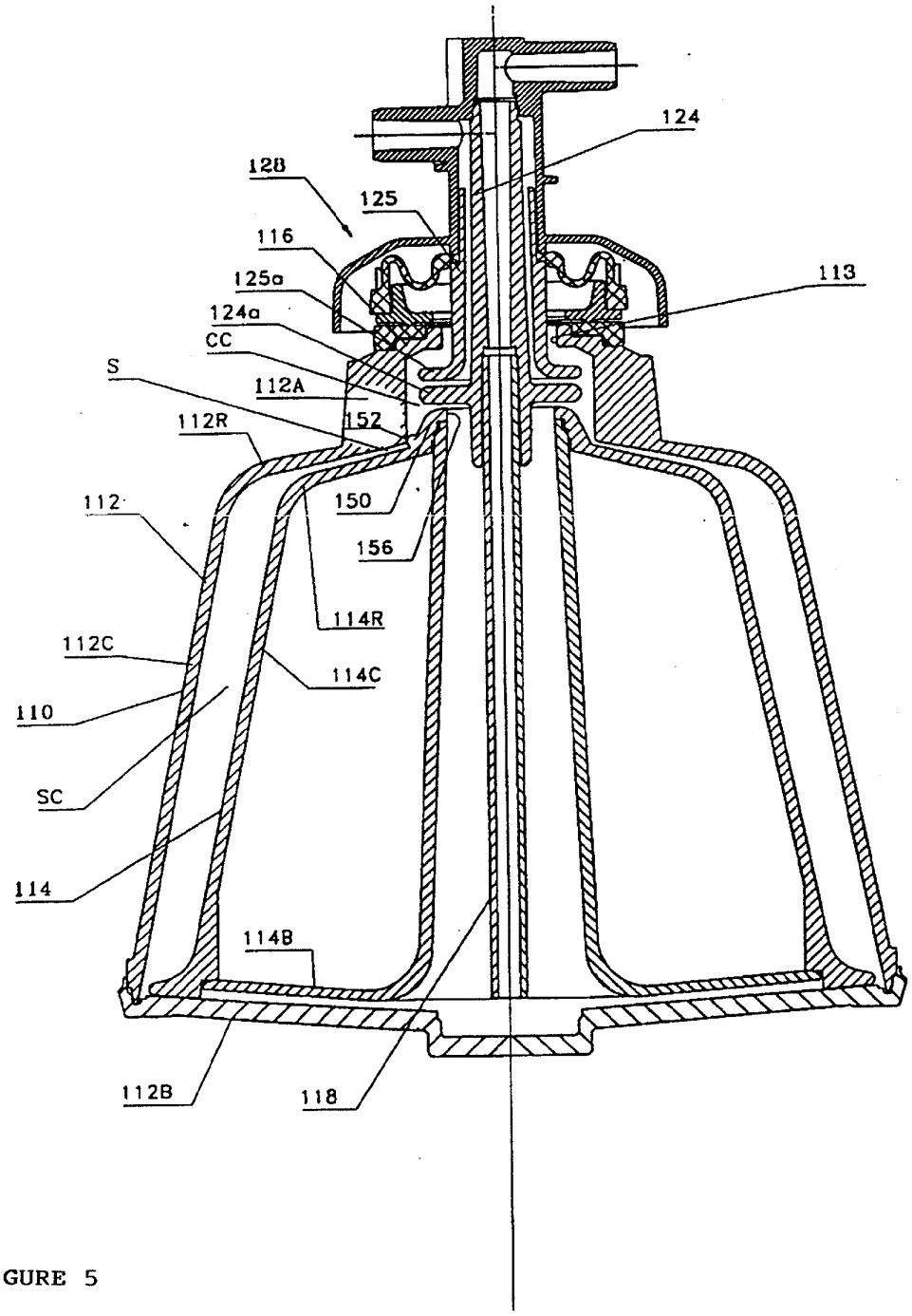


FIGURE 5

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FIGURE 6A

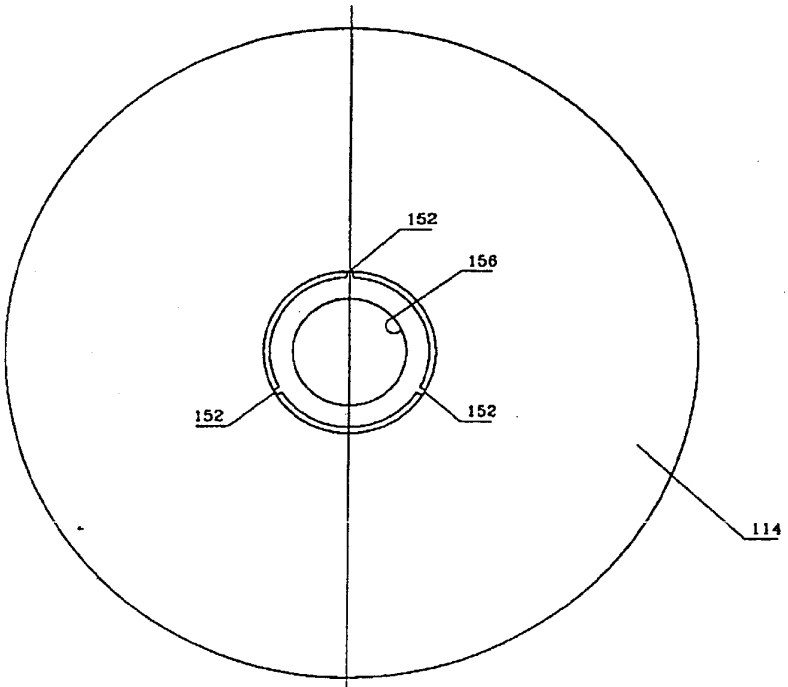
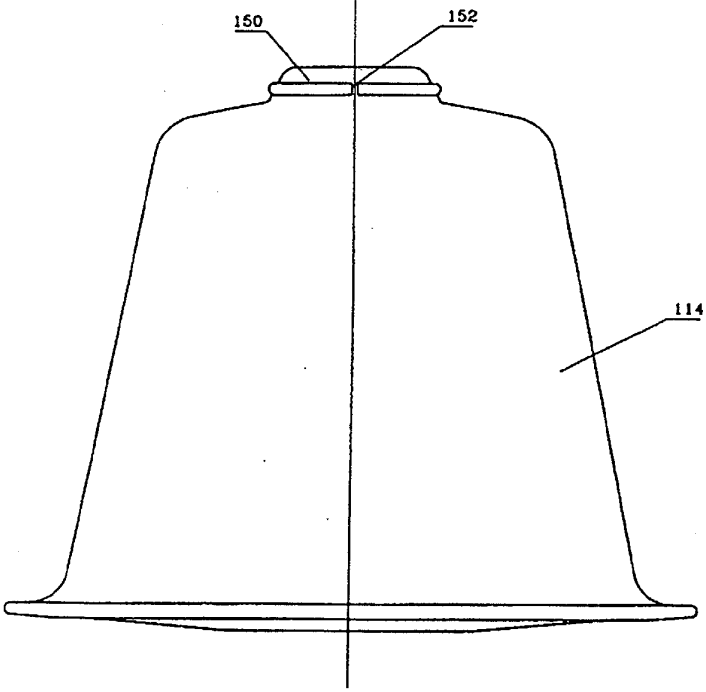


FIGURE 6B



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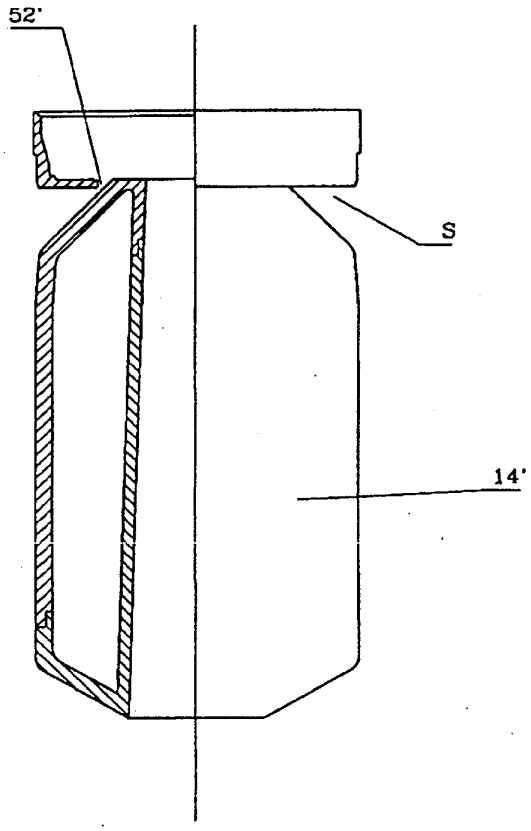


FIGURE 7

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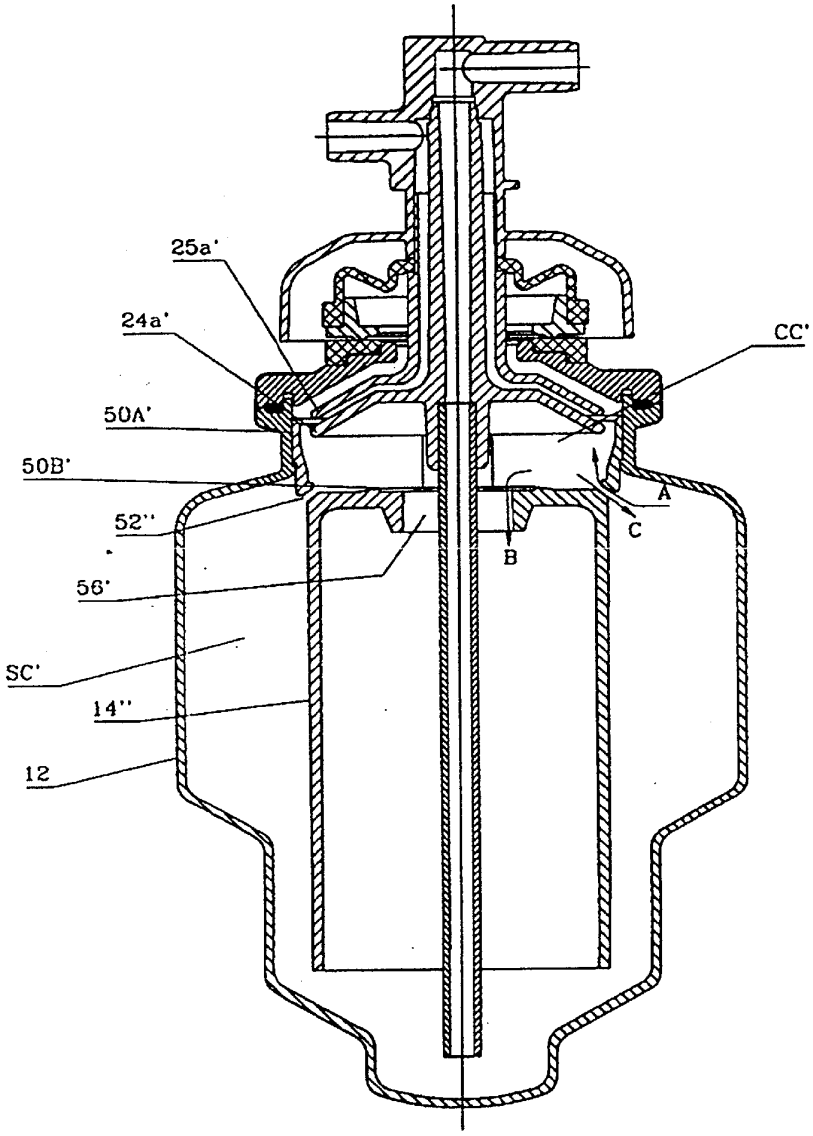


FIGURE 8

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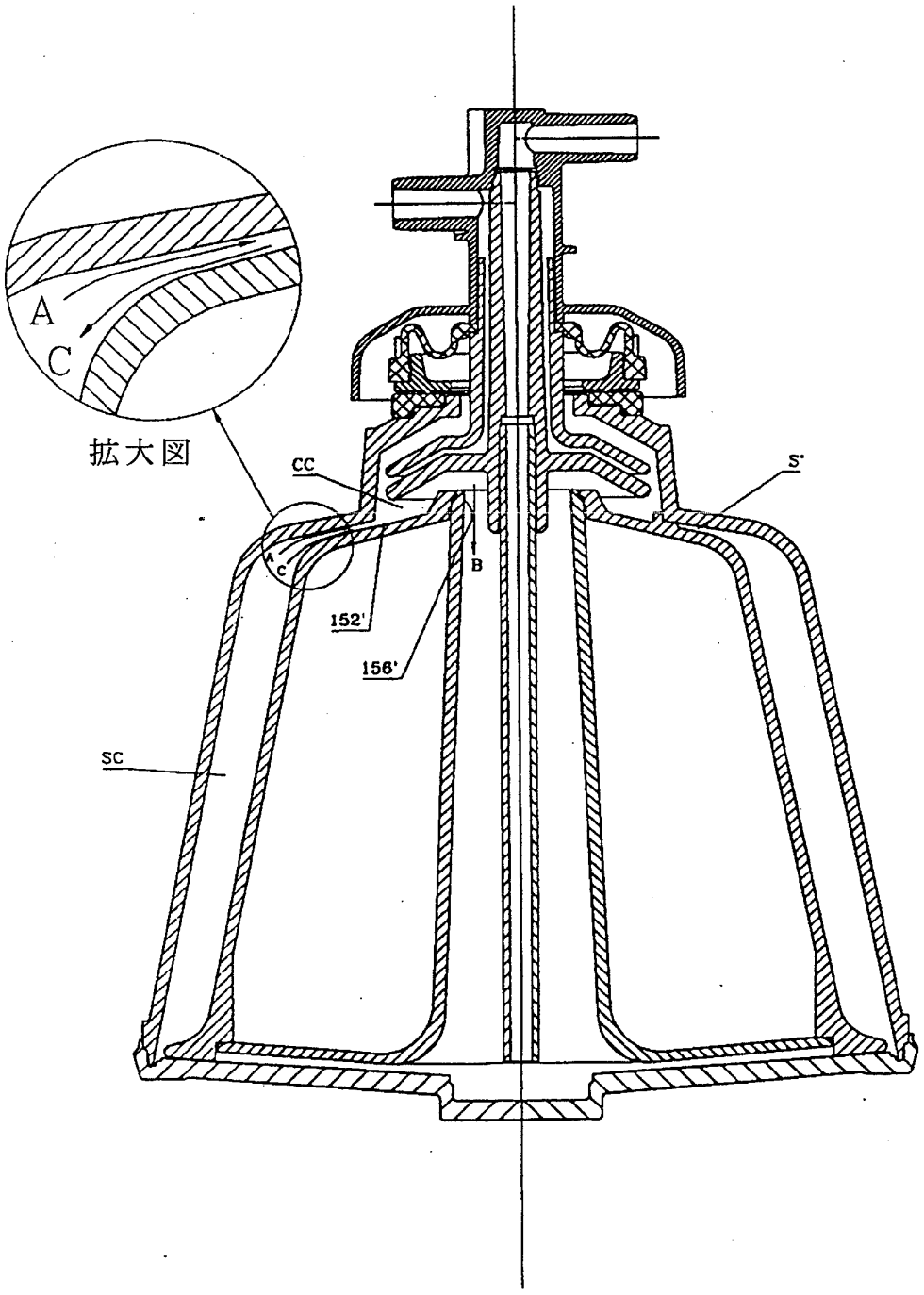


FIGURE 9

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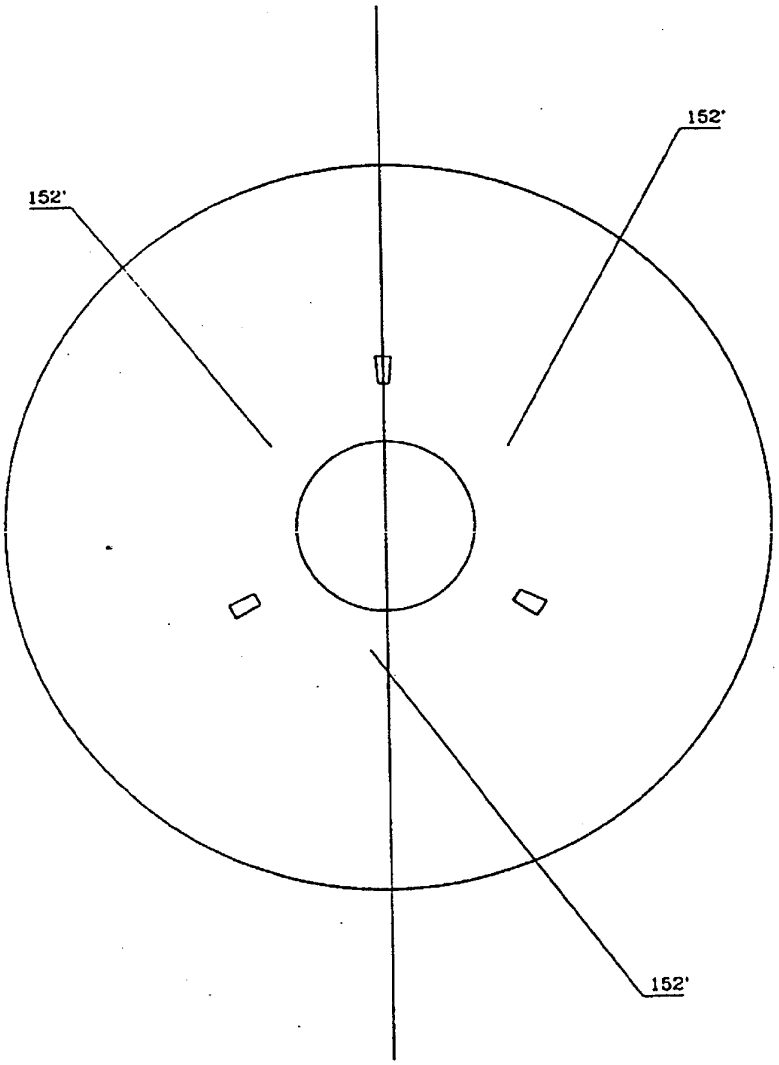


FIGURE 10

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 30 2266

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	US 3 565 330 A (A. LATHAM JR.) * column 5, line 5 - line 30 * * figure 1 * ---	1,6,13, 18,27,28	B04B5/04 B04B7/08
A,D	US 5 045 048 A (E.W. KALESKAS) * figure 1 * ---	1,6,13, 18,27,28	
A,D	US 4 983 158 A (T.D. HEADLEY) * figure 4 * -----	1,6,13, 18,27,28	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

B04B

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	8 July 1997	Leitner, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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Espacenet

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Inventor(s):

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Classification:
- **international:** ***B04B1/00; B04B5/04;*** (IPC1-7): B04B7/00
- **cooperative:** **B04B5/0428**; **B04B5/0442**

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Abstract not available for FR2258898 (A1)

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A1

DEMANDE DE BREVET D'INVENTION

(21) N° **75 02782**

(54) **Centrifugeuse pour le traitement de liquides biologiques, comme le sang.**

(51) Classification internationale (Int. Cl.²). **B 04 B 7/00.**

(22) Date de dépôt ..... 29 janvier 1975, à 15 h 34 mn.

(33) (32) (31) Priorité revendiquée : *Demandes de brevets déposées en République Fédérale d'Allemagne le 29 janvier 1974, n. P 24 04 036.6, le 21 février 1974, n. P 24 08 206.2 et le 31 août 1974, n. P 24 41 824.4 au nom de la demanderesse.*

(41) Date de la mise à la disposition du public de la demande ..... B.O.P.I. — «Listes» n. 34 du 22-8-1975.

(71) Déposant : Société dite : HERAEUS-CHRIST G.M.B.H., résidant en République Fédérale d'Allemagne.

(72) Invention de :

(73) Titulaire : *Idem* (71)

(74) Mandataire : Cabinet Beau de Loménie, 55, rue d'Amsterdam, 75008 Paris.

Vente des fascicules à l'IMPRIMERIE NATIONALE, 27, rue de la Convention — 75732 PARIS *CEDEX 15*

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La présente invention concerne une centrifugeuse pour le traitement de liquides biologiques, comme le sang, avec un récipient incorporé dans le rotor de la centrifugeuse et se composant d'un matériau flexible, repliable, avec au moins trois portions pour le liquide de traitement, le liquide biologique, les déchets, lesquelles sont reliées ensemble.

On connaît déjà des dispositifs pour le lavage du sang. Il s'agit soit de dispositifs dans lesquels des pompes péristaltiques agissent directement sur une poche flexible de sang (brevet des Etats-Unis d'Amérique 3 351 432)soit de dispositifs dans lesquels les canaux de refoulement entre une poche à sang et un récipient d'alimentation en liquide de lavage sont comprimés par une pompe péristaltique (brevet de la République Fédérale d'Allemagne 1 617 782) ou dans lesquels le liquide est entraîné par une pompe à vitesse variable (demande de brevet publiée de la République Fédérale d'Allemagne n° 2 039 899). La demande de brevet allemand publiée 2 039 898 consiste à rendre annulaire le récipient flexible à sang et la demande de brevet allemand 2 039 897 consiste à le placer dans un rotor avec le récipient d'alimentation.

Il est également connu de placer la poche à sang flexible dans le rotor d'une centrifugeuse et d'agir hydrauliquement sur celle-ci de façon que le processus de lavage se réalise automatiquement (demande de brevet de la République Fédérale d'Allemagne à la disposition du public, n° 2 254 403). Dans cette disposition connue, tous les récipients d'alimentation et unités auxiliaires se trouvent en dehors du rotor.

Le but de l'invention est de constituer une centrifugeuse de façon que le volume d'appareil soit suffisamment réduit pour que tous les dispositif annexes puissent être placés dans le carter d'une centrifugeuse courante de laboratoire et que les phases de travail nécessaires au processus de lavage soient simplifiées.

Conformément à l'invention, ce but est atteint dans une centrifugeuse du type décrit au début par le fait que le rotor est prévu pour recevoir un récipient d'une seule pièce en matériau flexible et pliable avec plusieurs portions pour le liquide de traitement, le liquide biologique et les déchets, que les portions du récipient sont placées en anneau les unes autour des autres, sont reliées les unes aux autres par des canaux obturables et sont placées dans des évidements correspondants du rotor, que le couvercle du rotor présente un support central pour un réservoir rigide destiné au liquide de lavage et une chambre pour la réception de poches flexibles pour le liquide biologique et le liquide lavé, ces poches étant raccordées par des tubulures au niveau central du récipient.

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L'avantage essentiel de l'invention est la création d'un ensemble fermé sur lui-même pour le traitement d'un liquide biologique, notamment pour le lavage du sang, ce qui permet une stérilité absolue. L'utilisation de bouteilles d'infusion et de poches multiples du commerce apporte une extension du domaine d'utilisation de la centrifugeuse de l'invention et la rend d'emploi commode et agréable.

Etant donné que, dans la centrifugeuse de l'invention, le dispositif de commande hydraulique est disposé en dehors du rotor, il peut être rapporté simplement à l'intérieur du carter d'une centrifugeuse de laboratoire de dimensions courantes. Comme avantage essentiel de l'invention, il faut cependant considérer qu'on peut placer dans le rotor de la centrifugeuse le liquide à laver dans des réservoirs de différentes formes. On peut utiliser notamment des poches en matière plastique flexibles, qui sont en une ou plusieurs pièces, de forme annulaire ou ajustée à celle des évidements du rotor à l'aide d'un adaptateur, ou qu'elles peuvent être composées selon un anneau.

D'autres caractéristiques et avantages de l'invention seront mieux compris à la lecture de la description qui va suivre d'un exemple de réalisation et en se référant aux dessins annexés, sur lesquels :

- la figure 1 représente de façon schématique un exemple de réalisation préféré de l'invention; et
- la figure 2 représente à une échelle agrandie le détail "A" de la figure 1.

Comme le montrent les figures 1 et 2, on a introduit un réservoir 3 dans le rotor 20 de la centrifugeuse qui est fermée par un couvercle 21 à l'aide d'une vis 22, ensuite, le rotor est placé sur le bout d'arbre 23 et il est accouplé au moteur d'entraînement.

Le récipient 3 se compose de deux feuilles de matière plastique 1 et 2 préformées et soudées ensemble, constituées d'un matériau flexible et pliable avec au moins trois portions pour le liquide de traitement, le liquide biologique et les déchets, chaque portion étant reliée avec la plus proche par des canaux obturables, le récipient ayant au moins une portion centrale 3 qui contient le liquide de traitement, une portion 5 annulaire entourant la portion 3 et pouvant recevoir le liquide biologique, et une portion 6 annulaire, concentrique à la portion 5, destinée aux déchets et se trouvant à une distance radiale plus grande de la portion 3.

Les feuilles de matière plastique pour le récipient sont flexibles et d'une épaisseur leur permettant d'être pliables. La feuille

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inférieure 1 du récipient et la feuille supérieure 2 sont soudées ensemble sur le pourtour extérieur, dans la zone 7. Le récipient 3 présente une portion centrale pour le liquide de traitement, notamment de lavage, et deux portions moyennes annulaires 5 qui entourent la portion centrale et reçoivent - pendant le fonctionnement - le liquide biologique comme le sang. Une portion extérieure 6 est concentrique à la portion 5 et elle est également annulaire. Cette portion 6 peut recevoir les déchets qui proviennent du traitement du liquide biologique, par exemple du lavage du sang. Entre la feuille inférieure 1 et la feuille supérieure 2 du récipient 3 se trouve une pièce de forme 8 qui est fixée dans les zones de paroi interne du récipient qui sont placées entre les différentes portions. Cette pièce 8 se compose de préférence également d'une matière plastique inerte et elle est soudée aux points 9, 10 et 11, alternativement avec la feuille inférieure et la feuille supérieure. La pièce 8 est disposée dans l'espace creux du récipient 3, entre les feuilles soudées 1 et 2 formant une poche à sang en une seule pièce, de façon qu'il se forme des canaux sur la partie supérieure, par exemple en 30, et sur la partie inférieure, par exemple en 32. Les repères 9 à 11 ont les significations suivantes :

9 : point de soudure de la feuille 1 avec la pièce 8
10 : point de soudure de la feuille 1 avec la pièce 8
11 : point de soudure de la feuille 2 avec la pièce 8

Entre 10 et 11 et entre 11 et 9 existe une ouverture 13, 14, comme le montre clairement la figure 2. Pour la fermeture des canaux, on peut prévoir des soupapes courantes non représentées. Le nombre et la forme des canaux ainsi que le choix des soupapes appropriées dépendent de chaque destination. La pièce 8 présente à peu près la forme d'une assiette et elle a un diamètre extérieur qui s'étend jusqu'au diamètre intérieur de la portion 6. Les canaux peuvent également être imprimés dans la pièce 8 dès la fabrication ou être préformés d'une autre manière. La pièce 8 doit bien entendu être placée avant la soudure de la feuille 1 avec la feuille 2.

Au cours de l'introduction du récipient de l'invention dans le rotor de la centrifugeuse, celui-ci vient en contact, au moins par la partie inférieure de sa portion 5, avec une membrane qui peut être sollicitée, par l'intermédiaire de canaux 19, par un liquide hydraulique pour la compression du contenu de la portion. Le bloc hydraulique est de préférence en dehors du rotor, mais à l'intérieur du carter de la centrifugeuse et il est relié au rotor de façon étanche au liquide. Il contient un circuit fermé

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de fluide qui permet de refouler le liquide dans la chambre représentée en dessous de la membrane et de l'en retirer.

Le dispositif de circulation hydraulique se compose d'une unité de pompage 50 avec la pompe 51 et la soupape magnétique 52. Celles-ci sont reliées à l'aide d'une garniture d'étanchéité 53 à anneau de glissement, par exemple en cuivre, au canal 19 qui débouche dans l'espace au-dessous de la membrane 18. L'unité de pompage 50 est, comme le moteur d'entraînement électrique M du rotor de la centrifugeuse, fixe par rapport au carter 54. Celui-ci comprend aussi, bien entendu, le rotor 20 et tous les éléments tournants.

Dans le couvercle 21 du rotor, on a prévu une ouverture centrale 46 qui est adaptée à la forme d'une bouteille 37 à infusion. Cette bouteille a un col 45 qui est fermé par un bouchon au travers duquel passent une tubulure de sortie 39 et une tubulure d'entrée 40. La tubulure 39 - de préférence un tuyau - sert au raccordement de la bouteille 37 à la portion centrale du récipient 3, pour laisser passer, comme liquide de lavage, la solution salée isotonique contenue dans la bouteille 37. De telles bouteilles correspondent à la norme DIN 58363 et permettent une vidange stérile avec les accessoires correspondants, notamment un filtre et des fermetures (non représentées), ainsi qu'une soupape 38. Il en est de même pour l'utilisation des poches multiples 33,34.Celles-ci sont disponibles dans le commerce comme poches à sang, comme l'indique le dessin, réunies de façon stérile l'une à l'autre en poche double et reliables avec le récipient 3. Il en résulte d'une manière connue qu'un tuyau se termine par une canule qui sert à percer, dans le récipient opposé, une membrane qui sert de soupape. Aussi bien la canule de l'un des récipients (poche à sang) que la membrane perforable sont protégées avant le raccordement par des couvercles, tels que des feuilles, qui ne doivent être enlevés que juste avant le couplage.

Pour le lavage du sang ou traitement analogue de liquides biologiques, le récipient 3 en feuille avec portion centrale et deux portions extérieure annulaires 5 et 6 formant un tout est introduit dans le rotor 20. La totalité du récipient est évacuée au début du processus de lavage, c'est-à-dire que les feuilles minces 1 et 2 sont serrées l'une contre l'autre ou sur la pièce 8.

Les poches multiples 33 et 34 sont raccordées au récipient 3 par la soupape 31 de la manière décrite précédemment. La poche 33 contient

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le liquide à laver et la poche 34 sert à la réception du liquide lavé après la fin du processus de lavage. La liaison entre la poche 34 et le récipient 33 est d'abord interrompue par le clamp 44. Après enlèvement du clamp 35, le contenu de la poche 33 coule dans la portion 5 du récipient 3 et le remplit jusqu'à environ la moitié. Si la poche 33 est vide, le tuyau de raccordement est également clampé en 35 ou, au choix, soudé. La poche 33 peut alors être coupée, mais elle peut aussi être placée avec la poche vide 34 dans l'évidement central 36 qui forme une chambre, et rester là avec elle pendant le processus de lavage. La chambre 36 peut constituer un élargissement de l'ouverture 46 du couvercle 21 et elle constitue un espace libre pour recevoir les poches multiples 33, 34 au-dessus du récipient 3 de la zone centrale du rotor. Au début, la soupape 31 pour le liquide biologique à laver n'est en liaison par le canal 32 qu'avec la portion 5. Le canal 30 sur la partie supérieure de la pièce 8, qui mène au récipient 6 à déchets, est fermé par un poussoir 29 de soupape qui repose sur la feuille 2. Le poussoir 29 est actionné de préférence par la force centrifuge.

La bouteille 37 contenant le liquide de lavage est raccordée par la tubulure 39 au travers de la soupape 38 à la portion centrale du récipient 3. Par le tube ascendant 40 qui est muni d'un filtre, l'air parvient de la chambre 36 à l'intérieur de la bouteille 37 et permet l'écoulement d'une partie du liquide de lavage, suivant la capacité de la portion centrale dans le récipient 3, qui ne contient qu'environ la moitié de la capacité de la portion 5.

Après mise en route de la centrifugeuse, celle-ci est accélérée à une vitesse de rotation qui est suffisamment élevée pour que le liquide entraîné en rotation dans la bouteille 37 monte suffisamment sur la paroi intérieure de la bouteille pour libérer l'ouverture d'écoulement du col de la bouteille.

Par suite de la force centrifuge pendant le fonctionnement du rotor 20, le contenu de la portion centrale du récipient 3 se vide dans la portion 5 et la remplit autant que le permettent les chambres dans le rotor en dessous de la feuille 1 et au-dessus de la feuille 2. Le liquide de lavage contenu dans la portion centrale du récipient 3 se mélange avec les globules rouges du sang dans la portion 5. Le mélange ou le lavage est aidé par le freinage violent du rotor de la centrifugeuse parce que le contenu de la portion 5 a tendance à continuer à tourner et qu'il est brassé violemment.

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Le rotor est entièrement arrêté et ensuite la portion centrale du récipient 3 se remplit à nouveau avec le liquide de lavage sortant du récipient 37. Mais ce liquide, quand la centrifugeuse est redémarrée, ne s'écoule cependant pas dans la portion 5, parce que celle-ci est entièrement remplie. Pour obtenir une sédimentation des globules rouges du sang et les extraire du liquide de lavage, le rotor est amené à une vitesse de rotation élevée. Ceci ouvre la soupape actionnée par la force centrifuge, par mouvement vers le haut du poussoir 29. Après achèvement de la sédimentation et pendant la rotation du rotor, un liquide d'entraînement est pompé dans la chambre 47 sous la membrane 18 par le bloc hydraulique signalé au début. Le liquide d'entraînement sollicite également le poussoir de soupape 43 qui ferme le canal 41, ce qui exclut un retour de la portion 5 dans la portion 3. De cette portion 5, le liquide de lavage est refoulé dans la portion 6 au travers du canal 32, du passage central 42 et du canal 30. A l'aide d'un dispositif de contrôle 55, 56 à cellule photoélectrique, on détecte le passage dans le canal 30 vers la portion 6 de globules rouges à la place du liquide de lavage incolore. La pompe 51 du circuit de liquide hydraulique est ensuite arrêtée, ce qui ouvre la soupape 43. Par suite, le liquide de lavage peut s'écouler de la portion centrale du récipient 3 par le canal 41 dans la portion 5 et remplir celle-ci à nouveau. Le liquide hydraulique de la chambre annulaire 47 est ainsi refoulé.

Le déroulement de la phase de travail décrite ci-dessus est répété jusqu'à épuisement du liquide de lavage.

Pour transférer les globules rouges lavés dans la poche 34, on retire la bouteille 37 après arrêt du rotor et la poche 34 repliée (éventuellement avec la poche 33) hors de la chambre 36. Après enlèvement du clamp 44, le bloc hydraulique est remis aussitôt en fonctionnement. Le canal 41 est alors fermé par le poussoir 43 (qui repose sur le côté inférieur de la feuille 1). A ce moment, les globules rouges lavés sont refoulés hydrauliquement par la membrane 18 dans la poche 34, au travers du canal 32 et de la soupape 31. Comme la soupape 29 est fermée à cet instant, les globules rouges ne peuvent pas parvenir dans la portion 6.

Une caractéristique essentielle de l'invention est en particulier la combinaison d'un récipient fermé en matériau pliable, flexible avec plusieurs portions, pour les liquides biologiques, logé dans le rotor d'une centrifugeuse de façon à être actionné hydrauliquement, et d'un procédé de fonctionnement d'une centrifugeuse avec un récipient de ce type pour le lavage du sang en utilisant des poches à sang et bouteilles d'infusion courantes.

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Bien entendu,diverses modifications peuvent être apportées par l'homme de l'art aux dispositifs ou procédés qui viennent d'être décrits uniquement à titre d'exemples non limitatifs, sans sortir du cadre de l'invention. C'est notamment le cas en ce qui concerne les récipients, réservoirs et autres configurations de divers types logeables dans le rotor, comme on l'a signalé. On préfère une unité que l'on peut introduire en entier dans le rotor et qui forme ainsi un système fermé facilement stérilisable. Il est évident également qu'en cas d'utilisation d'autres réservoirs ou récipients, les chambres de réception ou supports correspondants peuvent être adaptés à ceux-ci dans le rotor. La commande par cellule photoélectrique mentionnée dans la description est représentée schématiquement à l'intérieur de la chambre 36. Elle est cependant d'un type connu, avec une source de lumière 55 et un récepteur photoélectrique 56 qui est relié à un relais.

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REVENDICATIONS

1 - Centrifugeuse pour le traitement de liquides biologiques, notamment pour le lavage du sang, caractérisée par l'ensemble des propriétés suivantes :

le rotor est prévu pour recevoir un récipient d'une seule pièce en matériau flexible et pliable avec plusieurs portions pour le liquide de traitement, le liquide biologique et les déchets, les portions du récipient sont placées en anneau les unes autour des autres, sont reliées les unes aux autres par des canaux obturables et sont placées dans des évidements correspondants du rotor, le couvercle du rotor présente un support central pour un réservoir rigide destiné au liquide de lavage et une chambre pour la réception de poches flexibles pour le liquide biologique et le liquide lavé, ces poches étant raccordées par des tubulures au niveau central du récipient.

2 - Centrifugeuse selon la revendication 1, caractérisée en ce que, dans le couvercle du rotor, une bouteille d'infusion est maintenue dans une ouverture centrale adaptée, de façon que son col soit tourné vers le récipient.

3 - Centrifugeuse selon l'une quelconque des revendications 1 ou 2, caractérisée en ce que le couvercle du rotor présente un évidement central qui constitue, entre le support de la bouteille d'infusion et le récipient, une chambre servant à la réception de poches.

4 - Centrifugeuse selon l'une quelconque des revendications 1 à 3, caractérisée en ce que l'évidement central dans le couvercle du rotor est constitué par un élargissement de l'ouverture pour le support de la bouteille d'infusion.

5 - Centrifugeuse selon l'une quelconque des revendications 1 à 4, caractérisée en ce qu'on a réalisé un passage central dans la paroi terminale supérieure du récipient, en face du col de la bouteille à infusion.

6 - Centrifugeuse selon l'une quelconque des revendications précédentes, caractérisée en ce que la bouteille à infusion est reliée au récipient dans la partie centrale de celui-ci.

7 - Centrifugeuse selon l'une quelconque des revendications précédentes, caractérisée en ce qu'on a disposé entre la portion moyenne

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du récipient et sa portion extérieure une soupape manoeuvrée par la force centrifuge.

8 - Centrifugeuse selon l'une quelconque des revendications précédentes, caractérisée en ce qu'on a disposé entre la portion centrale du récipient et sa portion moyenne une soupape actionnée par un fluide hydraulique.

9 - Centrifugeuse selon l'une quelconque des revendications précédentes, caractérisée en ce qu'elle présente une ou plusieurs poches, simples ou multiples, en matière plastique souple, stérilisable, biologiquement et chimiquement inerte, qui peuvent être adaptées à la forme des évidements du rotor à l'aide d'adaptateur(s) ou assemblées en un anneau.

10 - Procédé de lavage du sang dans une centrifugeuse, caractérisé en ce que les globules rouges s'écoulent d'une poche à sang flexible dans la portion de lavage d'un récipient flexible à plusieurs portions, sous l'effet de la force centrifuge ou d'une pression exercée sur la poche, en ce qu'ils sont mélangés avec le liquide de lavage sortant d'un réservoir central, grâce à l'accélération et/ou au freinage, en ce qu'ils sont lavés, déposés et ensuite contrôlés par un dispositif à cellule photoélectrique et en ce qu'ils sont introduits dans une poche à sang vide à l'aide d'un liquide agissant hydrauliquement, directement ou indirectement, sur une paroi du récipient.

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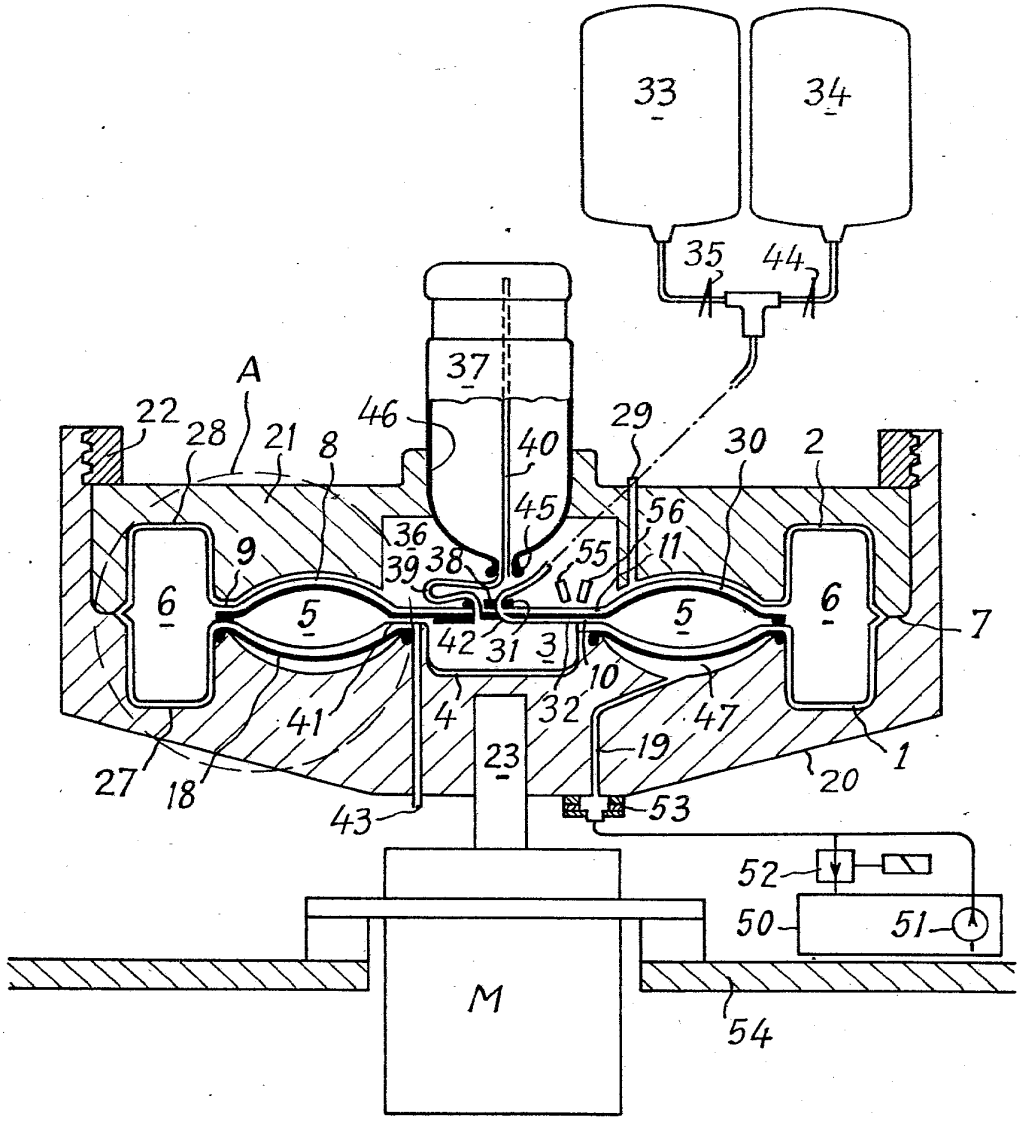


Fig. 1

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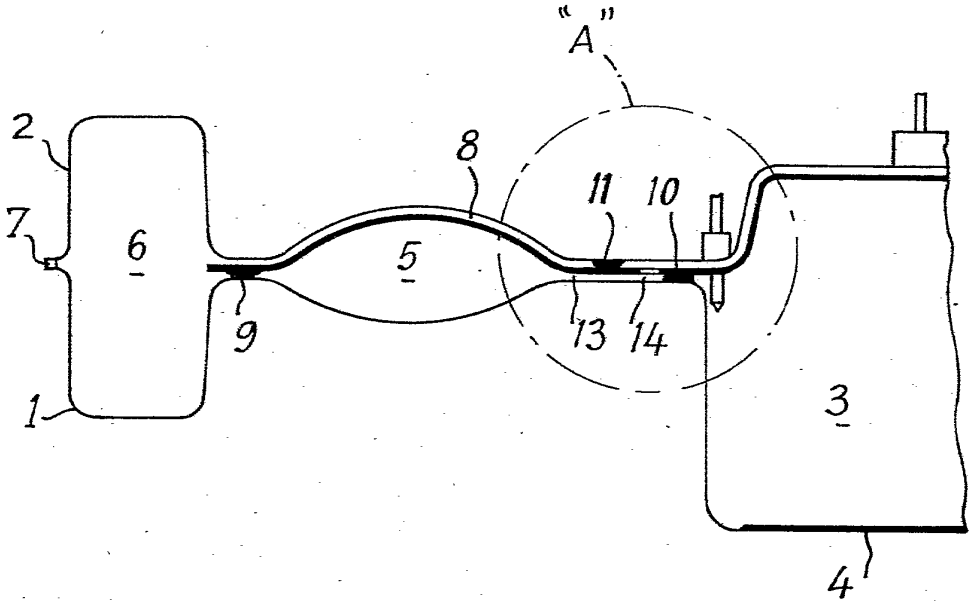


Fig-2

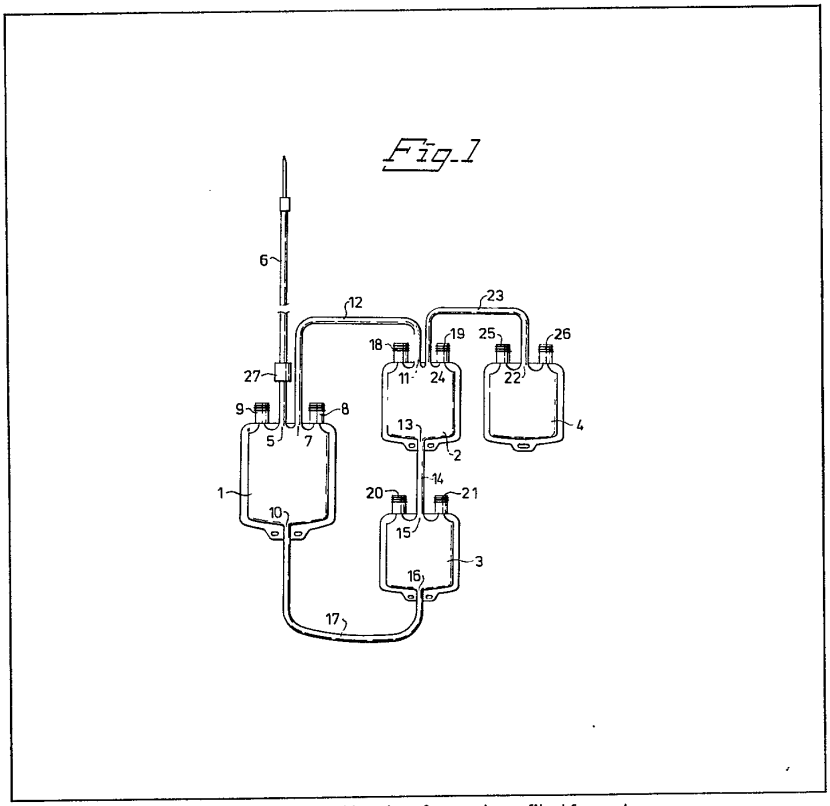
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(54) **Separating blood components**

(57) Blood is collected in a bag (1), which is then centrifuged to form an upper layer containing blood plasma, a lower layer containing red blood cells and an intermediate layer containing white blood cells. The upper and lower layers are then displaced through outlets at the top (7) and at the bottom (10) into one or more connected bags 2, 3, 4, by compressing the bag (1), so that substantially only the intermediate layer remains in the bag (1).

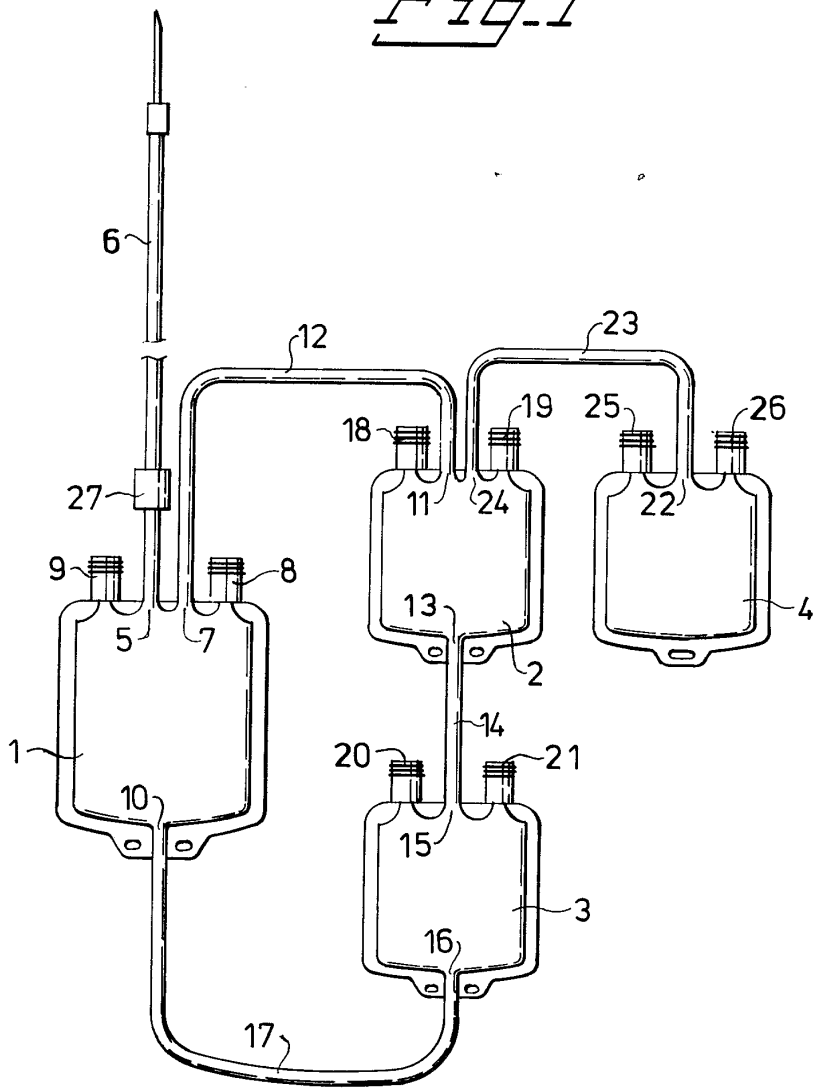


The drawings originally filed were informal and the print here reproduced is taken from a later filed formal copy.

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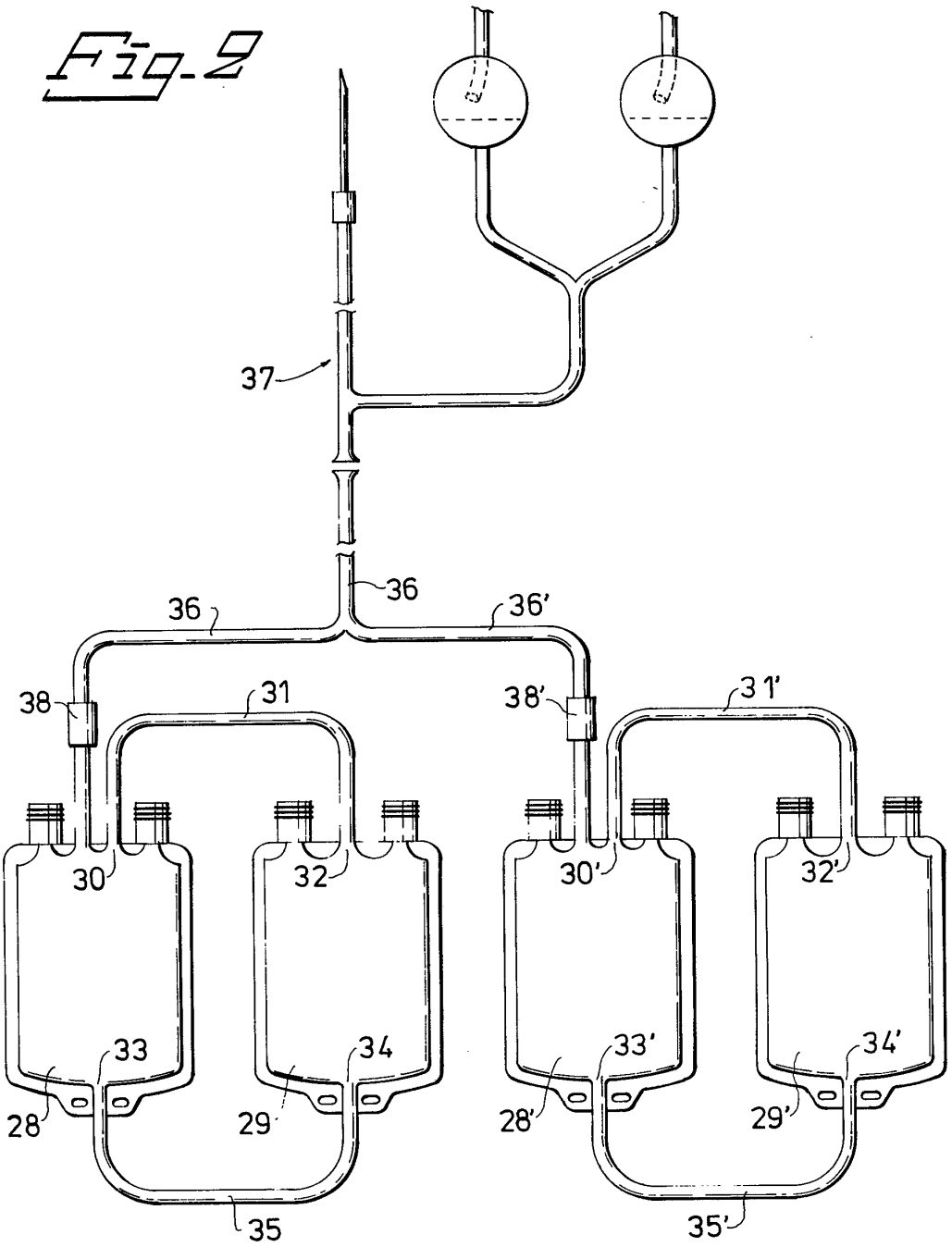
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Fig.1



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Fig. 2



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SPECIFICATION

Blood separation system

The present invention relates to an improved method of collecting, separating and storing blood components. The invention also relates to a blood bag system for use in this connection.

When collecting blood from a donor the cell components of the whole blood are usually separated from the plasma portion prior to storage and use. The separation is performed by sedimentation or, most frequently, by centrifugation, which yields an upper plasma layer, a thinner intermediate so-called buffy coat later containing white blood cells and possibly thrombocytes, and a lower layer of red blood cells. A number of various methods and devices for collection, separation and storage of the blood components are known. In the presently most frequently used method a closed sterile blood bag system of the well known "Fenwal"-type is utilized. This system usually comprises a relatively lage collecting bag and one or more transfer bags, which through connection tubes are connected to an outlet provided in the upper part of the collecting bag. After tapping of the blood to the collecting bag via a tapping tube, which also opens in the upper part of the bag, the collecting bag is centrifuged together with the transfer bag or bags, the collecting bag then being placed in a device for squeezing out the blood components. A simple and frequently used device of this kind consists of a vertical plate having a pressure plate pivotally journalled thereto, the latter being spring biased against the vertical plate. Thus, in order to squeeze out the contents of the collecting bag the bag is placed between the vertical plate and the spring biased pressure plate, blood plasma being pressed out through the outlet opening to one of the transfer bags via the connecting tube. The connecting tube to a possibly present second transfer bag is kept closed. When the buffy coat layer has reached the top edge of the collecting bag, the connection to the transfer bag with blood plasma is closed and the buffy coat layer is pressed outto the second transfer bag (after the tube connection has been opened) or the buffy coat layer is taken out through the tapping tube (which, however, may involve a contamination risk since the system then is not completely closed). Since the buffy coat layer has a tendency to stick to the bag walls, it is in most cases necessary to assist in the squeezing operation using the fingers. After the buffy coat layer has been squeezed out as much as possible the compression is interrupted, the blood plasma then being in one of the transfer bags, the red blood cells in the collecting bag and the buffy coat layer in the second transfer bag or other container.

The above described method has several disadvantages. Thus, squeezing out the blood components occupies the laboratory staff for a comparatively long time, since the squeezing operation must be monitored continuously and the squeezing of the buffy coat layer also requires manual assistance. Further, it is in practice only possible to get out 50 to 60% of the white blood cells due to the above mentioned adherence to the bag walls. A more automatized squeezing method is therefore desirable. The presently used blood bag systems and squeezing devices are, however, difficult to make more automatic. The present invention therefore aims to provide an improved procedure using a modified blood bag system for eliminating the above mentioned disadvantages.

According to one aspect of the invention, whole blood is tapped to a collecting bag having outlets both at the top and at the bottom, and after centrifugation, the blood plasma is pressed out through the upper outlet and the red blood cells through the lower outlet while keeping the buffy coat layer in the collecting bag. Hereby a system is obtained, which is suitable for automation and simultaneously results in a considerably improved separation of the white blood cells.

Simple automation is made possible in that blood plasma and red blood cells can be pressed out simultaneously through the upper and lower outlets respectively of the collecting bag. The collecting bag is then preferably squeezed by uniform compression long the whole bag area, e.g. between two vertical, substantially parallel plates. A suitable such device is described in more detail in the simultaneously filed Swedish Patent Application 7902760-3. Because the red blood cells have a greater viscosity than the plasma layer, the latter will leave the collecting bag faster than the red blood cells. Therefore, suitable means, e.g. a photocell, are provided for sensing when the blood cell layer has reached a suitable, predetermined level in the collecting bag, and said sensing device is made to activate shut-off means for the outlet tube from the top outlet of the collecting bag. The bag contents are then pressed out only through the lower outlet and are automatically stopped at a predetermined residual volume in the collecting bag, corresponding to the volume of the buffy coat layer plus a small volume of red blood cells. The interruption of the compression of the collecting bag can easily be achieved, e.g. by suitable preadjustable spacing means for the plates between which the collecting bag is compressed.

In a variant the sensing means (one or more photocells or the like) are positioned essentially at the level of the buffy coat layer already from the start of the squeezing operation, and the sensing means are arranged to maintain the buffy coat layer at essentially the same level during the entire squeezing operation. In this embodiment the sensing means will alternatingly shut off and open the top outlet of the blood bag in response to the movements of the buffy coat layer. Thus, the sensing means will shut off the top outlet (leaving the bottom outlet open) when the buffy coat layer moves upwards. Correspondingly, the sensing means will open the top outlet when the buffy coat layer falls below the sensed level. An important advatage obtained when using this embodiment is that there will be only insignificant contact between the red blood cells and the white blood cells sticking to the bag wall, resulting in a greater degree of purity of the separated red blood cell layer.

A blood bag system according to the invention

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therefore comprises a blood collecting bag having outlets both at the top and at the bottom, which outlets are connected to at least one additional blood bag via conduits which can be shut-off.

A suitable closed blood bag system for blood tapping/blood storage comprises a collecting bag and two possibly interconnected transfer bags. The bags are preferably coupled in "circle", i.e. such that each of the upper and lower outlets of the collecting bag is connected to a transfer bag, and that the two transfer bags are interconnected. Preferably, the upper outlet of the collecting bag is connected to the top portion of the first transfer bag, the bottom portion of this transfer bag is connected to the top portion of the second transfer bag, and the bottom portion of the last-mentioned transfer bag is connected to the lower outlet of the collecting bag. After collection of whole blood in the collecting bag the same is centrifugated in conventional manner together with the transfer bags. In order to squeeze out the blood components it is then only necessary to place the collecting bag in a suitable squeezing device operating automatically according to the above described principle, and to activate the compression mechanism. It is then possible to leave the apparatus, which automatically squeezes out the blood plasma layer to one of the transfer bags and the red blood cells to the other, with the buffy coat layer remaining in the collecting bag. The blood components separated into the different blood bags can then be used or stored as desired. A third transfer bag may optionally be connected to the transfer bag intended for the blood plasma, in case the primary centrifugation is adjusted such that the top layer consists of thrombocyte-rich plasma. After repeated centrifugation the plasma is squeezed into the third transfer bag, leaving a thrombocyte concentrate in the original plasma bag.

The method according to the invention can also advantageously be used for leucapheresis, wherein white blood cells are separated from the blood and the remainder is recycled to the patient. A blood bag system according to the invention used for this purpose suitably consists of two basically identical blood bags, the upper and lower outlets of one of the blood bags being connected to the corresponding outlets of the other. After collecting blood in one of the bags the two blood bags are centrifugated, whereupon the contents are squeezed out as above. Then only the buffy coat layer with the white blood cells remains in the collecting bag, whereas the blood plasma and the red blood cells have been transferred to the other blood bag. The buffy coat layer is then collected for further separation or direct use, while the contents of the second blood bag are retransfused to the patient. Since up to 95% of the white blood cells can be separated from the whole blood the required number of blood tappings is considerably reduced in comparison with conventional techniques. This, of course, is both labour-saving and more comfortable for the patient or the donor.

The above described blood bag system for lucapheresis having two blood bags connected in a closed circuit can also advantageously be used for plasmapheresis (wherein the blood plasma is separated from the other blood components) and thrombopheresis (wherein the thrombocytes are separated from the other blood components).

In order to avoid coagulation of the blood and to increase the shelf life the blood is on tapping mixed with a solution containing an anti-coagulant and a nutritent agent. Normally, this solution is present in the collecting bag from the start of the blood tapping. According to a preferred embodiment of the invention, however, at least the anti-coagulant is originally present in a transfer bag and is mixed with the blood in the collecting bag on tapping. By making the tapped blood meet a suitable amount of anti-coagulant, chosen with regard to the tapping flow and supplied by gravity of pumping, a more gentle treatment of the blood components is obtained.

The method and the blood bag system according to the invention will now be described more in detail with reference to some special embodiments thereof in connection with the accompanying drawings, wherein

Figure 1 is a schematic representation of a blood bag system suitable for blood tapping and blood separation, and

Figure 2 is a schematic representation of a blood bag system suitable for use in leucapheresis, plasmapheresis and thrombapheresis.

The blood bag system shown in Figure 1 comprises a collecting bag 1, two transfer bags 2 and 3 and optionally a further transfer bag 4. The blood bag 1 is in conventional manner provided with an inlet port 5 for a cannula-equipped blood tapping tube 6, an upper outlet port 7 and, in the shown case, pierceable tube connections 8 and 9. According to the invention the collecting bag 1 is also provided with a lower outlet port 10. The transfer bag 2 has an upper port 11, which through a tube 12 is connected to the upper port 7 of the collecting bag. Through a lower port 13 and a tube 14 the transfer bag 2 communicates with the transfer bag 3 by means of an upper port 15 of the latter. The transfer bag 3 is in turn connected to the lower port 10 of the collecting bag 1 via a lower port 16 and a tube 17. In the same way as the collecting bag 1 the transfer bags 2 and 3 are, in the shown case, provided with convntional pierceable tube connections 18, 19 and 20, 21 respectively. The optional third transfer bag 4 is via an upper port 22 and a tube 23 connected to an upper port 24 of the transfer bag 2. Also the transfer bag 4 is in the shown case provided with pierceable tube connections 25 and 26.

The above described blood bag system for collection, separation and storage of blood components may e.g. be used in the following way. Blood is tapped to the collecting bag 1 through the tapping tube 6 in conventional manner. The tube connections 12, 14 and 17 and, when a third transfer bag 4 is used, also the tube connection 23 are then shut off, e.g. by a tube clamp. A sterile anti-coagulant and nutrition solution can in conventional manner from the start be contained in the collecting bag, but according to the invention it is preferred that the anti-coagulant initially is in the transfer bag 2 for

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being fed into the collecting bag 1 through the conduit 12 by gravity or pumping simultaneously with the tapping of blood through the conduit 6. Since the blood which is tapped at the beginning of the process is not subjected to a large volume of the anti-coagulant solution, it is possible to achieve considerably milder treatment of those components of the blood which can be adversely effected by too great amounts of such a solution is achieved. In this variant the tube connection 12 between the collecting bag 1 and the transfer bag 2 is, of course, open when tapping the blood. By actuating those portions of the tube conduits 6 and 12 which are closest to the collecting bag 1 by means of any suitable pumping device, e.g. a properly designed segment or peristaltic pump with different pumping speeds for the two conduits, a suitable mixed flow (e.g. 1:7) of blood and anti-coagulant containing solution from the transfer bag 2 to the collecting bag 1 can be obtained. The blood tapping tube 6 is in this case preferably provided with a "cushion" portion 27, which can be affected by the pressure of the blood flow and which is monitored by a pressure sensor. The latter then controls the pumping speeds, so that the pumping of blood and anti-coagulant corresponds to the blood flow through the conduit 6, while maintaining a constant mixing proportion of blood and anti-coagulant solution. By operating as described above when tapping the blood it is not necessary to agitate the collecting bag, e.g. by rocking as is usual in conventional blood tapping, for obtaining good mixing of the blood and the added solution.

After completed blood tapping the conduit 6 is shut off, e.g. by welding, and the conduit 12 is shut off temporarily by a tube clamp, whereupon the whole bag system is centrifugated to form in the collecting bag an upper layer of blood plasma (normally about 60% of the blood volume), an intermediate comparatively very thin layer containing white blood cells and possibly thrombocytes - the so-called buffy coat layer - and a lower layer mainly containing red blood cells. For separation of the layers the collecting bag is introduced into a suitable squeezing or pressing device to squeeze out the contents through the upper and lowr ports 7 and 10. A suitable device is, as mentioned above, described in the simultaneously filed application No. 7902760-3 In this device the collecting bag is introduced between a vertical wall and a pressure plate, which is movable essentially prpendicularly thereto. The connecting conduits 12 and 17 are opened for passage of liquid, and the driving of the pressure plate, which is effected by suitable driving means, is activated. Blood plasma will then be pressed out from the collecting bag 1 via the tube conduit 12 to the transfer bag 2, and at the same time red blood cells are pressed out to the transfer bag 3 through the lower port 10 and the tube conduit 17. Because the layer of red blood cells has greater viscosity than the blood plasma the level of the red blood cells will slowly move upwards as the bag is compressed. For partial automation of the process the device is provided with e.g. a photocell, preferably provided on the pressure plate, sensing the upper level of the red blood cells in the collecting bag 1 when the same has reached such a level that substantially all blood plasma has been pressed out from the bag. The photocell is arranged to activate suitable shut-off means, such as a solenoid valve, blocking the connection between the collecting bag 1 and the transfer bag 2 by pinching the tube 12. The discharge from the collecting bag 1 then only takes place through the port 10 and the tube 17. The squeezing device is further preferably provided with appropriate means for preventing further compression of the collecting bag 1 when the lower level of the buffy coat layer approaches the port 10. This may e.g. be achieved by one or more pre-adjustable spacing means, which prevent further displacement of the pressure plate towards the wall portion when the volume of the collecting bag 1 corresponds to the volume of the buffy coat layer plus a marginal volume of red blood cells. After the means for compressing the collecting bag 1 have been activated, the operator can leave the device unattended, since the continued separation of blood components will be continued and completed automatically. A pr-requisite is of course that the transfer bag 3 is held in such a position that the liquid levels in the two bags are at approximately the same level when the separation is completed, since otherwise further discharge from the collecting bag can take place. Thus, after completed separation the blood plasma is in the transfer bag 2 and the red blood cells in the transfer bag 3, while the buffy coat layer remains in the collecting bag 1.

In an alternative embodiment of the above described automated procedure the photocell is positioned in the vicinity of the initial level of the buffy coat layer. As in the above embodiment the sensing means will shut off the connection between the collecting bag 1 and the transfer bag 2 when the buffy coat layer (or possibly the top level of the red blood cell layer) moves upwards and enters the level sensed by the sensing means. Conversely, the connection between the bags 1 and 2 will be re-opened when the buffy coat layer falls below the sensed level. As a result the buffy coat layer will move up and down past the photocell with a comparatively small amplitude of the movement. Thus, there will be a continuous flow from the collecting bag 1 to the transfer bag 3, and an intermittent flow from the said bag 1 to the transfer bag 2, the levels of the buffy coat layer and the red blood cell layer being essentially constant all the time. As a result only the uppermost portion of the red blood cell layer will get in contact with the white blood cells adhering to the all of the bag. This in turn results in higher purity of the separated red blood cell layer.

As mentioned above the added nutrient solution, whose main function is to permit extended storage of the red blood cells, can initially be contained in the collecting bag 1, but this solution is preferably from the beginning contained in the transfer bag 3. In this manner the solution will not be diluted by the blood plasma, and the composition of the solution can be optimized for storage of red blood cells.

After completed separation as above the connec-

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tion through the tubes 12 and 17 is blocked, e.g. by welding, and the collecting bag 1 is possibly separated from the transfer bags for storage or further processing of the blood components.

The above described blood bag system offers a high degree of flexibility. For instance, a thrombocyte concentrate may be prepared in the transfer bag 2 if the primary centrifugation is adjusted such that the upper layer will consist of thrombocyte rich plasma. After repeated centrifugation the plasma separated from the transfer bag 2 can be transferred to the third transfer bag 4 connected via the tube 23, whereby a closed system is obtained. Alternatively the plasma may be pressed out from the transfer bag 2 for industrial fractionation, e.g. through the inlet tube 12 or through the tube 23 without the transfer bag.

If the centrifugation is adjusted such that the transfer bag 2 after the separation contains cell-poor plasma, the latter can be separated, deep-frozen, and stored, suitably at temperatures below −50°C. The transfer bag 2 can also be maintained in association with the transfer bag 3. The twin-bag 2, 3 is then stored in a refrigerator with the tube connection 14 temporarily blocked, and it forms a system for the preparation of microaggregate-poor whole blood, if this should be desirable. The two bags can also at any time during the storage be repeated for individual use or storage.

As mentioned above the transfer bag 3 preferably from the beginning contains substances for optimum storage of red blood cells. When preparing a thrombocyte-rich plasma as above, a suitable amount of this storage solution can, if desired, be transferred from the transfer bag 3 to the transfer bag 2 before the separation process is started. In this way it is possible to adjust the pH-value to a desired level in the transfer bag 2.

As appears from the above the novel method according to the invention is labour-saving by allowing partial automation of the separation process. A considerable advantage is further the high degree of separation of the white blood cells (about 95%) which can be achieved because the buffy coat layer is maintained in the collecting bag 1 during separation. This can be utilized in so-called leucapheresis, i.e. separation of white blood cells and thrombocytes from the blood, as described below in connection with Figure 2.

The blood bag system for leucapheresis of Figure 2 comprises as a basic unit two interconnected blood bags 28 and 29, whose design essentially corresponds to the blood bag 1 of Figure 1. The blood bag 28 is connected via an upper port 30 and a connection tube 31 to a port 32 at the top of the blood bag 29. Similarly the bottom of the blood bag 28 is connected to the bottom of the blood bag 29 through lower ports 33 and 34 respectively and a connecting tube 35. The blood bag 28 is further provided with a blood tapping tube 36, opening at the top of the bag. For reasons explained further below the basic system is doubled, corresponding reference designations in the Figure being provided with prime marks. The refernce numeral 37 indicates a combined tapping and transfusion assembly, which in a way known *per se* comprises a blood tapping cannula and a tube connection having a drip chamber for the introduction of electrolyte solution and re-transfusion of blood.

In use the double twin-bag system is connected to the tapping/transfusion assembly 37 via the blood tapping tube 36. The connecting conduit 35 between the two blood bags 28 and 29 as well as the connection 36' are initially shut off by means of a tube clamp or the like. As in the system shown in Figure 1 a suitable amount of anti-coagulant solution is preferably placed n the blood bag 29 from the beginning. The anti-coagulant solution is then added continuously from the blood bag 29 to the blood bag 28 in the course of the tapping, conveniently by means of a tube pump as mentioned in connection with Figure 1 (the reference numerals 38 and 38' indicate "pressure cushions" corresponding to 27 in Figure 1).

After completion of the blood tapping the blood bag system 28, 29 is separated by sealing and cutting the tube 36 below the branching point thereof. The upper connection 31 between the bags 28 and 29 is shut off by means of a tube clamp, and the system is centrifugated. Similarly as above one obtains an upper plasma layer, an intermediate buffy coat layer and a lower layer with red blood cells. The coponents are squeezed out from the blood bag 28 in the same way as described above in connection with Figure 1 after opening of the tube connections 31 and 35. Blood plasma and red blood cells are pressed over to the blood bag 29 through the upper and lower tube connections 31 and 35 respectively, while the buffy coat layer remains in the collecting bag 28. The intermediate cell layer remaining in the blood bag 28 is collected for further separation or for direct use, whereas the contents of the blood bag 29 is re-transfused to the patient. Another tapping of blood is then performed in the same way using the blood bag system 28', 29'.

Thanks to the high degree of separation of the white blood cells the amount of blood to be tapped can be reduced considerably, which besides being labour-saving results in reduced strains on the patient or the blood donor.

The above described blood bag system can preferably also be used for such techniques as plasmapheresis and thrombapheresis. In the case of plasmapheresis blood tapping is made in the same way as above. After centrifugation there is obtained in the blood bag 29 an upper layer containing thrombocyte-poor plasma, an intermediate layer containing white blood cells and thrombocytes, and a lower layer, mainly comprised of red blood cells. During the squeezing procedure the lower tube connection 35 is blocked by means of a tube clamp or the like, so that blood plasma is transferred to the blood bag 29 via the upper tube connection 31, while the buffy coat layer and the red blood cells remain in the blood bag 28. The contents of the blood bag 28 are then transfused back into the blood donor.

In thrombapheresis blood tapping is made in the same way as in leucapheresis and plasmapheresis, followed by centrifugation to form an upper layer of thrombocyte-rich plasma. This upper layer is then

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pressed into the blood bag 29 in the same way as in the above described plasmapheresis process. After repeated centrifugation an upper layer of thrombocyte-poor plasma is obtained in the blood bag 29, and this plasma layer is then transferred from the blood bag 29 into the blood bag 28, after which the contents of the blood bag 28 are re-transfused to the patient or the blood donor.

An alternative thrombapheresis procedure is to start from the thrombocyte/leucocyte concentrate obtained in the above described leucapheresis and to separate the latter by centrifugation.

The method and the blood bag system according to the invention are, of course, not restricted to the above specially described and shown embodiments, but many variations and modifications are possible within the scope of the subsequent claims. This is especially true concerning the specific design of the individual blood bags, the number of tube connections, the design of the connecting tube systems, the temporary blocking of the tubes during the process, etc.

CLAIMS

1. A method of separating blood components contained in a blood sample, characterized by the steps of:

a) collecting a blood sample in a blood bag having at least one top portion outlet, and at least one bottom portion outlet

b) centrifuging said blood for separating said blood sample into an upper layer, a lower layer, and an intermediate layer; and

c) squeezing out said upper layer through said top outlet and said lower layer through said bottom outlet so as to leave essentially only said intermediate layer in said bag.

2. The method of claim 1, characterized by squeezing out said upper and lower layers through the respective outlets of the blood bag by compression of the latter over substantially the entire area thereof, and stopping the compression of the blood bag when a pre-determined residual volume remains in the blood bag.

3. The method of claim 1 or 2, chaacterized by the step of controlling the discharge of said upper layer from said blood bag so as to maintain said intermediate layer essentially at the same level in the blood bag during the squeezing operation.

4. The method of claim 3, characterized by the steps of continuously sensing a pre-determined level in said blood bag and closing said top outlet when said intermediate layer, or the top portion of said lower layer, reaches said pre-determined level, and opening said top outlet when said intermediate layer, or the top portion of said lower layer, falls below said pre-determined level.

5. The method of claim 1 or 2, characterized by stopping the flow of said upper layer when said intermediate layer, or the top portion of said lower-layer, has reached a pre-determined level, and continuing the squeezing out of said lower layer until a pre-determined residual volume remains in said blood bag.

6. The method of any one of claims 1 to 5 characterized in that said blood sample is whole blood, and in that the whole blood sample is centrifuged to form an upper layer containing blood plasma, a lower layer containing red blood cells, and an intermediate layer containing white blood cells.

7. The method of claim 6, characterized by discharging the upper layer containing blood plasma into a first transfer bag, and discharging the lower layer containing red blood cells into a second transfer bag, which may be connected to the first transfer bag.

8. The method of claim 6, characterized by discharging the upper layer containing blood plasma and the lower layer containing red blood cells into a common transfer bag.

9. The method of claim 6, 7 or 8, characterized by simultaneously adding an anti-coagulant to the whole blood when tapping the same to the blood bag, said anti-coagulant being supplied from a separate bag connected to said blood bag.

10. A blood bag system for separating blood components from a whole blood sample, comprising:

a) a blood bag arranged to receive the whole blood sample for separation of the same by centrifugation into an upper layer containing blood plasma, a lower layer containing red blood cells, and an intermediate layer containing white blood cells, said blood bag having at least one outlet at the top portion thereof, an at least one outlet at the bottom portion thereof;

b) a first transfer bag connected to said top portion outlet of the blood bag arranged to receive said upper layer containing plasma upon compression of the blood bag, and

c) a second transfer bag conncted to said bottom portion outlet of the first blood bag and arranged to receive said lower layer containing red blood cells upon compression of the blood bag.

11. The blood bag system of claim 10, characterized in that said top and bottom outlets of the blood bag are connected to a common transfer bag.

12. The blood bag system of claim 10, characterized in that said top and bottom outlets of the blood bag are connected to first and second transfer bags respectively, said top outlet of the blood bagbeing connected to a top inlet of the first transfer bag and the bottom outlet of the blood bag being connected to a bottom inlet of the second transfer bag, said first and second transfer bags optionally being interconnected.

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BLOOD PLASMA TAKING DEVICE AND CONTROL METHOD THEREOF

Inventor(s): YAMAUCHI TOSHIO ± (YAMAUCHI TOSHIO)

Applicant(s): NISSHO KK ± (NISSHO CORP, ; NISSO KK)

Classification: **- international:** ***A61B5/15; A61M1/02;*** (IPC1-7): A61B5/14; A61M1/02

- cooperative:

Application number: JP19880202264 19880812

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Abstract of JPH0252665 (A)

PURPOSE:To reduce the size and weight of the device by providing clamps to both inside and outside blood feed lines, both inside and outside blood return lines and a physiological salt soln. line respectively and providing a bubble sensor to the blood line on the side outer than a blood pump. CONSTITUTION:The outer blood return clamp 13 is provided to the outer blood feeding line 5 and an anticoagulant pump 15 is provided to an anticoagulant line 6. The blood pump 16 which can be operated forward and backward is provided on the blood line 7 and the bubble sensor 17 is mounted to the position outer than the pump 16. Further, the inner blood return clamp 18 is provided to the inner blood feed line 8 and the inner blood return clamp clamp 20 is provided to the inner blood return line 9. The outer blood return clamp 22 is provided to the outer blood return line 10 and the physiological salt soln. clamp 24 is provided to the physiological salt soln. line 11. The required pumps are decreased to 2 pieces in such a manner and the reduction of the size and weight of the system is possible.

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⑤4発明の名称　血漿採取装置とその制御方法

⑳特　願　昭63－202264

㉒出　願　昭63(1988)8月12日

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明細書

1、発明の名称

血漿採取装置とその制御方法

2、特許請求の範囲

（1）ドナーの血管に留置される留置針と、この留置針に接続された外側の送血ラインと、この外側の送血ラインの入口に抗血液凝固剤を導く抗血液凝固剤ラインと、この抗血液凝固剤ライン上に設けられた抗血液凝固剤ポンプと、前記外側の送血ラインに連続する送返血兼用の血液ラインと、この血液ライン上に設けられた正逆動作が可能な血液ポンプと、血漿分離器と、前記血液ラインから血漿分離器の下端入口に至る内側の送血ラインと、血漿分離器の上端出口よりも高い位置で該出口に接続された濃厚血液容器と、濃厚血液容器の出口から前記血液ラインの内端に至る内側の返血ラインと、血液ラインの外端から前記留置針に至る外側の返血ラインと、前記濃厚血液容器より高い液レベル位置から生理食塩水を濃厚血液容器の出口側に導く生理食塩水ラインと、血漿分離器から血漿を血漿容器に導く血漿ラインと、この血漿ライン上に設けられた自動流量制御手段とを備え、

前記各ラインのうち少なくとも内外両送血ラインと内外両返血ラインと生理食塩水ラインとにはそれぞれクランプが設けられ、かつ血液ポンプより外側の血液ラインには気泡センサが設けられてなる、

ことを特徴とする血漿採取装置。

（2）請求項第1項に記載の血漿採取装置を制御する方法であって、

採血モード時に、抗血液凝固剤ポンプの駆動により抗血液凝固剤を外側の送血ラインに供給するとともに、外側の送血ラインと血液ラインと内側の送血ラインとを血漿分離器の入口に連通させて血液ポンプを送血方向に駆動し、一方、血漿ラインでは血漿流量がほぼ平均化されるよう自動流量制御手段を動作させ、

返血モード時には、濃厚血液容器の出口に内側の返血ラインと血液ラインと外側の返血ラインとを連通させて血液ポンプを返血方向に駆動し、

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返血モード時に気泡センサにより気泡が検出された場合は、気泡の検出に応答して、血液ラインを内側の返血ラインを介して濃厚血液容器の出口に連通させ、血液ライン内の血液が濃厚血液容器に戻るよう、血液ポンプを送血方向に駆動し、

返血後の再採血時には、血液ラインを内側の返血ラインを介して濃厚血液容器の出口に連通させて血液ポンプを送血方向に駆動し血液ライン内の血液を一掃した後、前記した採血モードの動作に移り、

血液回収モード時には、生理食塩水ラインを通じて濃厚血液容器に生理食塩水を供給した後、血漿分離器の入口に内側の送血ラインと血液ラインと外側の返血ラインとを連通させ、濃厚血液容器内の生理食塩水を含む濃厚血液が血漿分離器を上から下へ流通するよう、血液ポンプを返血方向に駆動する、

ことを特徴とする血漿採取装置の制御方法。

3、発明の詳細な説明

＜産業上の利用分野＞

本発明は、ドナーからの献血による採血に際し、血漿分離器を使用して血漿のみを分離し、血球成分をドナーに返送する血漿採取装置と、その制御方法に関する。

＜従来の技術＞

従来の血漿採取装置としては、例えば第3図および第4図に示すものがある。

第3図に示す従来の装置は、ドナー側から血漿分離器1_oの入口に至る送血ライン2_oと、この送血ライン2_oに抗血液凝固剤を供給する抗血液凝固剤ライン3_oと、血漿分離器1_oの出口から濃厚血液容器4_oを介してドナー側に戻る返血ライン5_oと、血漿分離器1_oの2次出口から血漿容器6_oに至る血漿ライン7_oとを備え、送血ライン2_oには送血ポンプ8_oが、抗血液凝固剤ライン3_oには抗血液凝固剤ポンプ9_oが、返血ライン5_oには返血ポンプ10_oが、さらに血漿ライン7_oには血漿ポンプ11_oが、それぞれ設けられている。

また、送血ライン2_oには、血漿分離器1_oの手前に圧力センサ12_o付きのチャンバ13_oが介装され、返血ライン5_oにも、返血ポンプ10_oより下流側に圧力センサ14_o付きのチャンバ15_oが介装されている。

この装置は通常、2本の留置針を使用する。

第4図に示す装置は、送血ライン2_oと返血ライン5_oとのドナー側の部分を共通化して1本の血液ライン16_oにまとめ、この血液ライン16_o上に正逆動作が可能な血液ポンプ17_oを設け、さらに、送血ライン2_o上に循環ポンプ18_oを設けたものである。循環ポンプ18_oの上流側には生理食塩水ライン19_oが接続されている。図中、第2図の装置の各部と対応する部分には、同一の符号を付している。

この装置は、単一の留置針を使用する単針式の装置である。

＜発明が解決しようとする問題点＞

第3図に示した装置は、送血ポンプ8_o、抗血液凝固剤ポンプ9_o、返血ポンプ10_oおよび血漿ポンプ11_oの計4個のポンプを装備するものであるから、全体が大型化し、重量も増大し、そのため、献血用車両への積み込み、移動に不便であり、また、2本の留置針を使用するから、ドナーの負担が大きかった。

第4図に示した装置は、単針式であるため、ドナーの負担は軽減されるものの、やはり、4個のポンプを装備するので、全体が大型化し、重量も増大する、という問題があった。

これに対しては、4個のポンプのいずれかのものを省略したり、他のポンプと共用化することが考えられるのであるが、省略や共用化によりポンプの数を削減すると、血漿採取の効率が低下するなど、種々の不都合が発生するので、ポンプ数の削減は容易ではない。

例えば、血漿ポンプ11_oについて、これを省略すると、採血開始時には、血漿分離器1_oから多量の血漿が採取されるものの、一度に多量の血漿がろ過されるため、早期に目詰まりが生じ、採血周期の後半で血漿採取量が著しく減少し、採取周期全体での採取総量が少なくなる。

また、第4図に示すような単針式の装置では、

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採血と返血とを数回繰り返した後、血液回収モードに移り、濃厚血液容器4₀に生理食塩水を供給し、生理食塩水と濃厚血液との混合液をドナーに戻すのであるが、ここで、循環ポンプ18₀を省略すると、生理食塩水の供給が難しくなり、血液回収に時間がかかる、等の問題が生じる。

さらに、第4図に示す装置では、血液が流通するラインにそれぞれ圧力センサ12₀,14₀付きのチャンバ13₀,15₀が介装されており、これらチャンバ13₀,15₀は比較的に大型で、広いスペースを必要とするので、この点も、装置全体を大型化する要因となっていた。しかしながら、これらチャンバ13₀,15₀は、各ラインの血液の圧力の検出に必要であるほか、血液に混入した気泡の除去、すなわちエア抜きの役目を果たすので、省略することは難しい。

このほか、上記従来の装置では、血液ライン16₀に、血漿が未分離の血液も、血漿が分離された赤血球濃厚血液も流通するから、濃厚血液容器4₀から濃厚血液をドナーに返血した後に再び採血に移った場合、血液ライン16₀には濃厚血液が残留しており、この残留血液が血漿分離器1₀に送り込まれることになるから、血漿分離器1₀で目詰まりや、溶血を生じることがある、という問題もあった。

本発明は、上述の問題点に鑑みてなされたものであって、ポンプの数を削減するとともに、チャンバの省略を可能にして、装置の小型化、軽量化を図り、かつ、ポンプ数の削減やチャンバの省略に伴う不都合の発生を未然に防止し、効率よく血漿の採取を行えるようにすることを目的とする。

<問題点を解決するための手段>

本発明の血漿採取装置は、上記の目的を達成するために、ドナーの血管に留置される留置針と、この留置針に接続された外側の送血ラインと、この外側の送血ラインの入口に抗血液凝固剤を導く抗血液凝固剤ラインと、この抗血液凝固剤ライン上に設けられた抗血液凝固剤ポンプと、前記外側の送血ラインに連続する送返血兼用の血液ラインと、この血液ライン上に設けられた正逆動作が可能な血液ポンプと、血漿分離器と、前記血液ラインから血漿分離器の下端入口に至る内側の送血ラインと、血漿分離器の上端出口よりも高い位置で該出口に接続された濃厚血液容器と、濃厚血液容器の出口から前記血液ラインの内端に至る内側の返血ラインと、血液ラインの外端から前記留置針に至る外側の返血ラインと、前記濃厚血液容器より高い液レベル位置から生理食塩水を濃厚血液容器の出口側に導く生理食塩水ラインと、血漿分離器から血漿を血漿容器に導く血漿ラインと、この血漿ライン上に設けられた自動流量制御手段とを備え、前記各ラインのうち少なくとも内外両送血ラインと内外両返血ラインと生理食塩水ラインとにはそれぞれクランプが設けられ、かつ血液ポンプより外側の血液ラインには気泡センサが設けられている構成とした。

また、本発明の制御方法は、採血モード時に、抗血液凝固剤ポンプの駆動により抗血液凝固剤を外側の送血ラインに供給するとともに、外側の送血ラインと血液ラインと内側の送血ラインとを血漿分離器の入口に連通させて血液ポンプを送血方向に駆動し、一方、血漿ラインでは血漿流量がほぼ平均化されるよう自動流量制御手段を動作させ、返血モード時には、濃厚血液容器の出口に内側の返血ラインと血液ラインと外側の返血ラインとを連通させて血液ポンプを返血方向に駆動し、返血モード時に気泡センサにより気泡が検出された場合は、気泡の検出に応答して、血液ラインを内側の返血ラインを介して濃厚血液容器の出口に連通させ、血液ライン内の血液が濃厚血液容器に戻るよう、血液ポンプを送血方向に駆動し、返血後の再採血時には、血液ラインを内側の返血ラインを介して濃厚血液容器の出口に連通させて血液ポンプを送血方向に駆動し血液ライン内の濃厚血液を一掃した後、前記した採血モードの動作に移り、血液回収モード時には、生理食塩水ラインを通じて濃厚血液容器に生理食塩水を供給した後、血漿分離器の入口に内側の送血ラインと血液ラインと外側の返血ラインとを連通させ、濃厚血液容器内の生理食塩水を含む濃厚血液が血漿分離器を上か

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ら下へ流通するよう、血液ポンプを返血方向に駆動するようにした。

＜作用＞

本発明の血漿採取装置は、前記した方法で制御することにより、採血時には、ドナーから採取された血液に抗血液凝固剤が混合され、このように抗凝固化された血液が血漿分離器に送り込まれる。血漿分離器では、この採取血液から血漿が分離されて血漿容器に送られ、血漿が分離されたあとの赤血球濃厚血液は、濃厚血液容器に貯溜される。この場合、血漿ラインでは、自動流量制御手段により血漿の流量がほぼ平均化され、一時に多量の血漿がろ過されることがないので、血漿分離器で目詰まりが発生しない。

返血時には、濃厚血液容器に貯溜された濃厚血液が内側の返血ライン、血液ライン、外側の返血ラインおよび留置針を通じてドナーに戻される。この場合、返送する血液に気泡が含まれていると、この気泡が気泡センサで検出され、この検出に応答して血液ポンプの送り方向が逆転し、気泡を含む血液は、内側の返血ラインを逆に流通して濃厚血液容器に戻され、血漿分離器には流入せず、血漿分離器では気泡によるエアブロック等の支障が生じない。また、濃厚血液容器に戻された血液については、該容器の内部でエア抜きが行われる。したがって、エア抜きのためのチャンバの省略が可能となる。

返血後の再採血時には、採取血液の流通経路の一部である血液ラインに濃厚血液が残留しているが、この血液ライン内の残留血液は、採血周期の初期に、直接的に濃厚血液容器に戻され、血液ラインに濃厚血液が無くなった時点で、流通経路が血漿分離器側に切り替わる。したがって、残留した濃厚血液は血漿分離器に流入せず、血漿分離器には新たな採取血液のみが流入することになる。

さらに、血液回収時には、生理食塩水が液レベルのレベル差を利用して直接、濃厚血液容器に供給される。この場合、濃厚血液容器内の空気はエアラインから排出されるので、生理食塩水の導入に時間がかからない。また、生理食塩水と混合した濃厚血液は、血漿分離器を上から下へ通過することになり、この液には血液ポンプの吸引力と、液レベルの差による圧力が作用するから、迅速に流通する。したがって、血液回収を短時間で済ませることができる。

＜実施例＞

以下、本発明を図面に示す実施例に基づいて詳細に説明する。

第１図は本発明に係る血漿採取装置の構成図である。図に示すように、この実施例の血漿採取装置は、ドナーＤの血管に留置される単一の留置針１と、血漿分離器２とを備える。この血漿分離器２は、例えば中空糸で構成された膜型血漿分離器であり、装置内では上下の向きで支持され、その上端出口には、血漿が分離されたあとの赤血球濃厚血液を貯溜する濃厚血液容器３が設けられている。この濃厚血液容器３は、硬質の材料でケース状に成形されている。濃厚血液容器３には、少なくとも上下２段の液レベルを検出しうるレベルセンサ４が設けられている。

また、この血漿採取装置は、ドナーＤ側に位置する外側の送血ライン５と、抗血液凝固剤ライン６と、送返血兼用の血液ライン７と、血漿分離器２側に位置する内側の送血ライン８と、内側の返血ライン９と、外側の返血ライン１０と、生理食塩水ライン１１と、血漿ライン１２とを備えている。

外側の送血ライン５は、留置針１に接続されて血液ライン７の外端に接続しており、これには外側送血クランプ１３が設けられている。抗血液凝固剤ライン６は、抗血液凝固剤容器１４から抗血液凝固剤を外側の送血ライン５の入口に導くもので、これには抗血液凝固剤ポンプ１５が設けられている。

血液ライン７は、外側の送血ライン５および返血ライン１０と内側の送血ライン８および返血ライン９との間にあってこれらを相互に接続するもので、この血液ライン７上には正逆動作が可能な血液ポンプ１６が設けられ、血液ポンプ１６より外側位置に気泡センサ１７が取り付けられている。

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内側の送血ライン８は、血液ライン７の内端から血漿分離器２の下端入口に至るもので、その中途部には、内側送血クランプ１８と、圧力センサ１９とが設けられている。圧力センサ１９は、この実施例では、ラインの一部となる拡縮自在の筒体とこの筒体の拡縮に応じて検出信号を出力する部分とから構成されている。

内側の返血ライン９は、濃厚血液容器３の出口から血液ライン７の内端に至るもので、これには内側返血クランプ２０が設けられている。

外側の返血ライン１０は、血液ライン７の外端から留置針１に至るもので、これには、圧力センサ２１と外側返血クランプ２２とが設けられている。この圧力センサ２２は、前記した内側の送血ライン８上の圧力センサ１９と同一のものが使用される。

生理食塩水ライン１１は、生理食塩水容器２３から生理食塩水をレベル差を利用して濃厚血液容器３の出口に導くもので、これには、生理食塩水クランプ２４が設けられている。

血漿ライン１２は、血漿分離器２の下部２次出口から血漿を血漿容器２５に導くもので、これには、血漿クランプ２６と自動流量制御手段２７とが設けられている。自動流量制御手段２７としては、例えば、血漿通路の開度をモータの駆動により無段階的に変更する、いわゆる「オートクレンメ」が使用される。

さらに、濃厚血液容器３の上部と血漿分離器２の上部２次出口にはそれぞれ、エアフィルタ２８を介してエアライン２９，３０が接続され、両エアライン２９，３０は、単一のエアポンプ３１に接続されている。３２，３３は、各エアライン２９，３０に設けたエアクランプ、３４は吸排気用クランプである。

そして、検出手段である気泡センサ１７、圧力センサ１９，２１およびレベルセンサ４等の検出信号は、図示省略した制御部に入力し、抗血液凝固剤ポンプ１５、血液ポンプ１６、エアポンプ３１、各ライン上のクランプおよび自動流量制御手段２７は、前記制御部からの指令信号により制御されるようになっている。

次に、上記構成の装置の制御方法を第２図(a),(b),(c)のフローチャートに基づいて説明する。なお、１人のドナーに対しては、通常、採血と返血とを数回繰り返し、血漿採取量が一定量に達すると、血液回収モードに移り、残余の濃厚血液に生理食塩水を加えてドナーに戻すようになっている。

① 採血モード

第２図(a)に示すように、ステップS1で返血後の採血か否かを判断し、返血後の採血でなければ、ステップS2で、外側送血クランプ１３と内側送血クランプ１８とを開き、血液ポンプ１６を送血方向に駆動し(ステップS5)、同時に抗血液凝固剤ポンプ１５を駆動する(ステップS6)。この場合、外側返血クランプ２２と内側返血クランプ２０と生理食塩水クランプ２４とは閉じておく。血漿ライン１２では、血漿クランプ２６を開き(ステップS3)、自動流量制御手段２７を動作状態にする(ステップS4)。

これによって、ドナーから採取された血液に抗血液凝固剤が混合され、このように抗血液凝固化された血液が、外側の送血ライン５、血液ライン７および内側の送血ライン８を通じて血漿分離器２の下端入口に送り込まれる。血漿分離器２で分離された血漿は、血漿ライン１２を通じて血漿容器２５に送られ、一方、血漿が分離された赤血球濃厚血液は、濃厚血液容器３に貯溜される。

血漿ライン１２では、自動流量制御手段２７により血漿の流量が調整され、採血周期の初期に血漿の流量が過大になるのが抑えられる。これで、血漿分離器２の目詰まりが防止される。

また、ドナーによって採血流量が少なく、それに応じて血漿流量が少ない場合、あるいは採血周期の後半に血漿流量が減少した場合は、血漿量を判断するステップ(ステップS7)からステップS8に移り、エアポンプ３１からの圧力をエアライン２９を通じて濃厚血液容器３の上部に作用させる。これで、血漿分離器２の１次側の内圧が増大するから、血漿流量が増え、所要の血漿流量が確保さ

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れる。

一度返血を行った後に再び採血する場合は、ステップS1からステップS9に移り、内側送血クランプ18を閉じて内側返血クランプ20を開き、これによって、血液ライン7を濃厚血液容器3の出口に連通させ、この状態で血液ポンプ16を送血方向に駆動する（ステップS10）。これで、血液ライン7に残留している濃厚血液が濃厚血液容器3に戻される。そして、血液ライン7に濃厚血液が無くなった時点で、前記したステップS2以下の通常の採血モード（ステップS11）に移り、血液ライン7からの流通経路は血漿分離器2側に切り替わる。

したがって、濃厚血液は血漿分離器2に流入せず、血漿分離器2には新たな採取血液のみが流入することになる。

② 返血モード

第2図(b)に示すように、ステップT1で外側返血クランプ22と内側返血クランプ20とを開いて、濃厚血液容器3の出口に内側の返血ライン9と血液ライン7と外側の返血ライン10とを連通させ、この状態で、血液ポンプ16を返血方向に駆動する（ステップT2）。この場合、内外両送血クランプ13，18と、生理食塩水クランプ24とは閉じておき、また、抗凝血剤ポンプ15の駆動は停止する。

これで、濃厚血液容器3に貯溜された濃厚血液が内側の返血ライン9、血液ライン7、外側の返血ライン10および留置針1を通じてドナーに戻される。

返血時に気泡センサ17により気泡が検出された場合は、ステップT3からステップT4に移り、その検出信号に応答して、血液ライン7を内側の返血ライン9を介して濃厚血液容器3の出口に連通させるとともに、血液ポンプ16の駆動方向を切り替えて送血方向に駆動する。

これで、返血中であった気泡を含む血液は、内側の返血ライン9を逆に流通して濃厚血液容器3に戻され、血漿分離器2には流入しない。濃厚血液容器3に戻された血液については、該容器3の内部でエア抜きが行われる。

③ 血液回収モード

第2図(c)に示すように、まず、ステップU1で内側返血クランプ20を閉じておいて生理食塩水クランプ24および吸排気用クランプ34を開き（ステップU1）、濃厚血液容器3と生理食塩水容器23との液レベルのレベル差を利用して、生理食塩水を生理食塩水ライン11を通じて濃厚血液容器3に供給する。

濃厚血液容器3に所要量の生理食塩水が供給される（ステップU2の判断がYesになる）と、吸排気用クランプ34を閉じ（ステップU3）、内側送血クランプ18と外側返血クランプ22とを開いて（ステップU4）、血漿分離器2の入口に内側の送血ライン8と血液ライン7と外側の返血ライン10とを連通させ、この状態で血液ポンプ16を返血方向に駆動する（ステップU5）。

これで、濃厚血液容器3内の生理食塩水を含む濃厚血液は、血漿分離器2を上から下へ流通し、内側の送血ライン8を通ってドナーに戻されることになる。

＜発明の効果＞

以上のように、本発明によれば、所要のポンプを2個に削減することができ、システムを小型化、軽量化することができる。

また、本発明では、返血に気泡が含まれている場合、血液経路の切り替えにより、濃厚血液容器内でエア抜きを行うようにしたから、従来のような比較的に大型のチャンバを省略することができ、この点からも、システムの小型化、軽量化を図ることができる。

また、ポンプ数の削減に伴う不都合、例えば血漿採取量の不足、血漿分離器での目詰まりや溶血、血液回収の所要時間の増大等の不都合の発生が未然に防止され、効率のよい血漿採取を支障なく行うことができる。

4、図面の簡単な説明

第1図は本発明の一実施例の構成図、第2図(a)(b)(c)は採血、返血、血液回収の各モードの制御動作の説明に供するフローチャート、第3図および第4図はいずれも従来例の構成図である。

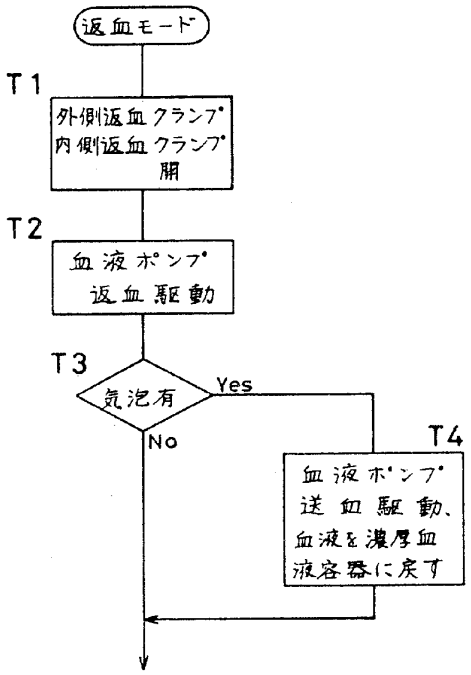
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1…留置針、2…血漿分離器、3…濃厚血液容器、5…外側の送血ライン、6…抗凝血剤ライン、7…血液ライン、8…内側の送血ライン、9…内側の返血ライン、10…外側の返血ライン、11…生理食塩水ライン、12…血漿ライン、15…抗凝血剤ポンプ、16…血液ポンプ、17…気泡センサ、27…自動流量制御手段。

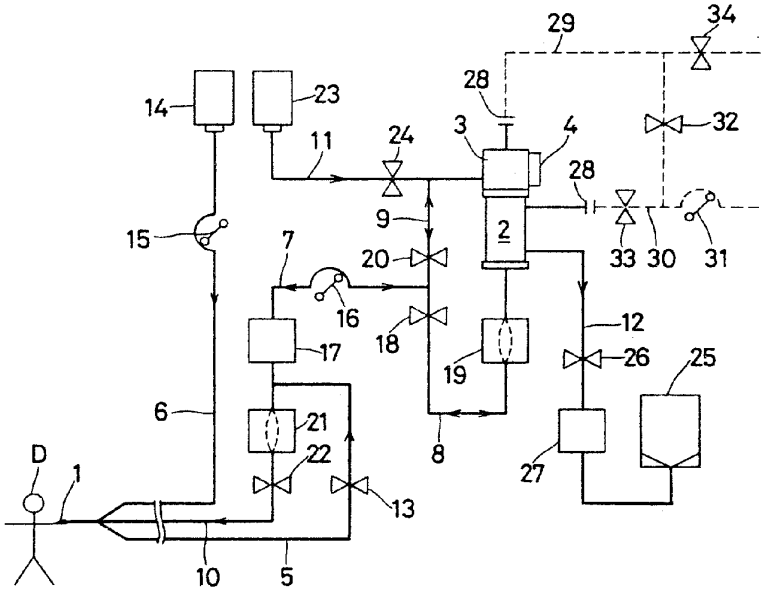
出願人　　株式会社ニッショー

代理人　　弁理士　岡田　和秀

第 2 図（b）

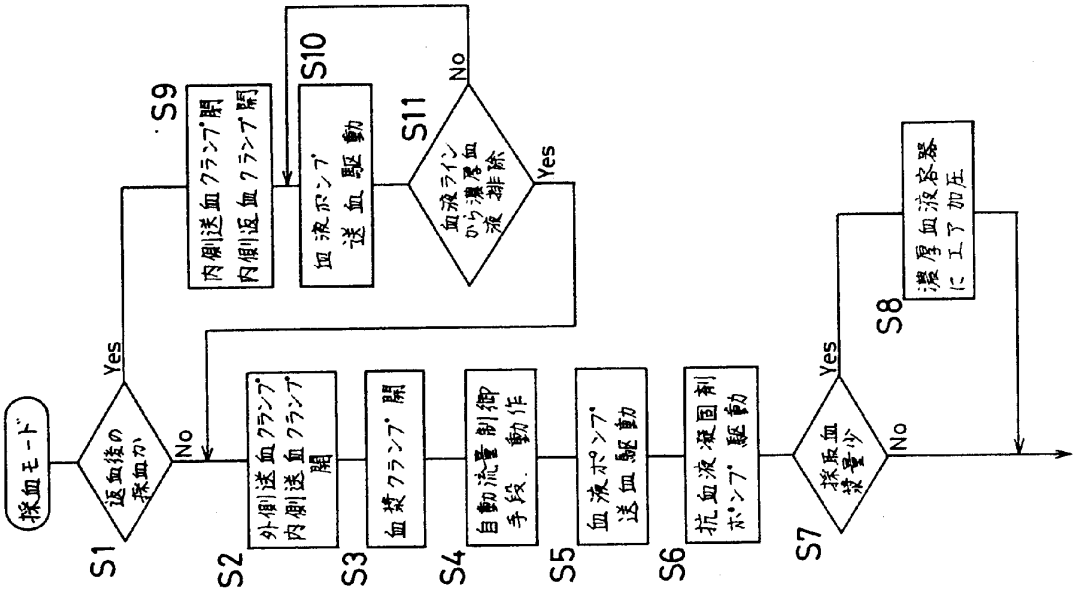


第 1 図

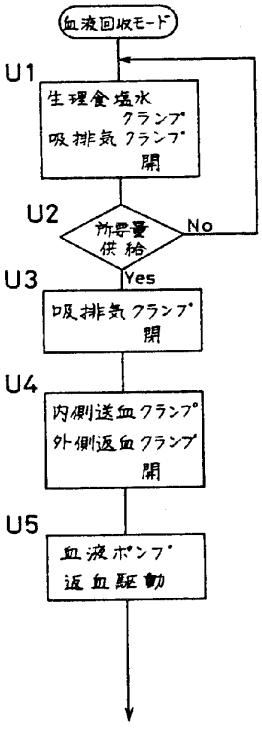


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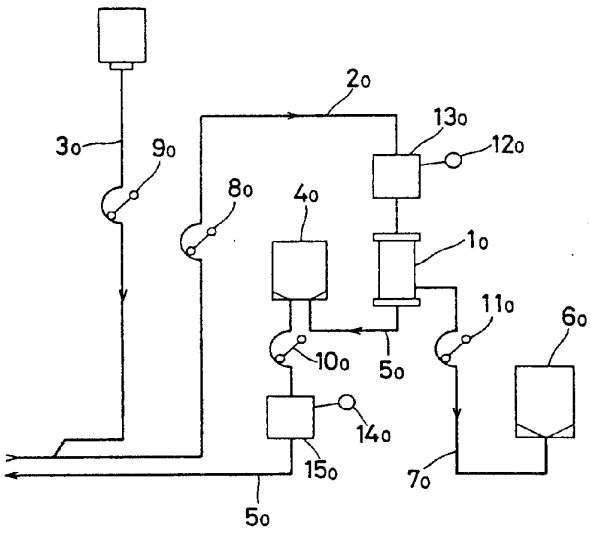
第 2 図（a）



第 2 図（c）

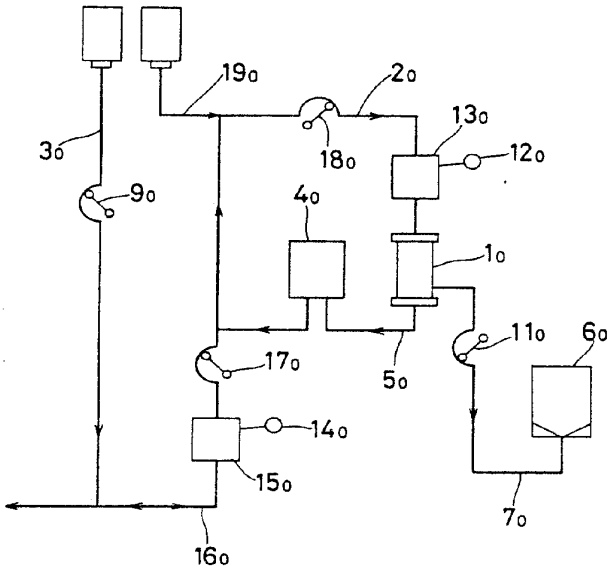


第 3 図



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第 4 図



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Espacenet

Bibliographic data: JPH03131268 (A) — 1991-06-04

METHOD AND DEVICE FOR CONTROLLING BLOOD PUMP IN EXTERNAL CIRCULATION BY SINGLE NEEDLE DEVICE

Inventor(s): HANSUUDEIITORIHI PORASHIETSUKU ± (HANSUUDEIITORIHI PORASHIETSUKU, ; HANSUUDEIITORIHI HORASHETSUKU)

Applicant(s): FRESENIUS AG ± (FRESENIUS AG, ; FURESENIUSU AG)

Classification: **- international:*A61M1/10; A61M1/14; A61M1/30;***
(IPC1-7): A61M1/10; A61M1/14; A61M1/30
- cooperative: A61M1/30; A61M1/302; A61M1/306

Application number: JP19900190348 19900718

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Also published as: DE3923836 (C1) EP0408955 (A2) EP0408955 (A3) EP0408955 (B1) JP2925259 (B2) more

Abstract of JPH03131268 (A)

PURPOSE: To avoid influence of recirculation and heighten the efficiency by operating an artery pump and a vein pump at a higher transport efficiency at the time of starting the respective pump phases. CONSTITUTION: A pressure sensor 31 provided in an artery leg 35 or a vein leg 35 is connected to a control unit 25 through an adjusting device 37 for adjusting the making connection of each pump 30, 49. The adjusting device 37 is operational-connected to the pumps 30, 40 disposed opposite to each other. Accordingly, the adjusting device 37 is operated with the maximum transport capability at the time of starting the making connection operation, and subsequently the making connecting operation of the pump can be adjusted to lower lower the transport capability to keep constant transport capacity. Thus, an effective blood flow from a patient or to a patient can be enlarged to the maximum to remarkably heighten the efficiency.

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⑲日本国特許庁（JP）　⑪特許出願公開

⑫公開特許公報（A）　平3－131268

⑤1Int. Cl.[5]	識別記号	庁内整理番号
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1/10	300	7720－4C
1/14	330	7720－4C

⑬公開　平成3年(1991)6月4日

審査請求　未請求　請求項の数 11　（全6頁）

⑤4発明の名称　シングルニードル装置による体外循環路における血液ポンプを制御するための方法及び装置

⑳特　願　平2－190348
㉒出　願　平2(1990)7月18日

優先権主張　㉜1989年7月19日㉝西ドイツ(DE)㉛P 39 23 836.9

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明　細　書

1. 発明の名称

シングルニードル装置による体外循環路における血液ポンプを制御するための方法及び装置

2. 特許請求の範囲

1)　患者と接続されているカニューレ(10)と、カニューレ(10)から分岐しておりそれぞれ動脈ポンプ(30)又は静脈ポンプ(40)が中に配置されているそれぞれ1つの動脈脚(35)及び静脈脚(45)を有するシングルニードル装置による体外循環路における血液ポンプを制御するための方法において、動脈ポンプ(30)と静脈ポンプ(40)とがそれぞれのポンプフェーズの開始時に、より高められた搬送率で作動されることを特徴とするシングルニードル装置による体外循環路における血液ポンプを制御するための方法。

2)　流れ方向で前記動脈ポンプ(30)の前に配置されている圧力センサ(31)により動脈ポンプ(30)の圧力制御が、前もって与えられている負圧が動脈ポンプ(30)の投入接続後に可及的短時間で設定されることを特徴とする特許請求の範囲第1項記載のシングルニードル装置による体外循環路における血液ポンプを制御するための方法。

3)　前記負圧が全フェーズにわたり一定に維持されることを特徴とする特許請求の範囲第2項記載のシングルニードル装置による体外循環路における血液ポンプを制御するための方法。

4)　前記前もって与えられている負圧に到達するまで前記動脈ポンプ(30)が最大稼働率、ひいては負圧を維持するのに十分な搬送能力で作動されれることを特徴とする特許請求の範囲第2項又は第3項記載のシングルニードル装置による体外循環路における血液ポンプを制御するための方法。

5)　前記静脈ポンプ(40)の下流に配置されている圧力センサ(41)により前記静脈ポンプ(40)の圧力制御が、前もって与えられている負圧がポンプ(40)の投入接続後に可及的短時間で設定されるように行われることを特徴とする特許請求の範囲第1項ないし第4項のうちのいずれか1項に記載のシングルニードル装置による体外循環路における

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血液ポンプを制御するための方法。

6) 前記負圧が全フェーズにわたり一定に維持されることを特徴とする特許請求の範囲第5項記載のシングルニードル装置による体外循環路における血液ポンプを制御するための方法。

7) 前記前もって与えられている負圧に到達するまで前記静脈ポンプ(40)が最大搬送稼働率、ひいては負圧を維持するために十分大きい搬送能力で作動されることを特徴とする特許請求の範囲第5項又は第6項に記載のシングルニードル装置による体外循環路における血液ポンプを制御するための方法。

8) 前記動脈ポンプ(30)が投入接続の際に100㎜Hgないし200㎜Hgの圧力に調整されることを特徴とする特許請求の範囲第1項ないし第7項のうちのいずれか1項に記載のシングルニードル装置による体外循環路における血液ポンプを制御するための方法。

9) 前記静脈ポンプ(40)が投入接続の際に+200㎜Hgないし300㎜Hgの圧力へ調整されることを特徴とする特許請求の範囲第1項ないし第8項のうちのいずれか1項に記載のシングルニードル装置による体外循環路における血液ポンプを制御するための方法。

10) 患者に接続する、1つの腔を形成し動脈脚(35)と静脈脚(45)とに連通するただ1つのカニューレ(10)と、前記動脈ポンプ(30)及び前記静脈ポンプ(40)と、血液処理機器(50)と、制御ユニット(25)と、動脈脚(35)及び静脈脚(45)の中に設けられており制御ユニット(25)に接続されているそれぞれ1つの圧力センサ(31,41)とを有する特許請求の範囲第1項ないし第9項のうちのいずれか1項に記載の方法を実施する装置において、圧力センサ(31,41)が、特にそれぞれの前記ポンプ(30,40)の投入接続を調整するそれぞれ1つの調整装置(37,47)を介して制御ユニット(25)と接続されていることと、調整ユニット(37,47)が、それぞれ対応して配置されているポンプ(30,40)と作動接続されていることを特徴とする特許請求の範囲第1項ないし第9項のうちのいずれか1項に記載の方法を実施する装置。

11) 前記動脈ポンプ(30)と前記静脈ポンプ(40)との間の領域内に、前記制御ユニット(25)に接続されている、圧力に依存してポンプ(30,40)を制御するための圧力センサ(24)が配置されていることを特徴とする特許請求の範囲第10項に記載の装置。

3. 発明の詳細な説明

a) 産業上の利用分野

本発明は、"Medizintechnik"誌第106号1986年刊146頁ないし148頁から公知のシングルニードル装置における体外循環路の血液ポンプを制御するための方法から出発し、このための装置も含む。本発明は体外透析循環路に特に適している。

b) 従来の技術

透析にシングルニードル装置すなわち単一針を有する装置を用いることは古くから公知である。今までの開発においては、装置全体の機能性を改善し、種々異なる問題を除去しようとするのが常であった。したがって例えば作動サイクルを実施するポンプのその都度の制御が改善された。このようなシングルニードル装置において基本的に発生する問題が、今までの公知の装置においては除去されず、解決方法に関して今までややなおざりにされてきた、何故ならば他の困難及び欠点が優先的であるように見えたからである。この問題はシングルニードル透析の実施の際の再循環に関する。

今まで公知の装置は1つ又は2つのポンプと、付加的に1つ又は多数のクランプとを用い、2つのポンプの間に透析器が配置されいる構成か、又は透析器が静脈ポンプの下流に設けられている構成が公知である。さらに、例えば空気室又は膨張室の形状に形成されている、部分的には空気により充填されている付加的なクランプを有するか、又は動脈ポンプの前にかつポンプの間にか又は静脈ポンプの後に設けられている袋を有する装置が存在する。これらの公知の装置は制御装置により作動され、時間に依存するか又は圧力－圧力依存するか又は圧力－時間依存するか又は容積－容積

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依存するか又は圧力－容積依存して制御される制御装置が公知である。

すべての公知の装置において、患者と接続されるただ1つのカニューレ又は1つの1腔状カテドラ(einlumiger Katheder)が用いられる。このカニューレ又はこのカテドラからホース系の動脈部分と静脈部分とが分岐し、これらの分岐は、嚥合するポンプにより又はクランプにより圧力的に系の他の部分から遮断されることが可能である。さらにすべての装置に共通しているのは、すでに透析された血液のかなりの部分が、この透析された血液が人体に戻る前に再び体外循環路にポンプ搬送されることである。これは再循環(Rezirkulation)と呼ばれる。再循環は"Medical&Biological Engineering and Computing"誌第17巻1979年9月刊578頁－582頁に詳しく説明されている。

血液の再循環は種々の原因を有する。まず初めに瘻の中の状態を指摘する。血液の流れを決める流れ抵抗が上流すなわち瘻の動脈側に位置するか、又は下流すなわちFistelの静脈側に位置するかに依存して種々異なる流れ状態が生じる。流れ抵抗が動脈側に位置する場合には動脈ポンプフェーズの間にわたり、動脈により供給される量より大きい量の血液が瘻からポンプにより排出される。これにより、静脈フェーズの間にカニューレの下流の瘻部分の中にポンプにより搬送される血液部分は吸込みにより逆流しひいては再循環される。カニューレの下流に流れ抵抗が位置する場合にも同様の状態となる。この場合には静脈フェーズの間に血液の一部がカニューレの上流の領域の中にポンプ搬送され、ついで動脈フェーズの間に再び吸込まれひいては再循環される。

カニューレの中の流れの状態に関して、静脈フェーズの終りにカニューレが、清浄化された血液により完全に充填されることを指摘しておく。この血液は次の動脈フェーズで再び体外循環路の中に吸込まれひいては再循環される。それぞれのカニューレ及びカテドラが小さい充填容積を有するようにすることによりこの問題を軽減しようとする試みが行われたが、再循環の問題を十分に満足いくようには解決することはできなかった。

再循環の別の1つの面は、使用ホース系から生じる。静脈ポンプフェーズの間にわたり、静脈ポンプと動脈ポンプ又はクランプとの間に位置する全ホース系は静脈帰還圧力にさらされる。ホースの可撓性と、場合に応じて動脈圧力導管の中に存在する空気クッションとに起因して体外ホース系のこの部分の充填容積は増加し、ホース系は"膨張"される。静脈フェーズの終りに静脈クランプと動脈ポンプ又はクランプとの間に、圧力のない状態に比して付加的な血液容積がホース系の中に貯蔵される。これに直接続く動脈フェーズでこの血液容積は再循環される。この動脈フェーズの間に負圧が生じるので充填容積は圧力なしの状態に比して低下し、したがって付加的に清浄化された血液が静脈ホースから吸込まれひいては再循環される。この動作は各サイクルで繰返される。この問題を付加的なクランプにより又は特別に形成されているホース導管により解決する提案が公知である。すべてのこれらの手段は実際上の理由から普及しなかった、何故ならば付加的なクランプを患者に直接に接続しなければならず、これにより患者は運動範囲を著しく制限されるからである。特別の非伸長性ホース導管の使用は経済的な面でも技術的な面でも、例えば材料問題に関して著しい欠点をもたらす。

再循環を決める別の1つのファクタは、動脈制御回路又は静脈制御回路における電子的遅延又は機械的遅延から生じる。したがって例えば、静脈ポンプがまだ搬送しているか、又は静脈クランプがまだ開放されているのに動脈ポンプがすでに始動することがある。今までに公知の装置ではこのような現象を、再循環が効果的に中断又は低減されるほどに除去することはできなかった。

再循環は体外循環路の効率ひいては透析器の効率を著しく左右する、何故ならば透析器を貫流する容積流は、瘻から実際に流出する血液量より再循環分だけより大きいからである。

c. 発明が解決しようとする課題

本発明の課題は、効率に対する再循環の好まし

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くない影響を大幅に回避し、ひいては効率を高める方法及び装置を提供することにあり、この装置は簡単な構成を有しかつ確実に動作し、さらにこの装置は、再循環と時間的に無関係な血液量を患者から取出す又は患者に戻すことが可能であるように作動することができる。

d. 課題を解決するための手段

上記課題は方法に関しては、動脈ポンプと静脈ポンプとがそれぞれのポンプフェーズの開始時に、より高められた搬送率で作動されることにより解決される。

本発明の方法は一連の利点を有する。本発明の理解は、まず初めに再循環の時間的経過を詳しく観察することにより容易になる。静脈ポンプフェーズの終りにはホース系に正の静脈帰還圧力が印加されている。この場合に、ホース系の伸長性に条件付けられて、すでに浄化された血液における特定の容積が動脈ホースの中に押圧される。動脈ホースは、カニューレに直接に隣接するホース区間の中に設けられている。

動脈フェーズの開始時に、すなわち正の静脈帰還圧力から負の動脈吸込み圧力への移行期間にまず初めに、動脈ホースの中に貯蔵されているこの血液容積が搬送され、次いで、静脈ホースの中に貯蔵されている血液容積が搬送され、次いで徐々に患者から血液が搬送される。したがって、動脈ポンプから搬送された円筒状液体の先端において、すでに浄化された血液を有する血液のセグメント化が生じる。この開始フェーズの間には患者から血液は搬送されない。動脈フェーズから静脈フェーズへの移行時に類似の動作が行われる。

本発明の方法はこの動作の欠点を回避する。本発明ではポンプの投入接続を行った都度に最大の容量流が搬送されるので、貯蔵容積を加速して搬送することは、この貯蔵容積のポンプ排出の後にそれぞれのポンプが、前もって与えられている吐出し量に戻し切換えされてから初めて行われる。

本発明ではポンプは例えば、前もって与えられているポンプ吐出し量一時間プロフィアルに依存して作動することもできる。しかし本発明ではポンプを圧力制御装置を介して作動することも可能である。このために、前もって与えられている動脈負圧が動脈ポンプの投入接続後に可及的短時間で設定され、この負圧が全フェーズにわたり一定に維持されるように動脈ポンプを作動する。

本発明では切換え後にまず初めに正の静脈帰還圧力が加わるので、調整回路により強制的に前もって与えられている時間内での圧力調整によりポンプが、前もって与えられている圧力値に到達するまで最大吐出し量で作動され、その後に初めてポンプは、一定の搬送が行われるように、かつその際に管が損傷されないように作動される。この方法により、患者からの又は患者への効果的な血液流を最大化することができる。したがって本発明では効率が著しく高まる。

以上、動脈ポンプの作動に関して本発明を説明した。静脈ポンプが同様の方法で作動され、その際に同様の効果が得られることは当業者には自明である。

装置に関して本発明の課題は、それぞれ動脈脚又は静脈脚の中に設けられている圧力センサが、特にそれぞれのポンプの投入接続を調整する調整装置を介して制御ユニットと接続されていることと、調整装置が、それぞれ対応して配置されているポンプと作動接続されている。したがって本発明の装置では、ポンプを投入接続動作の開始時には最大搬送能力で作動し、次いで搬送能力を低めて一定の搬送容積を維持するためにポンプの投入接続動作を調整する付加的な調整装置が設けられている。

本発明を理解するために、シングルニードル装置において公知の従来の圧力制御装置は、搬送動作自身の間の圧力状態のみに関してであり、したがって本発明の制御装置の他に設けることができる、何故ならばこれらの公知の制御方法はポンプフェーズの切換えに関してであり、これに対して本発明ではポンプ吐出し量、すなわちポンプの搬送能力が調整されるからである。

e. 実施例

第1図には線図でそれぞれポンプの作動時間に

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対するポンプ出力の依存性が示されている。この場合に、ポンプを投入接続するとポンプが最大搬送率で作動されることと、患者から一定の血液量を取出す又は患者に一定の血液量を供給するために搬送率が次いで一定値に低下することとが明瞭に分かる。

第2図は、シングルニードル透析器のための本発明の装置の概略図である。

本装置はカニューレ10を有し、カニューレ10は1腔状(einlumig)に形成され、患者と接続することができる。カニューレ10は動脈脚35と静脈脚45とに分岐する。動脈脚35の中には動脈ポンプ30が配置され、動脈ポンプ30の下流に走行しているホース36は空気室46と接続されている。空気室40から出ているホース46は静脈脚45と作動接続され、静脈ポンプ40は静脈脚45の中に設けられている。静脈ポンプ40の下流にホース51が設けられており、ホース51は透析器50と接続されている。透析器50からは、処理された血液がホース52を介して泡捕捉器53に供給される。泡捕捉器53の下流には静脈クランプ54が配置されている。

空気室21は通常は疎水性フィルタ23と接続されており、疎水性フィルタ23には第2の空気室22が後続し、第2の空気室22の出口側には圧力センサ24が設けられている。圧力センサ24から送出される圧力値は、制御ユニット25による圧力ー圧力制御に用いられる。

制御ユニット25はそれぞれ調整装置37,47と作動接続され、調整装置37,47はポンプ30,40の作動に用いられる。

動脈脚35と静脈脚45との双方の中にそれぞれ1つの圧力センサ31,41が設けられており、圧力センサ31,41により動脈脚35の中の動脈ポンプ30の吸込み圧力、又は静脈脚45の中の静脈ポンプ40の搬送圧力が測定される。圧力センサ31は動脈脚35とホース33,34と、挿入接続されている疎水性フィルタ32と接続されている。同様の方法で圧力センサ41の接続がホース43,44を介して行われ、ホース43と44との間に疎水性フィルタ42が配置されている。

2つの圧力センサ31,41の出力値はそれぞれ調整装置37,47に供給される。

透析器50の代わりに別の血液処理装置、例えばプラズマフィルタ又は吸収装置等を設けることもできる。

調整装置37及び47と、調整すべき構成素子又は制御ユニット25との対応する作動接続とを除いては図示の装置は従来の技術にほぼ対応する。したがって詳細な動作の説明は省く。

2つの調整装置37と47とは、オンにした場合に動脈ポンプと静脈ポンプとの双方が制御ユニット25により、前もって与えられている吸込み圧力又は搬送圧力に調整されるように作用する。なおこれらの圧力の代表的な値は、動脈ポンプでは－100㎜Hgと－200㎜Hgとの間にあり、静脈ポンプでは＋200㎜Hgと＋300㎜Hgとの間にある。

本発明は図示の実施例に制限されず、当業者は本発明の範囲内で種々の変形及び変更の可能性に容易に想到することができる。

4. 図面の簡単な説明

第1図は動脈ポンプ及び静脈ポンプのポンプ率の時間線図、第2図は本発明の装置の概略図である。

10…カニューレ、　21…空気室、
22…空気室、　23…フィルタ、
24…圧力センサ、　25…制御ユニット、
30…動脈ポンプ、　31…圧力センサ、
32…疎水フィルタ、　33…ホース、
34…ホース、　35…動脈脚、
36…ホース、　37…調整装置、
40…静脈ポンプ、　41…圧力センサ、
42…疎水フィルタ、　43…ホース、
44…ホース、　46…ホース、
47…調整装置、　50…透析器、
51…ホース、　52…ホース、
53…泡捕捉器、　54…静脈クランプ。

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Fig.1

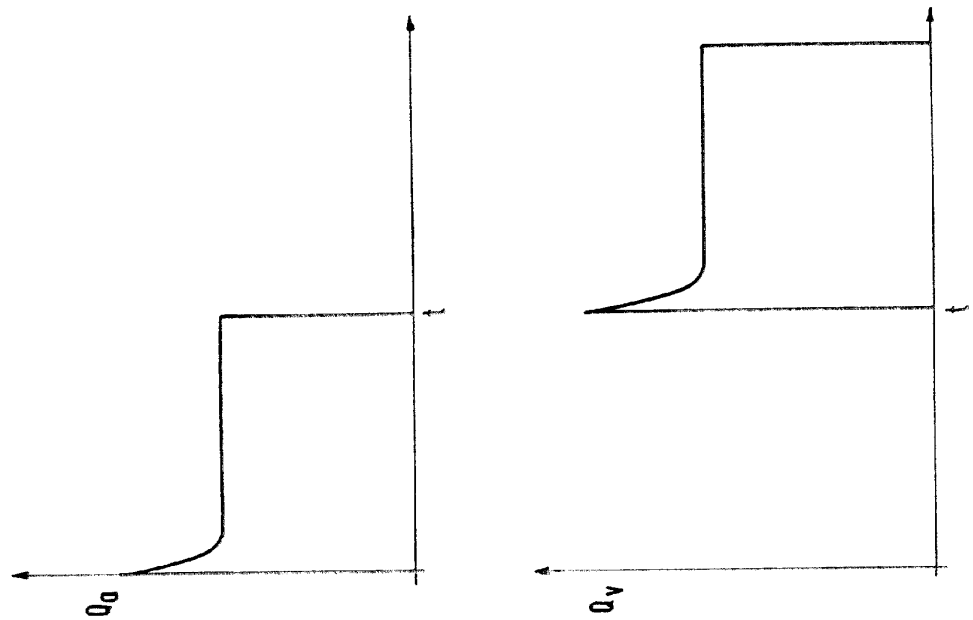
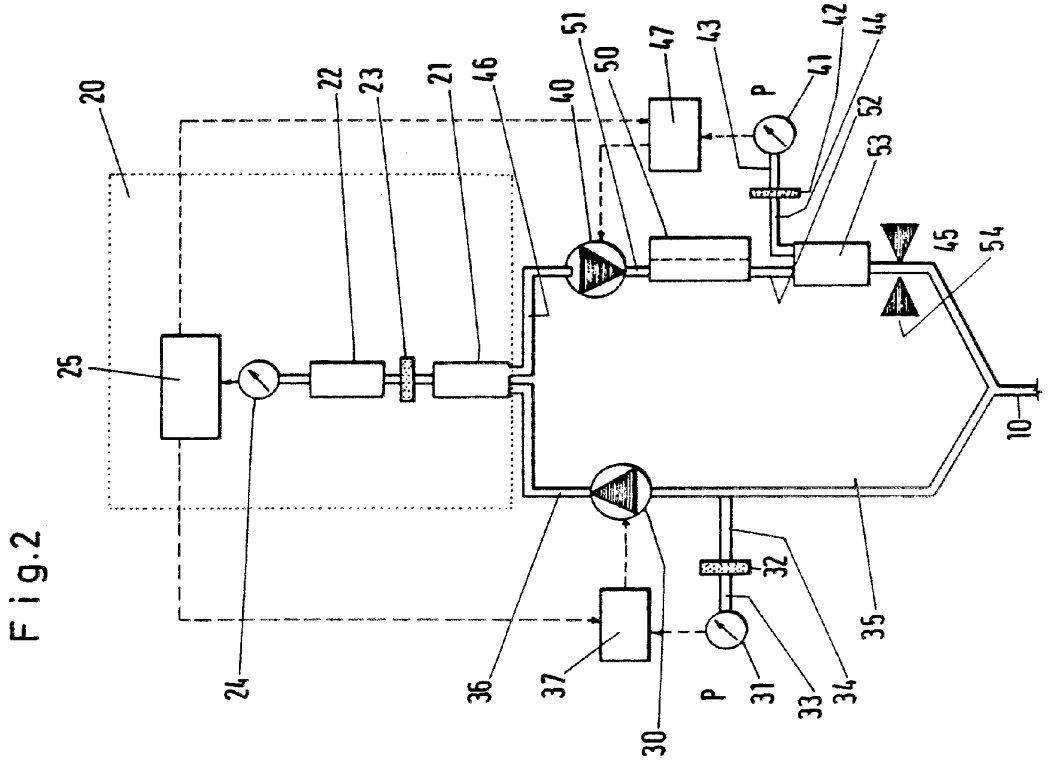


Fig.2



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Espacenet

Bibliographic data: JP2002291872 (A) — 2002-10-08

BLOOD COMPONENT COLLECTOR

Inventor(s): TAKAGI YOSHIMI; KIMURA SHIGEYUKI ± (TAKAGI YOSHIMI, ; KIMURA SHIGEYUKI)

Applicant(s): TERUMO CORP ± (TERUMO CORP)

Classification: **- international:** ***A61M1/02; A61M1/34; A61M1/36; A61M1/38; B01D35/02;*** (IPC1-7): A61M1/02; A61M1/34; B01D35/02

- cooperative: **A61M1/0218**; **A61M1/0231**; **A61M1/024**; **A61M1/3693**; **A61M1/3696**; **A61M1/38**; A61M2205/12

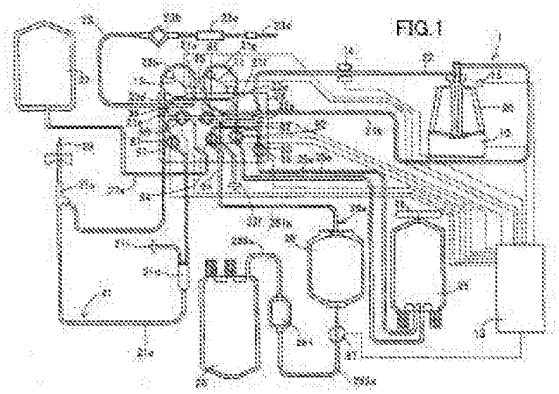
Application number: JP20010094102 20010328

Priority number (s): JP20010094102 20010328

Also published as: EP1374927 (A1) EP1374927 (A4) EP1374927 (B1) JP4050477 (B2) US2004112808 (A1) more

Abstract of JP2002291872 (A)

PROBLEM TO BE SOLVED: To provide a blood component collector capable of collecting high quality desired blood components. SOLUTION: The blood component collector 1 has a centrifugal separator 20 separating blood into a plurality of blood components, a first line 21 introducing blood into the centrifugal separator 20, a second line 22 discharging blood components from the centrifugal separator 20, a temporarily storing bag 26' connected to the second line 22 and temporarily storing thick platelet plasma, a leucocyte removing filter 261 separating and removing leucocytes, and a platelet collecting bag 26 storing the thick platelet plasma after passing through the leucocyte removal filter 261, and the platelet



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plasma concentrate in the temporarily storing bag 26' is transported to the platelet collecting bag 26 through the leucocyte removal filter 261, plasma is supplied, and platelets (thick platelet plasma after leucocytes are separated and removed) remaining in leucocyte removal filter 261 are collected in the platelet collection bag 26 together with plasma.

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		５４０			５４０	４Ｄ０６４
		５７０			５７０	
	1/34	５００		1/34	５００	
Ｂ０１Ｄ	35/02		Ｂ０１Ｄ	35/02	Ｚ	

審査請求　未請求　請求項の数９　ＯＬ　（全 19 頁）

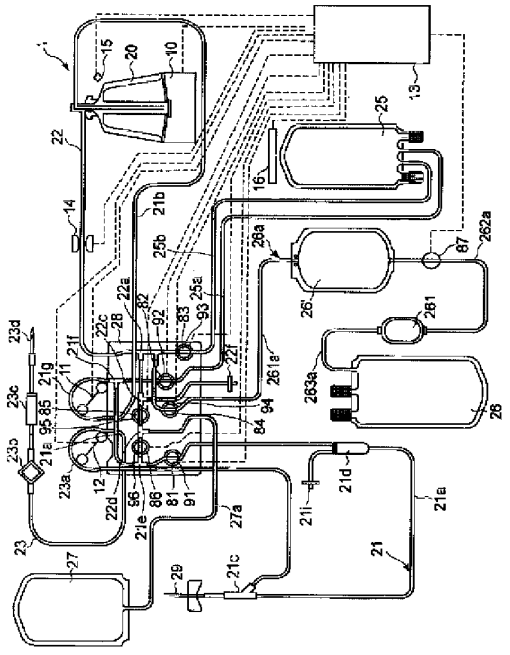
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(22)出願日　平成13年３月28日(2001.3.28)

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最終頁に続く

(54)【発明の名称】　血液成分採取装置

(57)【要約】
【課題】　品質の高い所望の血液成分を得ることができる血液成分採取装置を提供すること。
【解決手段】　血液成分採取装置１は、血液を複数の血液成分に分離する遠心分離器２０と、遠心分離器２０に血液を導入する第１のライン２１と、遠心分離器２０内から血液成分を排出する第２のライン２２と、第２のライン２２に接続され、濃厚血小板血漿を一時的に貯留する一時貯留バッグ２６’と、濃厚血小板血漿中から白血球を分離除去する白血球除去フィルター２６１と、白血球除去フィルター２６１内を通過した後の濃厚血小板血漿を貯留する血小板採取バッグ２６とを備え、一時貯留バッグ２６’内の濃厚血小板血漿を、白血球除去フィルター２６１を経て、血小板採取バッグ２６内へ移送し、その後、血漿を供給し、白血球除去フィルター２６１内に残存する血小板（白血球を分離除去した後の濃厚血小板血漿）を、血漿とともに血小板採取バッグ２６内に回収するよう構成されている。



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【特許請求の範囲】
【請求項１】　血液を複数の血液成分に分離するとともに分離された血液成分を採取する血液成分採取装置であって、
内部に貯血空間を有するローターと、前記貯血空間に連通する流入口および排出口とを有し、前記ローターの回転により前記流入口より導入された血液を前記貯血空間内で複数の血液成分に遠心分離する遠心分離器と、
前記流入口と、血液を採取する採血手段とを接続する第１のラインと、
前記排出口に接続された第２のラインと、
前記第２のラインに接続され、第１の血液成分を一時的に貯留する第１の容器と、
前記第１の容器に接続され、前記第１の血液成分中から所定の細胞を分離除去する細胞分離フィルターと、
前記細胞分離フィルターに接続され、前記細胞分離フィルター内を通過した後の前記第１の血液成分を貯留する第２の容器とを備え、
前記第１の容器内の前記第１の血液成分を、前記細胞分離フィルターを経て、前記第２の容器内へ移送し、
その後、第２の血液成分を供給し、前記細胞分離フィルター内に残存する前記所定の細胞を分離除去した後の前記第１の血液成分を、前記第２の血液成分とともに、前記第２の容器内に回収するよう構成されていることを特徴とする血液成分採取装置。
【請求項２】　血液を複数の血液成分に分離するとともに分離された血液成分を採取する血液成分採取装置であって、
内部に貯血空間を有するローターと、前記貯血空間に連通する流入口および排出口とを有し、前記ローターの回転により前記流入口より導入された血液を前記貯血空間内で複数の血液成分に遠心分離する遠心分離器と、
前記流入口と、血液を採取する採血手段とを接続する第１のラインと、
前記排出口に接続された第２のラインと、
前記第２のラインに接続され、第１の血液成分を一時的に貯留する第１の容器と、
前記第１の容器に供給用チューブを介して接続され、前記供給用チューブを介して供給された前記第１の血液成分中から所定の細胞を分離除去する細胞分離フィルターと、
前記細胞分離フィルターに排出用チューブを介して接続され、前記細胞分離フィルター内を通過した後の前記第１の血液成分を貯留する第２の容器とを備え、
前記第１の容器内の前記第１の血液成分を、前記供給用チューブ、前記細胞分離フィルターおよび前記排出用チューブを経て、前記第２の容器内に移送し、
その後、第２の血液成分を供給し、前記細胞分離フィルター内および前記排出用チューブの流路内に残存する前記所定の細胞を分離除去した後の前記第１の血液成分を、前記第２の血液成分とともに、回収するよう構成されていることを特徴とする血液成分採取装置。
【請求項３】　前記供給用チューブの流路の途中を開閉し得る流路開閉手段を有する請求項２に記載の血液成分採取装置。
【請求項４】　前記第２の血液成分の供給量により、前記第２の容器内の血液成分の総量を調整する請求項１ないし３のいずれかに記載の血液成分採取装置。
【請求項５】　前記第２の血液成分を貯留する第３の容器を有し、前記第２の血液成分は、前記第３の容器内から供給される請求項１ないし４のいずれかに記載の血液成分採取装置。
【請求項６】　前記第２の血液成分は、前記第１の容器内に残存する前記第１の血液成分とともに前記細胞分離フィルターに供給される請求項１ないし５のいずれかに記載の血液成分採取装置。
【請求項７】　前記第１の血液成分は、血小板を含む血漿である請求項１ないし６のいずれかに記載の血液成分採取装置。
【請求項８】　前記第２の血液成分は、血漿である請求項１ないし７のいずれかに記載の血液成分採取装置。
【請求項９】　前記細胞分離フィルターは、白血球除去フィルターである請求項１ないし８のいずれかに記載の血液成分採取装置。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】本発明は、血液を複数の血液成分に分離するとともに分離された血液成分を採取する血液成分採取装置に関する。
【０００２】
【従来の技術】採血を行う場合、現在では、血液の有効利用および供血者の負担軽減などの理由から、採血血液を遠心分離などにより各血液成分に分離し、輸血者に必要な成分だけを採取し、その他の成分は供血者に返還する成分採血が行われている。
【０００３】このような成分採血において、血小板製剤を得る場合、供血者から採血した血液を血液成分採取回路に導入し、該血液成分採取回路に設置された遠心ボウルと呼ばれる遠心分離器により、血漿、バフィーコートおよび赤血球に分離し、その内のバフィーコートから血小板を分離し、容器に回収して血小板製剤とし、残りの血漿、白血球および赤血球は、供血者に返血することが行われる。
【０００４】しかしながら、この方法では、多くの血小板を得ようとすると、それに混入する白血球の量も増大するため、発熱、同種抗原感作、ウィルス感染等の確率が高くなるという問題がある。
【０００５】そこで、得られた血小板を白血球除去フィルターに通過させ、白血球を分離除去し、この乏白血球血小板を容器に回収して血小板製剤とすることが提案さ

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れている。また、この際、白血球除去フィルターには、血小板が残存するので、血小板の収率を上昇させるために、生理食塩水や抗凝固剤のような洗浄液を用いて白血球除去フィルターの洗浄が行なわれている。

【０００６】しかしながら、この方法では、洗浄液が血小板製剤中に混入することになり、得られた血小板製剤の品質を低下するという問題がある。

【０００７】

【発明が解決しようとする課題】本発明の目的は、品質の高い所望の血液成分を得ることができる血液成分採取装置を提供することにある。

【０００８】

【課題を解決するための手段】このような目的は、下記（１）～（９）の本発明により達成される。

【０００９】（１）　血液を複数の血液成分に分離するとともに分離された血液成分を採取する血液成分採取装置であって、内部に貯血空間を有するローターと、前記貯血空間に連通する流入口および排出口とを有し、前記ローターの回転により前記流入口より導入された血液を前記貯血空間内で複数の血液成分に遠心分離する遠心分離器と、前記流入口と、血液を採取する採血手段とを接続する第１のラインと、前記排出口に接続された第２のラインと、前記第２のラインに接続され、第１の血液成分を一時的に貯留する第１の容器と、前記第１の容器に接続され、前記第１の血液成分中から所定の細胞を分離除去する細胞分離フィルターと、前記細胞分離フィルターに接続され、前記細胞分離フィルター内を通過した後の前記第１の血液成分を貯留する第２の容器とを備え、前記第１の容器内の前記第１の血液成分を、前記細胞分離フィルターを経て、前記第２の容器内へ移送し、その後、第２の血液成分を供給し、前記細胞分離フィルター内に残存する前記所定の細胞を分離除去した後の前記第１の血液成分を、前記第２の血液成分とともに、前記第２の容器内に回収するよう構成されていることを特徴とする血液成分採取装置。

【００１０】（２）　血液を複数の血液成分に分離するとともに分離された血液成分を採取する血液成分採取装置であって、内部に貯血空間を有するローターと、前記貯血空間に連通する流入口および排出口とを有し、前記ローターの回転により前記流入口より導入された血液を前記貯血空間内で複数の血液成分に遠心分離する遠心分離器と、前記流入口と、血液を採取する採血手段とを接続する第１のラインと、前記排出口に接続された第２のラインと、前記第２のラインに接続され、第１の血液成分を一時的に貯留する第１の容器と、前記第１の容器に供給用チューブを介して接続され、前記供給用チューブを介して供給された前記第１の血液成分中から所定の細胞を分離除去する細胞分離フィルターと、前記細胞分離フィルターに排出用チューブを介して接続され、前記細胞分離フィルター内を通過した後の前記第１の血液成分を貯留する第２の容器とを備え、前記第１の容器内の前記第１の血液成分を、前記供給用チューブ、前記細胞分離フィルターおよび前記排出用チューブを経て、前記第２の容器内に移送し、その後、第２の血液成分を供給し、前記細胞分離フィルター内および前記排出用チューブの流路内に残存する前記所定の細胞を分離除去した後の前記第１の血液成分を、前記第２の血液成分とともに、回収するよう構成されていることを特徴とする血液成分採取装置。

【００１１】（３）　前記供給用チューブの流路の途中を開閉し得る流路開閉手段を有する上記（２）に記載の血液成分採取装置。

【００１２】（４）　前記第２の血液成分の供給量により、前記第２の容器内の血液成分の総量を調整する上記（１）ないし（３）のいずれかに記載の血液成分採取装置。

【００１３】（５）　前記第２の血液成分を貯留する第３の容器を有し、前記第２の血液成分は、前記第３の容器内から供給される上記（１）ないし（４）のいずれかに記載の血液成分採取装置。

【００１４】（６）　前記第２の血液成分は、前記第１の容器内に残存する前記第１の血液成分とともに前記細胞分離フィルターに供給される上記（１）ないし（５）のいずれかに記載の血液成分採取装置。

【００１５】（７）　前記第１の血液成分は、血小板を含む血漿である上記（１）ないし（６）のいずれかに記載の血液成分採取装置。

【００１６】（８）　前記第２の血液成分は、血漿である上記（１）ないし（７）のいずれかに記載の血液成分採取装置。

【００１７】（９）　前記細胞分離フィルターは、白血球除去フィルターである上記（１）ないし（８）のいずれかに記載の血液成分採取装置。

【００１８】

【発明の実施の形態】以下、本発明の血液成分採取装置を添付図面に示す好適実施形態に基づいて詳細に説明する。

【００１９】図１は、本発明の血液成分採取装置の構成を示す平面図であり、図２は、血液成分採取装置が備える遠心分離器に遠心分離器駆動装置が装着された状態の部分破断断面図であり、図３～図６は、それぞれ、本発明の血液成分採取装置の作用を説明するためのフローチャートである。

【００２０】図１に示す血液成分採取装置１は、血液を複数の血液成分に分離するとともに分離された血液成分（特に、血小板）を採取するための装置であり、内部に貯血空間１４６を有するローター１４２と、貯血空間１４６に連通する流入口１４３および排出口１４４とを有し、ローター１４２の回転により流入口１４３より導入された血液を貯血空間１４６内で遠心分離する遠心分離

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器２０と、採血針２９と遠心分離器２０の流入口１４３とを接続する第１のライン２１と、遠心分離器２０の排出口１４４に接続された第２のライン２２と、第１のライン２１に接続された第３のライン２３と、第１のライン２１に接続された第１チューブ２５ａおよび第２のライン２２と接続された第２チューブ２５ｂを有する血漿採取バッグ２５と、第２のライン２２に接続された第３チューブ２６ａを有する血小板採取バッグ２６と、第２のライン２２に接続された第４チューブ２７ａを有するバフィーコート採取バッグ２７とを有する血液成分採取回路２を備えている。

【００２１】さらに、血液成分採取装置１は、遠心分離器２０のローター１４２を回転させるための遠心分離器駆動装置１０と、第１のライン２１のための第１の送液ポンプ１１と、第３のライン２３のための第２の送液ポンプ１２と、血液成分採取回路２の流路の途中を開閉し得る複数の流路開閉手段８１、８２、８３、８４、８５、８６、８７と、遠心分離器駆動装置１０、第１の送液ポンプ１１、第２の送液ポンプ１２および複数の流路開閉手段８１～８７を制御するための制御部（制御手段）１３と、濁度センサ１４と、光学式センサ１５と、重量センサ１６とを備えている。

【００２２】そこで、最初に、血液成分採取回路２について説明する。この血液成分採取回路２は、血液を採取する採血針（採血手段）２９と遠心分離器２０の流入口１４３とを接続し、第１のポンプチューブ２１ｇを備える第１のライン（採血および返血ライン）２１と、遠心分離器２０の排出口１４４と第１のライン２１とを接続するための第２のライン２２と、第１のライン２１の採血針２９の近くに接続され、第２のポンプチューブ２３ａを備える第３のライン（抗凝固剤注入ライン）２３と、第１のライン２１のポンプチューブ２１ｇより採血針２９側に接続された第１チューブ２５ａおよび第２のライン２２と接続された第２チューブ２５ｂとを有する血漿採取バッグ２５と、第２のライン２２に接続された第３チューブ２６ａを備える血小板採取バッグ２６と、第２のライン２２に接続された第４チューブ２７ａを備えるバフィーコート採取バッグ２７とを備えている。

【００２３】なお、採血手段としては、採血針２９に限られず、例えば、血液バッグなどの血液プールに接続するための接続部（例えば、金属もしくは合成樹脂針等）でもよい。この採血針２９としては、例えば、公知の金属針が使用される。

【００２４】第１のライン２１は、採血針２９が接続された採血針側第１ライン２１ａと、遠心分離器２０の流入口１４３とを接続された遠心分離器側第１ライン２１ｂとを有している。

【００２５】採血針側第１ライン２１ａは、軟質樹脂製チューブが複数接続されて形成されている。この採血針側第１ライン２１ａは、採血針２９側より、第３のライン２３との接続用分岐コネクター２１ｃと、気泡およびマイクロアグリゲート除去のためのチャンバー２１ｄと、第２のライン２２との接続用分岐コネクター２１ｅと、血漿採取バッグ２５の第１チューブ２５ａとの接続用分岐コネクター２１ｆとを備えている。

【００２６】また、チャンバー２１ｄには、通気性かつ菌不透過性のフィルター２１ｉが接続されている。

【００２７】一方、遠心分離器側第１ライン２１ｂは、第１チューブ２５ａとの接続用分岐コネクター２１ｆに接続されており、その付近に形成された第１のポンプチューブ２１ｇを有している。

【００２８】遠心分離器２０の排出口１４４と第１のライン２１とを接続する第２のライン２２は、一端が遠心分離器２０の排出口１４４に接続され、他端が第１のライン２１の接続用分岐コネクター２１ｅに接続されている。

【００２９】この第２のライン２２は、遠心分離器２０側から、血漿採取バッグ２５の第２チューブ２５ｂならびに血小板採取バッグ２６の第３チューブ２６ａとの接続用分岐コネクター２２ａと、気泡除去用フィルター２２ｆを備えるチューブとの接続用分岐コネクター２２ｃと、バフィーコート採取バッグ２７の第４チューブ２７ａとの接続用分岐コネクター２２ｄとを備えている。

【００３０】第３のライン２３は、一端が第１のライン２１に設けられた接続用分岐コネクター２１ｃに接続されている。

【００３１】この第３のライン２３は、コネクター２１ｃ側より、第２のポンプチューブ２３ａと、異物除去用フィルター２３ｂと、気泡除去用チャンバー２３ｃと、抗凝固剤容器接続用針２３ｄとを備えている。

【００３２】血漿採取バッグ（第３の容器）２５は、血漿（第２の血液成分）を採取（貯留）するための容器であり、第１のライン２１のポンプチューブ２１ｇより採血針２９側に位置する分岐コネクター２１ｆに接続された第１チューブ２５ａと、第２のライン２２の分岐コネクター２２ａに接続された第２チューブ２５ｂとを有している。すなわち、血漿採取バッグ２５および第２チューブ２５ｂにより、血漿を採取する血漿採取用分岐ラインが構成されている。

【００３３】血小板採取バッグ（第２の容器）２６は、後述する白血球除去フィルター２６１を通過した後の血小板を含む血漿（第１の血液成分）を採取（貯留）するための容器であり、第２のライン２２の分岐コネクター２２ａに接続された第３チューブ２６ａを備えている。なお、以下の説明では、血小板を含む血漿（第１の血液成分）を、「濃厚血小板血漿」と言い、血小板採取バッグ２６内に採取（貯留）された濃厚血小板血漿を、「血小板製剤」と言う。

【００３４】また、第３チューブ２６ａの途中には、濃厚血小板血漿（第１の血液成分）を一時的に貯留する一

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時貯留バッグ（第１の容器）２６’、および、濃厚血小板血漿中から白血球（所定の細胞）を分離除去する白血球除去フィルター（細胞分離フィルター）２６１が設置されている。

【００３５】換言すれば、第３チューブ２６ａは、３つのチューブ２６１ａ、２６２ａおよび２６３ａで構成されており、チューブ２６１ａは、分岐コネクター２２ａと一時貯留バッグ２６’とを接続し、チューブ２６２ａは、一時貯留バッグ２６’と白血球除去フィルター２６１とを接続し、また、チューブ２６３ａは、白血球除去フィルター２６１と血小板（血小板製剤）採取バッグ２６とを接続している。

【００３６】チューブ２６２ａは、一時貯留バッグ２６’から白血球除去フィルターに濃厚血小板血漿を供給する供給用チューブを構成し、また、チューブ２６３ａは、白血球除去フィルター２６１から白血球を分離除去した後の濃厚血小板血漿を排出する（血小板採取バッグ２６に供給する）排出用チューブを構成する。

【００３７】すなわち、第３チューブ２６ａ（チューブ２６１ａ、２６２ａ、２６３ａ）、一時貯留バッグ２６’、白血球除去フィルター２６１および血小板採取バッグ２６により、血小板（血小板製剤）を採取する血小板採取用分岐ラインが構成されている。

【００３８】また、これらの一時貯留バッグ２６’、白血球除去フィルター２６１および血小板採取バッグ２６は、血液成分採取装置１を組み立てた状態で、白血球除去フィルター２６１が一時貯留バッグ２６’より低い位置に、さらに、血小板採取バッグ２６が白血球除去フィルター２６１より低い位置にセットされる。

【００３９】また、白血球除去フィルター２６１としては、例えば、両端に流入口および排出口を有するケーシング内に、例えば、ポリプロピレン、ポリエステル、ポリウレタン、ポリアミド等の合成樹脂よりなる織布、不織布、メッシュ、発泡体等の多孔質体を１層または２層以上積層した沪過部材を挿入して構成したもの等を用いることができる。

【００４０】バフィーコート採取バッグ２７は、バフィーコートを採取するための容器であり、第２のライン２２の分岐コネクター２２ｄに接続された第４チューブ２７ａを備えている。すなわち、バフィーコート採取バッグ２７および第４チューブ２７ａにより、バフィーコートを採取するバフィーコート採取用分岐ラインが構成されている。

【００４１】上述した第１～第３のライン２１～２３の形成に使用される各チューブ、各ポンプチューブ２１ｇ、２３ａ、さらに、各バッグ２５～２７に接続されている各チューブ２５ａ、２５ｂ、２６ａ（２６１ａ、２６２ａ、２６３ａ）、２７ａの構成材料としては、ポリ塩化ビニルが好ましい。

【００４２】これらのチューブがポリ塩化ビニル製であれば、十分な可撓性、柔軟性が得られるので取り扱いがし易く、また、クレンメ等による閉塞にも適するからである。

【００４３】また、上述した各分岐コネクター２１ｃ、２１ｅ、２１ｆ、２２ａ、２２ｃ、２２ｄの構成材料についても、それぞれ、前記チューブで挙げた構成材料と同様のものを用いることができる。

【００４４】なお、各ポンプチューブ２１ｇ、２３ａとしては、後述する各送液ポンプ（例えば、ローラーポンプ等）１１、１２により押圧されても損傷を受けない程度の強度を備えるものが使用されている。

【００４５】血漿採取バッグ２５、血小板採取バッグ２６、一時貯留バッグ２６’、バフィーコート採取バッグ２７は、それぞれ、樹脂製の可撓性を有するシート材を重ね、その周縁部を融着（熱融着、高周波融着、超音波融着等）または接着剤により接着等して袋状にしたものが使用される。

【００４６】各バッグ２５～２７、２６’に使用される材料としては、それぞれ、例えば、軟質ポリ塩化ビニルが好適に使用される。

【００４７】なお、血小板採取バッグ２６に使用されるシート材としては、血小板保存性を向上するためにガス透過性に優れるものを用いることがより好ましい。

【００４８】このようなシート材としては、例えば、ポリオレフィンやＤｎＤＰ可塑化ポリ塩化ビニル等を用いること、また、このような素材を用いることなく、上述したような材料のシート材を用い、厚さを比較的薄く（例えば、０．１～０．５ｍｍ程度、特に、０．１～０．３ｍｍ程度）したものが好適である。

【００４９】また、血小板採取バッグ２６の内部には、例えば、ＧＡＣ、ＰＡＳ、ＰＳＭ－１のような血小板保存液が予め入れられていてもよい。

【００５０】このような血液成分採取回路２の主要部分は、図１に示すように、カセット式となっている。すなわち、血液成分採取回路２は、各ライン（第１のライン２１、第２のライン２２、第３のライン２３）および各チューブ（第１チューブ２５ａ、第２チューブ２５ｂ、第３チューブ２６ａ、第４チューブ２７ａ）を部分的に収納し、かつ部分的にそれらを保持し、言い換えれば、部分的にそれらが固定されたカセットハウジング２８を備えている。

【００５１】カセットハウジング２８には、第１のポンプチューブ２１ｇの両端および第２のポンプチューブ２３ａの両端が固定され、これらのポンプチューブ２１ｇ、２３ａは、それぞれ、カセットハウジング２８より、各送液ポンプ（例えば、ローラーポンプ等）１１、１２の形状に対応したループ状に突出している。このため、第１および第２のポンプチューブ２１ｇ、２３ａは、それぞれ、各送液ポンプ１１、１２への装着が容易である。

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【００５２】さらに、カセットハウジング２８は、カセットハウジング２８内に位置する複数の開口部９１～９６を備えている。

【００５３】血液成分採取回路２に設けられている遠心分離器２０は、通常、遠心ボウルと呼ばれており、遠心力により血液を複数の血液成分に分離する。

【００５４】遠心分離器２０は、図２に示すように、上端に流入口１４３が形成された鉛直方向に伸びる管体１４１と、管体１４１の回りで回転し、上部１４５に対し液密にシールされた中空のローター１４２とを有している。

【００５５】ローター１４２には、その周壁内面に沿って環状の貯血空間１４６が形成されている。この貯血空間１４６は、図３中下部から上部に向けてその内外径が漸減するような形状（テーパ状）をなしており、その下部は、ローター１４２の底部に沿って形成されたほぼ円盤状の流路を介して管体１４１の下端開口に連通し、その上部は、排出口１４４に連通している。また、ローター１４２において、貯血空間１４６の容積は、例えば、１００～３５０ｍＬ程度とされ、ローター１４２の回転軸からの最大内径（最大半径）は、例えば、５５～６５ｍｍ程度とされる。

【００５６】このようなローター１４２は、血液成分採取装置１が備える遠心分離器駆動装置１０によりあらかじめ設定された所定の遠心条件（回転速度および回転時間）で回転する。この遠心条件により、ローター１４２内の血液の分離パターン（例えば、分離する血液成分数）を設定することができる。

【００５７】本実施形態では、図２に示すように、血液がローター１４２の貯血空間１４６内で内層より血漿層１３１、バフィーコート層１３２および赤血球層１３３に分離されるように遠心条件が設定される。

【００５８】次に、図１に示す血液成分採取装置１の全体構成について説明する。血液成分採取装置１は、遠心分離器２０のローター１４２を回転させるための遠心分離器駆動装置１０と、第１のライン２１の途中に設置された第１の送液ポンプ１１と、第３のライン２３の途中に設置された第２の送液ポンプ１２と、血液成分採取回路２（第１のライン２１、第２のライン２２、第１チューブ２５ａ、第２チューブ２５ｂ、および、第３チューブ２６ａ）の流路の途中を開閉し得る複数の流路開閉手段８１、８２、８３、８４、８５、８６、８７と、遠心分離器駆動装置１０、第１の送液ポンプ１１、第２の送液ポンプ１２および複数の流路開閉手段８１～８７を制御するための制御部（制御手段）１３とを備えている。

【００５９】さらに、血液成分採取装置１は、第２チューブ２５ｂとの接続部２２ａより遠心分離器２０側（上流側）の第２のライン２２に装着（設置）された濁度センサ１４と、遠心分離器２０の近傍に設置された光学式センサ１５と、血漿の重量を血漿採取バッグ２５ごと重量測定するための重量センサ１６とを備えている。

【００６０】制御部１３は、第１の送液ポンプ１１および第２の送液ポンプ１２のための２つのポンプコントローラ（図示せず）を備え、制御部１３と第１の送液ポンプ１１および第２の送液ポンプ１２とはポンプコントローラを介して電気的に接続されている。

【００６１】遠心分離器駆動装置１０が備える駆動コントローラ（図示せず）は、制御部１３と電気的に接続されている。

【００６２】各流路開閉手段８１～８７は、それぞれ、制御部１３に電気的に接続されている。

【００６３】また、濁度センサ１４、光学式センサ１５および重量センサ１６は、それぞれ、制御部１３と電気的に接続されている。

【００６４】制御部１３は、例えばマイクロコンピュータで構成されており、制御部１３には、上述した濁度センサ１４、光学式センサ１５および重量センサ１６からの検出信号が、それぞれ、随時入力される。

【００６５】制御部１３は、濁度センサ１４、光学式センサ１５および重量センサ１６からの検出信号に基づき、予め設定されたプログラムに従って、血液成分採取装置１の各部の作動、すなわち、各送液ポンプ１１、１２の回転、停止、回転方向（正転／逆転）を制御するとともに、必要に応じ、各流路開閉手段８１～８７の開閉および遠心分離器駆動装置１０の作動を制御する。

【００６６】第１の流路開閉手段８１は、第１のポンプチューブ２１ｇより採血針２９側において第１のライン２１を開閉するために設けられている。

【００６７】第２の流路開閉手段８２は、血漿採取バッグ２５の第１チューブ２５ａを開閉するために設けられている。

【００６８】第３の流路開閉手段８３は、血漿採取バッグ２５の第２チューブ２５ｂを開閉するために設けられている。

【００６９】第４の流路開閉手段８４は、血小板採取バッグ２６の第３チューブ２６ａ（チューブ２６１ａ）を開閉するために設けられている。

【００７０】第５の流路開閉手段８５は、第２のライン２２とバフィーコート採取バッグ２７の第４チューブ２７ａとの接続部（分岐コネクター２２ｄ）より遠心分離器２０側（上流側）の位置にて、第２のライン２２を開閉するために設けられている。

【００７１】第６の流路開閉手段８６は、第１のライン２１との接続部（分岐コネクター２１ｅ）と第４チューブ２７ａとの接続部（分岐コネクター２２ｄ）との間（第２のライン２２と第４チューブ２７ａとの接続部より下流側）の位置にて、第２のライン２２を開閉するために設けられている。

【００７２】また、第７の流路開閉手段８７は、第３チューブ２６ａ（チューブ２６２ａ）を開閉するために設

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けられている。

【００７３】各流路開閉手段８１～８７は、それぞれ、第１のライン２１、第２のライン２２、第１チューブ２５ａ、第２チューブ２５ｂ、第３チューブ２６ａ（チューブ２６１ａ、２６２ａ）を挿入可能な挿入部を備え、該挿入部には、例えば、ソレノイド、電動モーター、シリンダ（油圧または空気圧）等の駆動源で作動するクランプを有している。具体的には、ソレノイドで作動する電磁クランプが好適である。

【００７４】これらの流路開閉手段（クランプ）８１～８７は、それぞれ、制御部１３からの信号に基づいて作動する。

【００７５】遠心分離器駆動装置１０は、図２に示すように、遠心分離器２０を収納するハウジング２０１と、脚部２０２と、駆動源であるモータ２０３と、遠心分離器２０を保持する円盤状の固定台２０５とを有している。

【００７６】ハウジング２０１は、脚部２０２の上部に載置、固定されている。また、ハウジング２０１の下面には、ボルト２０６によりスペーサー２０７を介してモータ２０３が固定されている。

【００７７】モータ２０３の回転軸２０４の先端部には、固定台２０５が回転軸２０４と同軸でかつ一体的に回転するように嵌入されており、固定台２０５の上部には、ローター１４２の底部が嵌合する凹部が形成されている。

【００７８】また、遠心分離器２０の上部１４５は、図示しない固定部材によりハウジング２０１に固定されている。

【００７９】このような遠心分離器駆動装置１０では、モータ２０３を駆動すると、固定台２０５およびそれに固定されたローター１４２が、例えば、回転数３０００～６０００ｒｐｍ程度で回転する。

【００８０】ハウジング２０１には、その側部（図２中、左側）に光学式センサ１５が設置されている。

【００８１】この光学式センサ１５は、貯血空間１４６に向って投光するとともにその反射光を受光するように構成されている。

【００８２】光学式センサ１５は、投光部１５１から光（例えばレーザー光）を照射（投光）し、ローター１４２の反射面１４７で反射された反射光を受光部１５２で受光する。そして、受光部１５２においてその受光光量に応じた電気信号に変換される。

【００８３】このとき、投光光および反射光は、それぞれ、貯血空間１４６内の血液成分を透過するが、血液成分の界面（本実施形態では、血漿層１３１とバフィーコート層１３２との界面Ｂ）の位置に応じて、投光光および反射光が透過する位置における各血液成分の存在比が異なるため、それらの透過率が変化する。これにより、受光部１５２での受光光量が変動（変化）し、この変動を受光部１５２からの出力電圧の変化として検出することができる。

【００８４】すなわち、光学式センサ１５は、受光部１５２での受光光量の変化に基づき、血液成分の界面の位置を検出することができる。

【００８５】なお、光学式センサ１５が検出する血液成分の界面としては、界面Ｂに限られず、例えば、バフィーコート層１３２と赤血球層１３３との界面であってもよい。

【００８６】ここで、貯血空間１４６内の各層１３１～１３３は、それぞれ、血液成分により液体の色が異なっており、特に、赤血球層１３３は、赤血球の色に伴い赤色を呈している。このため、光学式センサ１５の精度向上の観点からは、投光光の波長に好適な範囲が存在し、この波長範囲としては、特に限定されないが、例えば、６００～９００ｎｍ程度であるのが好ましく、７５０～８００ｎｍ程度であるのがより好ましい。

【００８７】濁度センサ１４は、第２のライン２２中を流れる流体の濁度を検知するためのものであり、濁度に応じた電圧値を出力する。具体的には、濁度が高い時には低電圧値、濁度が低い時には高電圧値を出力する。

【００８８】この濁度センサ１４により、例えば、第２のライン２２中を流れる流体の空気から血漿への置換、血漿中の血小板濃度の変化、血漿中への赤血球の混入等を検出することができる。

【００８９】第１のポンプチューブ２１ｇが装着される第１の送液ポンプ１１、および、第２のポンプチューブ２３ａが装着される第２の送液ポンプ１２としては、それぞれ、例えば、ローラーポンプなどの非血液接触型ポンプが好適に用いられる。

【００９０】また、第１の送液ポンプ（血液ポンプ）１１としては、いずれの方向にも血液を送ることができるものが使用される。具体的には、正回転と逆回転が可能なローラーポンプが用いられている。

【００９１】次に、血液成分採取装置１を用いた血液成分採取操作について、血小板採取操作を行なう場合を一例として、図１、図３ないし図６に示すフローチャートを参照しつつ説明する。

【００９２】血液成分採取装置１は、制御部１３の制御により、第１の血漿採取工程と、定速血漿循環工程と、第２の血漿採取工程と、加速血漿循環工程と、第３の血漿採取工程と、血小板採取工程と、返血工程とを有する血小板採取操作を行なうよう作動する。

【００９３】また、本実施形態では、血小板採取操作を繰り返して３回（第１サイクル～第３サイクル）行い、さらに、最終回（第３サイクル）以外の血小板採取工程の終了後であって、返血工程の開始前に、バフィーコート採取工程を行い、かつ、次回の血小板採取操作における第１の血漿採取工程の開始前にバフィーコート返還工程を行うようになっている。

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【００９４】さらに、本発明では、最終サイクルの血小板採取操作を行なうのに並行して、血液成分採取装置１は、制御部１３の制御により、一時貯留バッグ２６’内に一時的に採取（貯留）した濃厚血小板血漿を、白血球除去フィルター２６１に供給して、濃厚血小板血漿中の白血球を分離除去する沪過操作を行なうよう構成されている。なお、供血者（ドナー）の拘束時間を短縮する観点からは、この沪過操作を、最終サイクルの血小板採取操作と同時に（特に、血小板採取操作の早い段階の工程において）開始するのが好ましく、本実施形態の血液成分採取装置１では、沪過操作を最終サイクルの血小板採取操作における第２の血漿採取工程の開始とほぼ同時に開始するように構成されている。

【００９５】［０］　まず、最初に、第３のライン２３と採血針２９とを、抗凝固剤でプライミングし、その後、ドナー（供血者）の血管に採血針２９を穿刺する。

【００９６】［１］　第１サイクルの血小板採取操作（図３および図４参照）

［１１］　まず、血液成分採取装置１は、第１の血漿採取（第１のＰＰＰ採取）工程を行なう。第１の血漿採取工程では、ローター１４２の貯血空間１４６内に血液を導入し、血液を遠心分離することにより分離された血漿（ＰＰＰ）を血漿採取バッグ２５内に採取する。

【００９７】第１の血漿採取工程では、まず、制御部１３は、血漿（第２の血液成分）の採取を行なう（図３のステップＳ１０１）。

【００９８】具体的には、制御部１３の制御により、第１の流路開閉手段８１および第４の流路開閉手段８４を開放し、他の流路開閉手段を閉塞した状態で、第１の送液ポンプ１１を所定の回転速度（好ましくは２５０ｍＬ／min以下程度、より好ましくは４０～１５０ｍＬ／min程度、例えば６０ｍＬ／min）で作動（正転）して、ドナーから採血を開始する。

【００９９】また、この採血と同時に、制御部１３の制御により、第２の送液ポンプ１２を作動して、第３のライン２３を介して、例えばＡＣＤ－Ａ液のような抗凝固剤を供給し、この抗凝固剤を採血血液中に混入させる。

【０１００】このとき、第２の送液ポンプ１２の回転速度は、制御部１３により、採血血液に対して抗凝固剤が所定比率（好ましくは１／２０～１／６程度、例えば１／１０）で混合されるように制御される。

【０１０１】これにより、血液（抗凝固剤加血液）は、第１のライン２１を介して移送され、遠心分離器２０の流入口１４３より管体１４１を経てローター１４２の貯血空間１４６内に導入される。

【０１０２】このとき、遠心分離器２０内の空気（滅菌空気）は、第２のライン２２および第３チューブ２６ａを介して一時貯留バッグ２６’内に送り込まれる。

【０１０３】また、前記採血と同時にまたはこれと前後して、制御部１３は、遠心分離器駆動装置１０を作動し、ローター１４２を所定の回転数で回転するよう制御する。

【０１０４】このローター１４２の回転により、貯血空間１４６内に導入された血液は、内側から血漿層（ＰＰＰ層）１３１、バフィーコート層（ＢＣ層）１３２、赤血球層（ＣＲＣ層）１３３の３層に分離される。

【０１０５】なお、ローター１４２の回転数としては、好ましくは３０００～６０００ｒｐｍ程度、より好ましくは４２００～５８００ｒｐｍ程度とされる。また、以下の工程において、特に記載しない限り、制御部１３は、ローター１４２の回転数を変更させない。

【０１０６】さらに、前記採血および前記抗凝固剤の供給を継続し、貯血空間１４６の容量を越える血液（約２７０ｍＬ）が貯血空間１４６内に導入されると、貯血空間１４６内は完全に血液により満たされ、遠心分離器２０の排出口１４４から血漿（ＰＰＰ）がオーバーフローする。

【０１０７】このとき、第２のライン２２に設置された濁度センサ１４は、第２のライン２２中を流れる流体が、空気から血漿に変わったことを検出し、制御部１３は、この濁度センサ１４の検出信号に基づき、第４の流路開閉手段８４を閉塞し、かつ、第３の流路開閉手段８３を開放するよう制御する。

【０１０８】これにより、第２のライン２２および第２チューブ２５ｂを介して血漿を血漿採取バッグ（第３の容器）２５内に導入、採取する。

【０１０９】なお、血漿採取バッグ２５は、その重量が重量センサ１６により計測されており、計測された重量信号は制御部１３に入力される。

【０１１０】次いで、制御部１３は、重量センサ１６からの情報（重量信号）に基づき、血漿採取バッグ２５内に所定量の血漿が採取されたか否かを判断する（図３のステップＳ１０２）。

【０１１１】なお、この血漿の採取量（所定量）としては、好ましくは１０～１５０ｇ程度、より好ましくは２０～４０ｇ程度とされる。

【０１１２】ステップＳ１０２において、血漿採取バッグ２５内に所定量の血漿が採取されていない場合には、制御部１３は、ステップＳ１０１に戻り、再度、ステップＳ１０１以降を繰り返す。

【０１１３】また、ステップＳ１０２において、血漿採取バッグ２５内に所定量の血漿が採取された場合には、制御部１３は、本工程［１１］（第１の血漿採取工程）を終了して、定速血漿循環工程に移行する。

【０１１４】［１２］　次に、血液成分採取装置１は、定速血漿循環（定速ＰＰＰ循環）工程を行なう。定速血漿循環工程では、血漿採取バッグ２５内の血漿を貯血空間１４６内に定速にて循環させる。

【０１１５】定速血漿循環工程では、まず、制御部１３は、血漿の循環を行なう（図３のステップＳ１０３）。

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【０１１６】具体的には、制御部１３の制御により、第１の流路開閉手段８１を閉塞し、第２の流路開閉手段８２を開放するとともに、第２の送液ポンプ１２を停止し、第１の送液ポンプ１１を所定の回転速度（好ましくは６０～２５０ｍＬ／min程度、例えば２００ｍＬ／min）で作動（正転）する。

【０１１７】これにより、採血を一時中断するとともに、血漿採取バッグ２５内の血漿を第１チューブ２５ａおよび第１のライン２１を介して貯血空間１４６内に一定速度で導入し、遠心分離器２０の排出口１４４から流出してきた血漿を第２のライン２２および第２チューブ２５ｂを介して血漿採取バッグ２５内に回収する。すなわち、血漿採取バッグ２５内の血漿を貯血空間１４６内に定速にて循環させる。

【０１１８】次いで、制御部１３は、定速ＰＰＰ循環を開始してから所定時間（好ましくは１０～９０秒程度、例えば３０秒）が経過したか否かを判断する（図３のステップＳ１０４）。

【０１１９】ステップＳ１０４において、定速ＰＰＰ循環を開始してから所定時間が経過していない場合には、制御部１３は、ステップＳ１０３に戻り、再度、ステップＳ１０３以降を繰り返す。

【０１２０】また、ステップＳ１０４において、定速ＰＰＰ循環を開始してから所定時間が経過した場合には、制御部１３は、本工程［１２］（定速血漿循環工程）を終了して、第２の血漿採取工程に移行する。

【０１２１】［１３］　次に、血液成分採取装置１は、第２の血漿採取（第２のＰＰＰ採取）工程を行なう。第２の血漿採取工程では、ローター１４２の貯血空間１４６内に血液を導入し、血液を遠心分離することにより分離された血漿を血漿採取バッグ２５内に採取する。

【０１２２】なお、この第２の血漿採取工程では、重量センサ１６により血漿の採取量を計測するのに代わり、血漿層１３１とバフィーコート層１３２との界面Ｂの位置を検出する以外、前記工程［１１］（第１の血漿採取工程）と同様の工程を行なう。

【０１２３】第２の血漿採取工程では、まず、制御部１３は、血漿の採取を行なう（図３のステップＳ１０５）。

【０１２４】なお、このとき、制御部１３は、第２の流路開閉手段８２を閉塞し、第１の流路開閉手段８１を開放するよう制御する。

【０１２５】これにより、貯血空間１４６内の赤血球量が増加、すなわち、赤血球層１３３の層厚が増大するのに伴い、界面Ｂも徐々に上昇（ローター１４２の回転軸方向へ移動）する。

【０１２６】次いで、制御部１３は、光学式センサ１５からの検出信号（界面位置検出情報）に基づき、界面Ｂが所定レベル（第１の位置）に到達したか否かを判断する（図３のステップＳ１０６）。

【０１２７】なお、この界面Ｂの第１の位置としては、第１の光学式センサ１５からの検出信号（受光部１５２からの出力電圧）が、好ましくは１～２Ｖ程度となった時点の位置とされる。

【０１２８】ステップＳ１０６において、界面Ｂが第１の位置に到達していない場合には、制御部１３は、ステップＳ１０５に戻り、再度、ステップＳ１０５以降を繰り返す。

【０１２９】また、ステップＳ１０５において、界面Ｂが第１の位置に到達した場合には、制御部１３は、本工程［１３］（第２の血漿採取工程）を終了して、加速血漿循環工程に移行する。

【０１３０】［１４］　次に、血液成分採取装置１は、加速血漿循環（加速ＰＰＰ循環）工程を行なう。加速血漿循環工程では、血漿採取バッグ２５内の血漿を貯血空間１４６内に加速させながら循環させる。

【０１３１】加速血漿循環工程では、まず、制御部１３は、血漿の循環を行なう（図３のステップＳ１０７）。

【０１３２】具体的には、制御部１３の制御により、第１の流路開閉手段８１を閉塞し、第２の流路開閉手段８２を開放するとともに、第２の送液ポンプ１２を停止し、かつ、第１の送液ポンプ１１の回転速度が一定の加速度にて増加（増大）するように作動（正転）する。

【０１３３】これにより、採血を一時中断するとともに、血漿採取バッグ２５内の血漿を第１チューブ２５ａおよび第１のライン２１を介して貯血空間１４６内に加速させながら導入し、遠心分離器２０の排出口１４４から流出してきた血漿を第２のライン２２および第２チューブ２５ｂを介して血漿採取バッグ２５内に回収する。すなわち、血漿採取バッグ２５内の血漿を貯血空間１４６内に加速させながら循環させる。

【０１３４】なお、このとき、制御部１３は、第１の送液ポンプ１１の回転速度を、前記定速ＰＰＰ循環より遅い速度（初速：例えば６０ｍＬ／min）から、一定の加速度にて増加（増大）するように制御する。

【０１３５】この加速条件（加速度）としては、好ましくは１～１０ｍＬ／min／sec程度、より好ましくは３～６ｍＬ／min／sec程度とされる。また、加速度は、一定でなくてもよく、例えば、前記範囲内で段階的または連続的に変化するものであってもよい。

【０１３６】次いで、制御部１３は、血漿の貯血空間１４６内への循環速度が最高速度に到達したか否か、すなわち、第１の送液ポンプ１１の回転速度が最高速度（好ましくは１３０～２５０ｍＬ／min程度、例えば１７０ｍＬ／min）に到達したか否かを判断する（図３のステップＳ１０８）。

【０１３７】このステップＳ１０８は、血漿の貯血空間１４６内への循環速度が最高速度に到達するまで継続される。

【０１３８】また、ステップＳ１０８において、血漿の

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貯血空間１４６内への循環速度が最高速度に到達した場合、制御部１３は、本工程［１４］（加速血漿循環工程）を終了して、第３の血漿採取工程に移行する。

【０１３９】［１５］　次に、血液成分採取装置１は、第３の血漿採取（第３のＰＰＰ採取）工程を行なう。第３の血漿採取工程では、ローター１４２の貯血空間１４６内に血液を導入し、血液を遠心分離することにより分離された血漿を血漿採取バッグ２５内に採取する。

【０１４０】第３の血漿採取工程では、まず、制御部１３は、血漿の採取を行なう（図３のステップＳ１０９）。

【０１４１】次いで、制御部１３は、重量センサ１６からの情報（重量信号）に基づき、血漿採取バッグ２５内に所定量の血漿が採取されたか否かを判断する（図３のステップＳ１１０）。

【０１４２】なお、この血漿の採取量（所定量）としては、好ましくは２～３０ｇ程度、より好ましくは５～１５ｇ程度とされる。

【０１４３】また、ステップＳ１１０において、血漿採取バッグ２５内に所定量の血漿が採取された場合には、制御部１３は、本工程［１５］（第３の血漿採取工程）を終了して、血小板採取工程に移行する（図４の①に移行する）。

【０１４４】［１６］　次に、血液成分採取装置１は、血小板採取（ＰＣ採取）工程を行なう。血小板採取工程では、血漿採取バッグ２５内の血漿を、貯血空間１４６内に第１の加速度にて加速させながら循環させ、次いで、第１の加速度より大きい第２の加速度に変更して、この第２の加速度にて加速させながら循環させて、貯血空間１４６内より血小板を流出させ、濃厚血小板血漿を一時貯留バッグ２６’内に採取（貯留）する。

【０１４５】血小板採取工程では、まず、制御部１３は、第１の加速度による血漿循環（ＰＰＰ循環）を行なう（図４のステップＳ１１１）。

【０１４６】具体的には、制御部１３の制御により、第１の流路開閉手段８１を閉塞し、第２の流路開閉手段８２を開放するとともに、第２の送液ポンプ１２を停止し、かつ、第１の送液ポンプ１１の回転速度を第１の加速度にて増加（増大）するよう作動（正転）する。

【０１４７】これにより、採血を中断するとともに、血漿採取バッグ２５内の血漿を第１チューブ２５ａおよび第１のライン２１を介して貯血空間１４６内に第１の加速度にて加速させながら導入し、遠心分離器２０の排出口１４４から流出してきた血漿を第２のライン２２および第２チューブ２５ｂを介して血漿採取バッグ２５内に回収する。すなわち、血漿採取バッグ２５内の血漿を貯血空間１４６内に第１の加速度にて加速させながら循環させる。

【０１４８】このとき、貯血空間１４６内に血漿を第１の加速度にて加速させながら循環すると、赤血球層１３３の拡散（層厚の増大）が生じて、界面Ｂも徐々に上昇（ローター１４２の回転軸方向へ移動）する。

【０１４９】この第１の加速度としては、好ましくは０．５～１０ｍＬ／min／sec程度、より好ましくは１．５～２．５ｍＬ／min／sec程度とされる。なお、第１の加速度は、一定でなくてもよく、例えば、前記範囲内で段階的または連続的に変化するものであってもよい。

【０１５０】また、第１の加速度によるＰＰＰ循環での第１の送液ポンプ１１の初速としては、好ましくは４０～１５０ｍＬ／min程度、より好ましくは５０～８０ｍＬ／min程度とされる。

【０１５１】次いで、制御部１３は、血漿の貯血空間１４６内への循環速度が所定速度に到達するまで、ステップＳ１１１を継続する（図４のステップＳ１１２）。

【０１５２】なお、この血漿の循環速度、すなわち、第１の送液ポンプ１１の回転速度としては、好ましくは１００～１８０ｍＬ／min程度、より好ましくは１４０～１６０ｍＬ／min程度とされる。

【０１５３】また、ステップＳ１１２において、血漿の貯血空間１４６内への循環速度が所定速度に到達した場合には、制御部１３は、第２の加速度による血漿循環（ＰＰＰ循環）を行なう（図４のステップＳ１１３）。

【０１５４】具体的には、制御部１３の制御により、第１の送液ポンプ１１の加速度を、第１の加速度から第２の加速度に変更して、第１の送液ポンプ１１の回転速度を第２の加速度にて増加（増大）するよう作動（正転）する。これにより、血漿採取バッグ２５内の血漿を貯血空間１４６内に第２の加速度にて加速させながら循環させる。

【０１５５】このとき、貯血空間１４６内に血漿を第２の加速度にて加速させながら循環すると、赤血球層１３３の拡散（層厚の増大）が生じて、界面Ｂも徐々に上昇（ローター１４２の回転軸方向へ移動）するとともに、バフィーコート層１３２中の血小板（ＰＣ）が遠心力に抗して浮上し（舞い上がり）、ローター１４２の排出口１４４へ向って移動する。

【０１５６】この第２の加速度としては、第１の加速度より大きくなるよう設定され、好ましくは３～２０ｍＬ／min／sec程度、より好ましくは５～１０ｍＬ／min／sec程度とされる。なお、第２の加速度は、一定でなくてもよく、例えば、前記範囲内で段階的または連続的に変化するものであってもよい。

【０１５７】次いで、制御部１３は、血漿の貯血空間１４６内への循環速度が最高速度に到達したか否か、すなわち、第１の送液ポンプ１１の回転速度が最高速度（好ましくは１２０～３００ｍＬ／min程度、例えば２００ｍＬ／min）に到達したか否かを判断する（図４のステップＳ１１４）。

【０１５８】ステップＳ１１４において、血漿の貯血空間１４６内への循環速度が最高速度に到達していない場

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合には、制御部１３は、ステップＳ１１３に戻り、再度、ステップＳ１１３以降を繰り返す。

【０１５９】また、ステップＳ１１４において、血漿の貯血空間１４６内への循環速度が最高速度に到達した場合には、制御部１３は、血漿循環継続（ＰＰＰ循環継続）を行なう（図４のステップＳ１１５）。

【０１６０】具体的には、制御部１３は、第１の送液ポンプ１１の回転速度を、前記ステップＳ１１５における最高速度で維持（保持）するよう制御する。これにより、血漿の貯血空間１４６内への循環速度を、好ましくは１２０～３００ｍＬ／min程度、例えば２００ｍＬ／minとする。

【０１６１】次いで、制御部１３は、ＰＰＰ循環継続を開始してから所定時間（好ましくは５～１５秒程度、例えば１０秒）が経過したか否かを判断する（図４のステップＳ１１６）。

【０１６２】ステップＳ１１６において、ＰＰＰ循環継続を開始してから所定時間が経過していない場合には、次いで、制御部１３は、濁度センサ１４からの出力電圧（ＰＣ濃度電圧）が所定値（好ましくは２．５～３．５Ｖ程度、例えば、３．０Ｖ）以下に低下したか否かを判断する（図４のステップＳ１１７）。

【０１６３】ステップＳ１１７において、濁度センサ１４からの出力電圧が所定値以下に低下していない場合には、制御部１３は、ステップＳ１１５に戻り、再度、ステップＳ１１５以降を繰り返す。

【０１６４】ステップＳ１１５～Ｓ１１７を繰り返している間に、ステップＳ１１６において、ＰＰＰ循環継続を開始してから所定時間が経過した場合には、制御部１３は、本工程［１６］（血小板採取工程）を終了して、バフィーコート採取工程に移行する。

【０１６５】また、ステップＳ１１７において、濁度センサ１４からの出力電圧が所定値以下に低下した場合には、すなわち、ローター１４２の排出口１４４から血小板が流出するのに伴い、第２のライン２２中を流れる血漿中の血小板濃度が所定値以上に到達した場合には、制御部１３は、血小板（ＰＣ）の採取を行なう（図４のステップＳ１１８）。

【０１６６】具体的には、制御部１３は、濁度センサ１４の検出信号に基づき、第３の流路開閉手段８３を閉塞し、かつ、第４の流路開閉手段８４を開放するよう制御する。

【０１６７】これにより、第２のライン２２および第３チューブ２６ａ（チューブ２６１ａ）を介して濃厚血小板血漿を一時貯留バッグ２６’内へ導入し、採取（貯留）する。なお、このとき、第７の流路開閉手段８７は、閉塞しているため、濃厚血小板血漿は、一時貯留バッグ２６’内から流出しない。

【０１６８】また、制御部１３は、濁度センサ１４からの出力電圧（検出信号）に基づき、一時貯留バッグ２６’内の血小板濃度（累積ＰＣ濃度）を算出する。なお、この血小板濃度は、ＰＣ採取を開始してから上昇を続け、一旦、最高濃度に到達した後、下降に転じる。

【０１６９】次いで、制御部１３は、ＰＣ採取を開始してから所定時間（好ましくは１０～２５秒程度、例えば１５秒）が経過したか否かを判断する（図４のステップＳ１１９）。

【０１７０】ステップＳ１１９において、ＰＣ採取を開始してから所定時間が経過していない場合には、次いで、制御部１３は、濁度センサ１４の出力電圧（ＰＣ濃度電圧）が所定値以下に到達したか否かを判断する（図４のステップＳ１２０）。

【０１７１】この濁度センサ１４の出力電圧の所定値としては、第２のライン２２中を流れる血漿中に赤血球（ＣＲＣ）の混入が生じる時点付近の値とされ、好ましくは０．５Ｖ以下程度とされる。

【０１７２】ステップＳ１２０において、濁度センサ１４の出力電圧が所定値以下に到達していない場合には、次いで、制御部１３は、一時貯留バッグ２６’内の濃厚血小板血漿が所定量に到達したか否かを判断する（図４のステップＳ１２１）。

【０１７３】なお、この濃厚血小板血漿の採取量（所定量）としては、好ましくは２０～１００ｍＬ程度、より好ましくは４０～７０ｍＬ程度とされる。

【０１７４】ステップＳ１２１において、一時貯留バッグ２６’内の濃厚血小板血漿が所定量に到達しない場合には、制御部１３は、ステップＳ１１８に戻り、再度、ステップＳ１１８以降を繰り返す。

【０１７５】ステップＳ１１８～Ｓ１２１を繰り返している間に、ステップＳ１１９において、ＰＣ採取を開始してから所定時間が経過した場合、または、ステップＳ１２０において、濁度センサ１４の出力電圧が所定値以下に到達した場合には、制御部１３は、本工程［１６］（血小板採取工程）を終了して、バフィーコート採取工程に移行する。

【０１７６】また、ステップＳ１２１において、一時貯留バッグ２６’内の濃厚血小板血漿が所定量に到達した場合には、制御部１３は、本工程［１６］（血小板採取工程）を終了して、バフィーコート採取工程に移行する。

【０１７７】［１７］　次に、血液成分採取装置１は、バフィーコート採取（ＢＣ採取）工程を行なう。バフィーコート採取工程では、ローター１４２の貯血空間１４６内からバフィーコートを流出させ、採取する。

【０１７８】バフィーコート採取工程では、まず、制御部１３は、バフィーコートの採取を行なう（図４のステップＳ１２２）。

【０１７９】具体的には、制御部１３の制御により、第４の流路開閉手段８４を閉塞し、第５の流路開閉手段８５を開放するとともに、第１の送液ポンプ１１を所定の

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回転速度（好ましくは、６０～３００ｍＬ／min程度、例えば２０５ｍＬ／min）で作動（正転）する。

【０１８０】これにより、血漿採取バッグ２５内の血漿を第１チューブ２５ａおよび第１のライン２１を介して貯血空間１４６内に所定速度で導入し、ローター１４２の排出口１４４から流出してきたバフィーコートを第２のライン２２および第４チューブ２７ａを介してバフィーコート採取バッグ２７内に導入、採取する。

【０１８１】なお、このバフィーコート採取工程では、制御部１３は、ローター１４２の回転数を変更する。

【０１８２】このローター１４２の回転数としては、前記工程［１１］～［１６］におけるローター１４２の回転数より、例えば１００～３００ｒｐｍ程度低く設定され、具体的には、４５００～４６００ｒｐｍ程度であるのが好ましい。

【０１８３】次いで、制御部１３は、バフィーコート採取バッグ２７内に所定量のバフィーコートが採取されたか否かを判断する（図４のステップＳ１２３）。

【０１８４】具体的には、制御部１３は、バフィーコートの採取量（所定量）を、採血量、ドナーのヘマトクリット値および前記血小板採取工程において採取した血小板の量から算出し、かかる算出した採取量から第１の送液ポンプ１１を回転する回数を決定して、第１の送液ポンプ１１が算出した採取量を採取するのに必要な回数、回転したか否かを判断する。

【０１８５】ステップＳ１２３において、バフィーコート採取バッグ２７内に所定量のバフィーコートが採取されていない場合、すなわち、第１の送液ポンプ１１が必要回数、回転していない場合には、制御部１３は、ステップＳ１２２に戻り、再度、ステップＳ１２２以降を繰り返す。

【０１８６】また、前記ステップＳ１２３において、バフィーコート採取バッグ２７内に所定量のバフィーコートが採取された場合、すなわち、第１の送液ポンプ１１が必要回数、回転した場合には、制御部１３は、全ての流路開閉手段８１～８７を閉塞した状態とし、第１の送液ポンプ１１を停止して、本工程［１７］（バフィーコート採取工程）を終了する。

【０１８７】［１８］　次に、血液成分採取装置１は、遠心分離器２０を停止する工程を行なう。

【０１８８】この工程では、まず、制御部１３は、遠心分離器２０の減速を行なう（図４のステップＳ１２４）。

【０１８９】具体的には、制御部１３の制御により、遠心分離器駆動装置１０の回転数を減少して、ローター１４２を減速する。

【０１９０】さらに、制御部１３は、遠心分離器２０の停止を行なう（図４のステップＳ１２５）。

【０１９１】具体的には、制御部１３の制御により、遠心分離器駆動装置１０の回転を停止して、ローター１４２を停止する。

【０１９２】［１９］　次に、血液成分採取装置１は、返血工程を行なう。返血工程では、ローター１４２の貯血空間１４６内の血液成分を返血する。

【０１９３】返血工程では、制御部１３は、返血を行なう（図４のステップＳ１２６）。具体的には、制御部１３の制御により、第１の流路開閉手段８１を開放するとともに、第１の送液ポンプ１１を所定の回転速度（好ましくは２０～１２０ｍＬ／min程度、例えば９０ｍＬ／min）で作動（逆転）する。

【０１９４】これにより、ローター１４２の貯血空間１４６内に残存する血液成分（主に、赤血球）は、遠心分離器２０の排出口１４４から排出され、第１のライン２１を介してドナーに返血（返還）される。

【０１９５】なお、血液成分の総量（返血量）は、採血量、血漿採取量および濃厚血小板血漿採取量から算出される。

【０１９６】そして、制御部１３の制御により、かかる血液成分の総量（返血量）をドナーに返血するのに必要とする回数、第１の送液ポンプ１１を回転した後、第１の流路開閉手段８１を閉塞するとともに、第１の送液ポンプ１１を停止して、本工程［１９］（返血工程）を終了する。これにより、第１サイクルの血小板採取操作を終了する。

【０１９７】［２］　第２サイクルの血小板採取操作（図５および図４参照）

続いて、第２サイクルの血小板採取操作を行なう。

【０１９８】第２サイクルの血小板採取操作では、第１の血漿採取工程の開始前に、バフィーコート返還工程を行なう以外は、前記第１サイクルの血小板採取操作と同様の工程を行なう。

【０１９９】［２０］　まず、血液成分採取装置１は、バフィーコート返還（ＢＣ返還）工程を行なう。バフィーコート返還工程では、採取されたバフィーコートをローター１４２の貯血空間１４６内に返還する。

【０２００】バフィーコート返還工程では、まず、制御部１３は、バフィーコートの返還を行なう（図５のステップＳ２０Ｘ）。

【０２０１】具体的には、制御部１３の制御により、第４の流路開閉手段８４および第６の流路開閉手段８６を開放し、他の流路開閉手段を閉塞した状態で、第１の送液ポンプ１１を所定の回転速度（好ましくは６０～２５０ｍＬ／min程度、例えば１００ｍＬ／min）で作動（正転）し、かつ、遠心分離器駆動装置１０を所定の回転数（例えば、４８００ｒｐｍ）で作動する。

【０２０２】これにより、バフィーコート採取バッグ２７内のバフィーコートが第４チューブ２７ａおよび第１のライン２１を介して遠心分離器２０の流入口１４３より管体１４１を経てローター１４２の貯血空間１４６内に導入される。このとき、遠心分離器２０内の空気は、

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第２のライン２２を介して一時貯留バッグ２６’内に送り込まれる。

【０２０３】次いで、制御部１３は、バフィーコート採取バッグ２７内に、返還するバフィーコートが無くなったか否かを判断する（図５のステップＳ２０Ｙ）。

【０２０４】具体的には、制御部１３は、バフィーコートの採取量から第１の送液ポンプ１１を回転する回数を決定して、第１の送液ポンプ１１がバフィーコートを返還するのに必要な回数、回転したか否かを判断する。

【０２０５】ステップＳ２０Ｙにおいて、返還するバフィーコートが残存する場合、すなわち、第１の送液ポンプ１１が必要回数、回転していない場合には、制御部１３は、ステップＳ２０Ｘに戻り、再度、ステップＳ２０Ｘ以降を繰り返す。

【０２０６】また、ステップＳ２０Ｙにおいて、返還するバフィーコートが無くなった場合、すなわち、第１の送液ポンプ１１が必要回数、回転した場合には、制御部１３は、本工程［２０］（バフィーコート返還工程）を終了して、第１の血漿採取工程に移行する。

【０２０７】［２１］～［２９］　前記工程［１１］～［１９］と同様の工程をそれぞれ行なう。これにより、第２サイクルの血小板採取操作を終了する。

【０２０８】［３］　第３サイクル（最終サイクル）の血小板採取操作（図５および図６参照）

続いて、第３サイクルの血小板採取操作を行なう。

【０２０９】第３サイクルの血小板採取操作では、バフィーコート採取工程を行わず、さらに、血小板採取用分岐ラインを血漿で洗浄するライン洗浄工程を行なう以外は、前記第２サイクルの血小板採取操作と同様の工程を行なう。

【０２１０】［３０］～［３２］　前記工程［２０］～［２２］と同様の工程をそれぞれ行なう。

【０２１１】［３３］　前記工程［２３］と同様の工程を行なう。また、本工程［３３］（第２の血漿採取工程）を行なうのとほぼ同時に、制御部１３は、一時貯留バッグ２６’内に一時的に採取（貯留）した濃厚血小板血漿を、白血球除去フィルター２６１に供給して、濃厚血小板血漿の沪過、すなわち、濃厚血小板血漿中の白血球の分離除去を行なう。

【０２１２】具体的には、制御部１３の制御により、第７の流路開閉手段８７を開放する。これにより、一時貯留バッグ２６’内の濃厚血小板血漿を、落差（自重）により、チューブ２６２ａ、白血球除去フィルター２６１およびチューブ２６３ａを経て、血小板採取バッグ２６内に移送する。このとき、濃厚血小板血漿は、そのほとんどが、白血球除去フィルター２６１の沪過部材を通過するが、白血球は沪過部材に捕捉される。このため、血小板製剤中の白血球の除去率を極めて高いものとすることができる。

【０２１３】なお、濃厚血小板血漿の一時貯留バッグ２６’内から血小板採取バッグ２６への移送は、ポンプを用いて行なうようにしてもよい。

【０２１４】また、第７の流路開閉手段８７は、制御部１３の制御により作動するものに代わり、手動によりチューブ２６２ａの流路の途中を開閉し得るクレンメ等であってもよい。

【０２１５】［３４］～［３５］　前記工程［２４］～［２５］と同様の工程をそれぞれ行なう。

【０２１６】［３６］　前記工程［２６］と同様の工程を行なう。なお、本工程［３６］において、一時貯留バッグ２６’内に採取された濃厚血小板血漿は、順次、白血球除去フィルター２６１に供給され、沪過される。

【０２１７】［３Ａ］　次に、血液成分採取装置１は、ライン洗浄工程を行なう。ライン洗浄工程では、血漿採取バッグ２５内から血漿を血小板採取用分岐ラインに供給し、血小板採取用分岐ラインを洗浄する。

【０２１８】ライン洗浄工程では、制御部１３は、血小板採取用分岐ラインへの血漿供給（ＰＰＰ供給）を行なう（図６のステップＳ３２７）。

【０２１９】具体的には、第２の流路開閉手段８２および第４の流路開閉手段８４の開放状態を維持しつつ、制御部１３の制御により、第１の送液ポンプ１１の回転速度およびローター１４２の回転数を変更する。

【０２２０】この第２の送液ポンプ１１の回転速度としては、好ましくは２５０ｍＬ／min以下程度、より好ましくは４０～２５０ｍＬ／min程度とされる。

【０２２１】また、ローター１４２の回転数としては、前記工程［３０］～［３６］におけるローター１４２の回転数より、例えば３００～８００ｒｐｍ程度高く設定され、具体的には、５０００～５５００ｒｐｍ程度であるのが好ましい。

【０２２２】これにより、血漿採取バッグ２５内の血漿を、第１チューブ２５ａ、第１のライン２１、ローター１４２（遠心分離器２０）、第２のライン２２およびチューブ２６１ａを介して、すなわち、一時貯留バッグ（第１の容器）２６’の上流側から、一時貯留バッグ２６’、チューブ２６２ａ、白血球除去フィルター２６１、チューブ２６３ａを経て、血小板採取バッグ２６内に導入（供給）する。

【０２２３】このとき、白血球除去フィルター２６１内およびチューブ２６３ａの流路内に残存する血小板（白血球を分離除去した後の濃厚血小板血漿）は、血漿とともに血小板採取バッグ２６内に回収されるので、血小板製剤中の血小板の収率を高くすることができる。

【０２２４】しかも、血漿を一時貯留バッグ２６’の上流側から供給することにより、血漿は、一時貯留バッグ２６’内およびチューブ２６２ａの流路内に残存する濃厚血小板血漿（第１の血液成分）とともに、白血球除去フィルター２６１に供給されるので、血小板製剤中の血小板の収率をより向上することができる。

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【０２２５】また、この血漿の供給量により、血小板製剤（血小板採取バッグ２６内の血液成分）の総量を調整するようにするのが好ましい。これにより、別途、血小板製剤の総量を調整する操作を省略することができ、時間短縮に有利である。また、かかる調整を血液成分採取回路２内（クローズド状態）で行なうことができるため、無菌状態を維持することできるという利点もある。

【０２２６】このような血漿の供給量としては、好ましくは５～２００ｍＬ程度、より好ましくは１２～１５０ｍＬ程度とされる。

【０２２７】なお、この血漿の供給量は、重量センサ１６により血漿採取バッグ２５の重量の変化（減少）として検出されている。

【０２２８】そして、重量センサ１６の検出信号に基づき、所定量の血漿を血小板採取用分岐ラインに供給した後、制御部１３は、流路開閉手段８１～８４、８６を閉塞した状態とし、第１の送液ポンプ１１を停止するよう制御して、本工程［３Ａ］（ライン洗浄工程）を終了する。

【０２２９】なお、本工程［３Ａ］に先立って、制御部１３は、ローター１４２の回転を維持しつつ、第１の送液ポンプ１１を、一旦停止するように制御してもよい。これにより、前記工程［３６］（血小板採取工程）において、ローター１４２の貯血空間１４６内で拡散（層厚が増大）していたバフィーコート層１３２および赤血球層１３３を圧縮（層厚を減少）することができるので、本工程［３Ａ］（ライン洗浄工程）において、ローター１４２の排出口１４４から流出する血漿中にバフィーコートあるいは赤血球が混入するのをより確実に防止することができる。

【０２３０】また、本工程［３Ａ］は、一時貯留バッグ２６’内からの濃厚血小板血漿の排出が終了した後に、開始するようにしてもよい。これは、一時貯留バッグ２６’付近のチューブ２６２ａに、例えば、流路内の気泡の存在を検出することができる気泡センサ等を設置することにより実現することができる。

【０２３１】［３８］～［３９］　前記工程［２８］～［２９］と同様の工程を行なう。なお、前記工程［２７］と同様の工程は、省略される。これにより、第３サイクルの血小板採取操作を終了する。

【０２３２】なお、血小板採取操作は、３回行なう場合に限定されず、必要に応じて、１または２回、あるいは、４回以上行なってもよい。

【０２３３】このような血液成分採取装置１では、血液より分離、採取された濃厚血小板血漿中から、白血球除去フィルター２６１により白血球を分離除去するため、白血球の混入が極めて低い血小板製剤を得ることができる。

【０２３４】しかも、白血球除去フィルター２６１内およびチューブ２６３ａの流路内に残存する血小板を、血漿により洗い流して血小板採取バッグ２６内に回収するため、血小板の収率が極めて高い血小板製剤を得ることができる。

【０２３５】また、血小板を、血漿（血液成分）を用いて回収する（洗い流す）ので、例えば、生理食塩水、抗凝固剤を用いる場合に比べて、より品質の高い血小板製剤を得ることができる。

【０２３６】また、血液成分採取装置１では、血液成分採取回路２の構成も、適宜設定可能であり、図示の構成に限定されない。

【０２３７】例えば、血漿採取バッグ２５と血小板採取用分岐ラインとを接続するチューブ（ライン）を設けるようにしてもよい。この場合、血漿採取バッグ２５内の血漿を血小板採取用分岐ラインへ供給（移送）する方法としては、落差によるもの、あるいは、ポンプによるもののいずれであってもよい。なお、この場合においても、血漿採取バッグ２５は、一時貯留バッグ２６’の上流側に接続されているのが好ましい。

【０２３８】また、例えば、血漿採取バッグ２５と異なる第２の血漿採取バッグを設け、この第２の血漿採取バッグ内に、ライン洗浄工程において、血小板採取用分岐ラインに供給する血漿を貯留するようにすることもできる。

【０２３９】さらに、血液成分採取装置１では、血小板採取操作（血液成分採取操作）の各工程における条件も、適宜設定可能であり、また、必要に応じて、任意の工程を追加および／または省略することもできる。

【０２４０】以上、本発明の血液成分採取装置を図示の実施形態に基づいて説明したが、本発明は、これらに限定されるものではない。血液成分採取装置を構成する各部は、同様の機能を発揮し得る任意の構成のものと置換することができる。

【０２４１】例えば、本発明では、光学式センサは、図示のものに限定されず、例えば、ラインセンサ等であってもよい。

【０２４２】なお、本発明の血液成分採取装置は、血小板製剤を得るのに適用する場合に限らず、例えば、血液中から血漿製剤、アルブミン製剤、赤血球製剤等を製造する場合に適用してもよく、また、細胞分離フィルターにより分離除去する細胞も、白血球（リンパ球）に限定されない。

【０２４３】

【実施例】次に、本発明の具体的実施例について説明する。

【０２４４】（実施例）血液成分採取回路（テルモ株式会社製「テルモアフェレーシスセット（白血球除去フィルター付き）」）、および、血液成分採取装置（テルモ株式会社製「テルモアフェレーシス装置ＡＣ－５５０」）を改造して、図１に示す血液成分採取装置を組み立てた。この装置を用いて、前述した工程に従って血小

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板採取操作（４回）を行なった。

【０２４５】また、血小板採取操作における各工程での条件を以下に示す。検出する血液成分の界面は、血漿層とバフィーコート層との界面とした。

【０２４６】

［第１の血漿採取工程］
ローター　；　回転数　：４８００ｒｐｍ
第１の送液ポンプ；　回転速度　：６０ｍＬ／min
工程終了条件　；　採取量が３０ｇとなったとき
［定速血漿循環工程］
ローター　；　回転数　：４８００ｒｐｍ
第１の送液ポンプ；　回転速度　：２００ｍＬ／min
工程終了条件　；　３０秒経過したとき
［第２の血漿採取工程］
ローター　；　回転数　：４８００ｒｐｍ
第１の送液ポンプ；　回転速度　：６０ｍＬ／min
工程終了条件　；　第１の光学式センサの出力電圧が１．８Ｖとなったとき
［加速血漿循環工程］
ローター　；　回転数　：４８００ｒｐｍ
第１の送液ポンプ；　回転速度　：６０ｍＬ／min（初速）、
５．０ｍＬ／min／sec（加速度）
工程終了条件　；　第１の送液ポンプの回転速度が１７０ｍＬ／minとなったとき
［第３の血漿採取工程］
ローター　；　回転数　：４８００ｒｐｍ
第１の送液ポンプ；　回転速度　：６０ｍＬ／min
工程終了条件　；　採取量が１０ｇとなったとき
［血小板採取工程］
ローター　；　回転数　：４８００ｒｐｍ
第１の送液ポンプ；　回転速度　：６０ｍＬ／min（初速）
２ｍＬ／min／sec（第１の加速度）
回転速度が１５０ｍＬ／minとなった時点で加速度の変更
１０ｍＬ／min／sec（第２の加速度）
２００ｍＬ／min（最高速度）
工程終了条件　；　濃厚血小板血漿の採取量が５０ｍＬとなったとき
［バフィーコート採取工程］
ローター　；　回転数　：４６００ｒｐｍ
第１の送液ポンプ；　回転速度　：２０５ｍＬ／min
工程終了条件　；　算出されたバフィーコート量が採取されたとき
［返血工程］
第１の送液ポンプ；　回転速度　：９０ｍＬ／min
工程終了条件　；　算出された返血量が返血されたとき
［バフィーコート返還工程］
ローター　；　回転数　：４８００ｒｐｍ
第１の送液ポンプ；　回転速度　：１００ｍＬ／min
工程終了条件　；　算出されたバフィーコート量が返還されたとき
［ライン洗浄工程］
ローター　；　回転数　：５２００ｒｐｍ
第１の送液ポンプ；　回転速度　：６０ｍＬ／min
工程終了条件　；　１５ｍＬの血漿が供給されたとき

【０２４７】（比較例）血液成分採取回路（テルモ株式　　会社製「テルモアフェレーシスセット（白血球除去フィ

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ルター付き）」）、および、血液成分採取装置（テルモ株式会社製「テルモアフェレーシス装置ＡＣ－５５０」）を改造して、図１に示す血液成分採取装置を組み立てた。ライン洗浄工程を省略した以外は、この装置を用いて、前記実施例と同様にして、血小板採取操作（４回）を行なった。

【０２４８】なお、比較例の血小板採取操作は、実施例と同一のドナーを用い、実施例の血小板採取操作を行なってから２週間後に行なった。

【０２４９】（評価）実施例および比較例で得られた一時貯留バッグ内の濃厚血小板血漿、および、血小板採取バッグ内の血小板製剤の採取量を測定した。

【０２５０】また、一時貯留バッグ内の濃厚血小板血漿、および、血小板採取バッグ内の血小板製剤をそれぞれサンプリングし、これらに含まれる血小板数および白血球数を、それぞれ測定した。この測定には、血球計数装置（Ｓｙｓｍｅｘ社製、Ｓｙｓｍｅｘ（Ｒ）ＳＥ－９０００）を用いた。但し、Ｓｙｓｍｅｘ（Ｒ）ＳＥ－９０００における白血球数の測定下限は、０．１×10^2ｃｅｌｌｓ／μＬであるため、測定下限を下回ったサンプルは、白血球数をＮａｇｅｏｔｔｅ［１：９］法により測定した。その結果を、表１に示す。

【０２５１】

【表１】

表１

		一時貯留バッグ内（濃厚血小板血漿）	血小板採取バッグ内（血小板製剤）
実施例	採取量　［ｍＬ］	２００	２００
	血小板数［ｃｅｌｌｓ／ｂａｇ］	２．１９×10^{11}	２．１１×10^{11}
	白血球数［ｃｅｌｌｓ／ｂａｇ］	３．０×10^7	１．０×10^4
比較例	採取量　［ｍＬ］	２００	２００
	血小板数［ｃｅｌｌｓ／ｂａｇ］	２．３６×10^{11}	２．１８×10^{11}
	白血球数［ｃｅｌｌｓ／ｂａｇ］	５．６×10^7	１．０×10^4

【０２５２】上記表１に示すように、実施例では、ライン洗浄工程を行なったことにより、比較例に比べて、血小板採取用分岐ライン内での血小板のロス（損失）をより低減することができ、血小板製剤中への血小板の収率をより高くすることができた。

【０２５３】なお、実施例および比較例では、いずれも、血小板製剤中から白血球が十分に除去されていた。

【０２５４】

【発明の効果】以上述べたように、本発明の血液成分採取装置によれば、細胞分離フィルターにより、所定の細胞を分離除去するため、例えば血小板製剤のような血液製剤を得るのに際し、その血小板製剤（血液製剤）中の白血球（特に、リンパ球）の除去率が高くなり、発熱、同種抗原感作、ウィルス感染等の確率を低下することができ、安全性が高い。

【０２５５】また、本発明の血液成分採取装置によれば、例えば血小板製剤のような血液製剤を得るのに際し、細胞分離フィルターに残存する血小板を、例えば血漿（血液成分）を媒介として回収するため、血小板製剤中の血小板の収率が高くなり、しかも、血小板を血液成分を用いて回収するので、血小板の損傷（ダメージ）が少なく、品質の高い血小板製剤（血液製剤）を得ることができる。

【図面の簡単な説明】

【図１】本発明の血液成分採取装置の構成を示す平面図である。

【図２】血液成分採取装置が備える遠心分離器に遠心分離器駆動装置が装着された状態の部分破断断面図である。

【図３】本発明の血液成分採取装置の作用を説明するためのフローチャートである。

【図４】本発明の血液成分採取装置の作用を説明するためのフローチャートである。

【図５】本発明の血液成分採取装置の作用を説明するためのフローチャートである。

【図６】本発明の血液成分採取装置の作用を説明するためのフローチャートである。

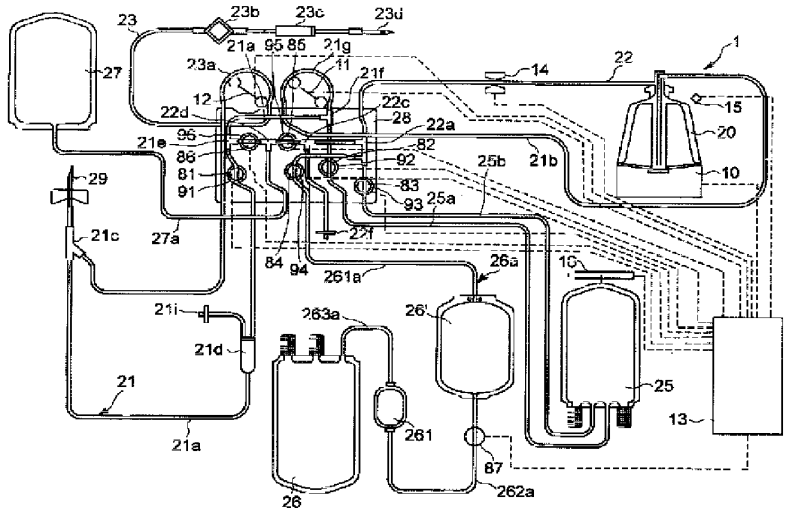
【符号の説明】

１	血液成分採取装置
２	血液成分採取回路
１０	遠心分離器駆動装置
１１	第１の送液ポンプ
１２	第２の送液ポンプ
１３	制御部
１４	濁度センサ
１５	光学式センサ
１６	重量センサ
２０	遠心分離器
２１	第１のライン
２２	第２のライン
２３	第３のライン
２５	血漿採取バッグ
２６	血小板採取バッグ
２６’	一時貯留バッグ
２６１	白血球除去フィルター
２６ａ	第３チューブ

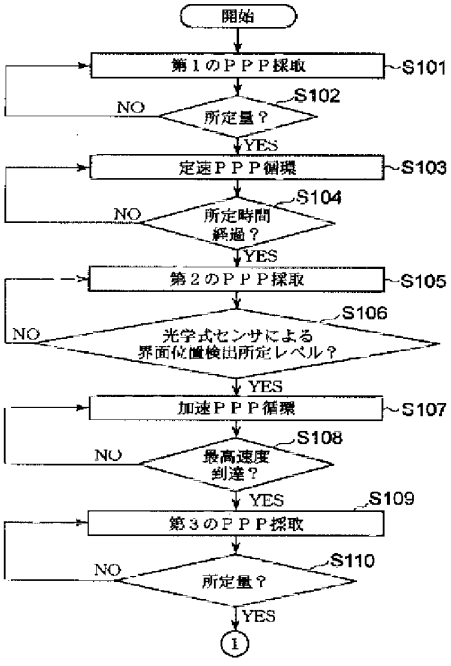
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２６１ａ～２６３ａ	チューブ	９１～９６	第１～第６の開口部
２７	バフィーコート採取バッグ	１３１	血漿層
２８	カセットハウジング	１３２	バフィーコート層
２９	採血針	１３３	赤血球層
８１～８７	第１～第７の流路開閉手段		

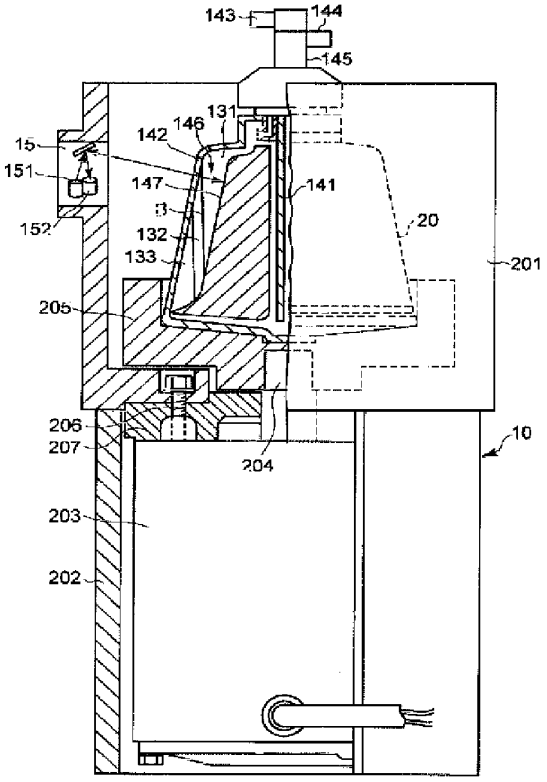
【図１】



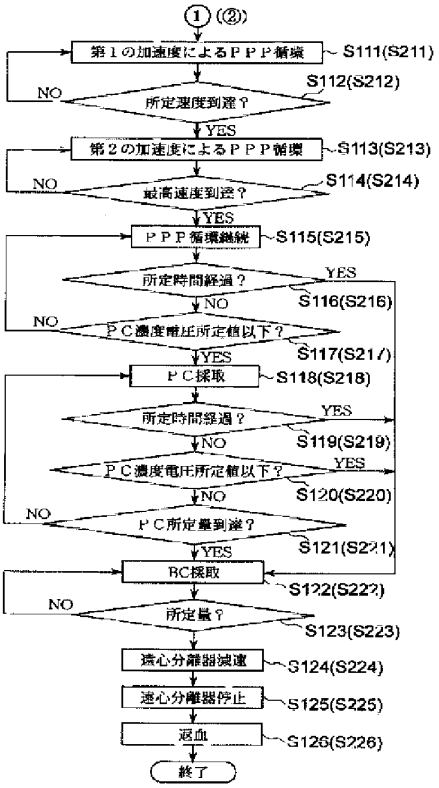
【図３】



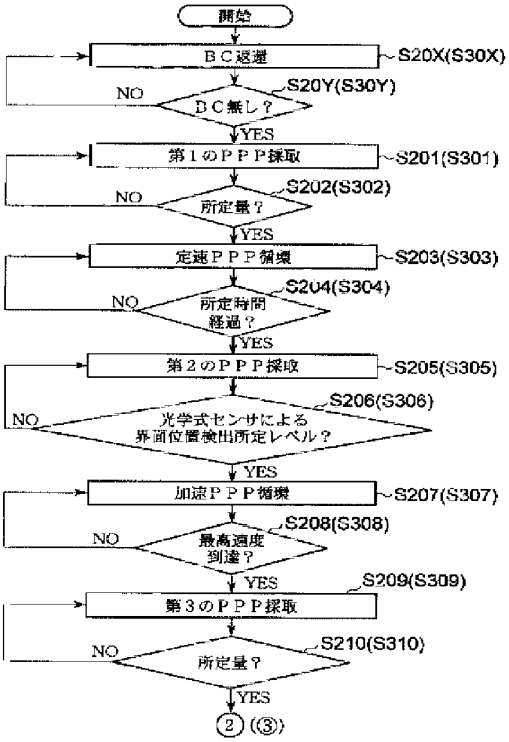
【図2】


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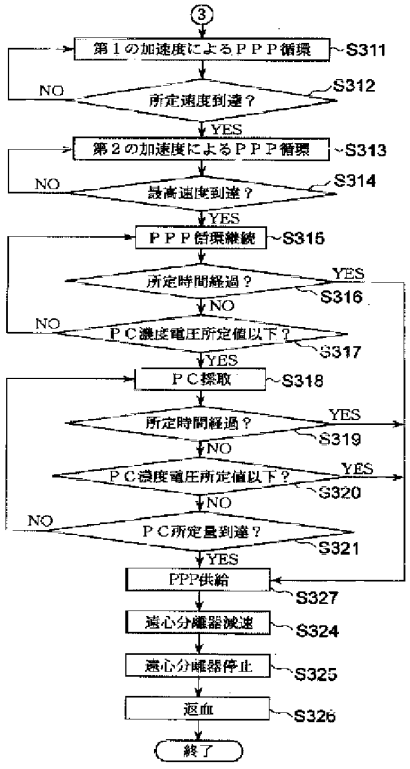
【図4】


①(②)
第1の加速度によるPPP循環
S111(S211)
S112(S212)
所定速度到達?
NO
YES
第2の加速度によるPPP循環
S113(S213)
S114(S214)
最高速度到達?
NO
YES
PPP循環継続
S115(S215)
所定時間経過?
YES
NO
S116(S216)
PC濃度電圧所定値以下?
NO
YES
S117(S217)
PC採取
S118(S218)
所定時間経過?
YES
NO
S119(S219)
PC濃度電圧所定値以下?
YES
NO
S120(S220)
PC所定量到達?
NO
YES
S121(S221)
BC採取
S122(S222)
所定量?
NO
S123(S223)
遠心分離器減速
S124(S224)
遠心分離器停止
S125(S225)
返血
S126(S226)
終了

【図5】



【図6】



フロントページの続き

Fターム(参考) 4C077 AA12 AA13 BB02 BB04
4D064 AA29 BQ01 BQ08

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Espacenet

Bibliographic data: JP2008506424 (A) — 2008-03-06

BLOOD COMPONENT SEPARATION SYSTEM WITH STATIONARY SEPARATION CHAMBER

Inventor(s):

Applicant(s):

Classification: **- international:** ***A61M1/02; A61M1/36; B01D43/00***
- cooperative: **A61M1/30**; **A61M1/302**; **A61M1/303**; **A61M1/308**; **A61M1/3693**; **A61M1/3696**; **G02B21/32**; **G02B27/42**; **G02B27/4205**

Application number: JP20070519311 20050627 Global Dossier

Priority number (s): US20040583929P 20040628 ; WO2005US22608 20050627

Also published as: CN101304781 (A) CN101304781 (B) EP1765228 (A2) EP1765228 (A4) JP4699457 (B2) more

Abstract not available for JP2008506424 (A)
Abstract of corresponding document: WO2006012352 (A2)

Provided is a blood processing system having a stationary component separation chamber. Individual blood components as well as other particles and contaminates are separated from blood flowing through the separation chamber by optical traps configured to manipulate specific components are projected into the flow field of the chamber. Cells or particles of the selected components that are manipulated by the optical traps then may be directed from the flow field to individual reservoirs to collect quantities of the selected components.

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(43)公表日　平成20年3月6日(2008.3.6)

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B01D 43/00	(2006.01)	B01D	43/00	Z	
A61M 1/36	(2006.01)	A61M	1/36	500	

審査請求 未請求　予備審査請求 未請求　（全 17 頁）

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(86)(22)出願日　平成17年6月27日 (2005.6.27)
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(87)国際公開番号　WO2006/012352
(87)国際公開日　平成18年2月2日 (2006.2.2)
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(32)優先日　平成16年6月28日 (2004.6.28)
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アメリカ合衆国マサチューセッツ州０２１８４，ブレイントゥリー，ウッド・ロード　４００
４００　Ｗｏｏｄ　Ｒｏａｄ，Ｂｒａｉｎｔｒｅｅ，Ｍａｓｓａｃｈｕｓｅｔｔｓ　０２１８４，Ｕｎｉｔｅｄ　Ｓｔａｔｅｓ　ｏｆ　Ａｍｅｒｉｃａ
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最終頁に続く

(54)【発明の名称】静止した分離チャンバを備えている血液成分分離システム

(57)【要約】
本発明は、静止した成分分離チャンバを有する血液処理システムを提供する。個々の血液成分及び他の粒子や汚染物質が、チャンバの流れの場内に投射される特定の成分を操作するように構成されている光学トラップにより、分離チャンバを介して流れる血液から分離される。さらに、光学トラップにより操作される選択された成分の細胞又は粒子は、流れの場から個々の容器に導かれ、選択された成分量を収集する。
【選択図】　なし

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【特許請求の範囲】
【請求項1】
血液経路と、
血液経路光学トラップ要素と連通する分離チャンバを有する処理システムと、当該光学トラップ要素が、当該分離チャンバ内に光を投射し、そこを通過する血液から少なくとも１つの成分の分離を達成するように構成され、前記分離チャンバが、そこを介して進む血液の流量特性を生成し、光学トラップをもたらすように構成され、
前記血液経路と連通し、分離された成分を収集する成分容器と連通する少なくとも１つの出口と、
経路の入口から、前記処理システムの分離チャンバへ血液を押し出す、前記処理システムの上流にあるドローポンプと、
前記処理システムの下流で血液経路と連通する返血容器と、前記入口に分離されず残された成分とともに血液を押し戻すための、当該返血容器の下流の返血ポンプとからなる血液成分分離システム。
【請求項2】
前記血液経路と連通して全血を収容するように構成されているとともに、前記ドローポンプから押し出された血液を受容する入口及び、移送ポンプにより前記処理システムの分離チャンバに直接引き出される血液を受容する出口を有する緩衝容器をさらに含む請求項１記載の血液成分分離システム。
【請求項3】
前記システムの入口で導管継手を介して前記血液経路と連通する抗凝固剤容器と、所定の速度で、前記血液経路内に前記導管を介して抗凝固剤を選択的に押し出すよう構成されている抗凝固剤ポンプとをさらに含む請求項１記載の血液成分分離システム。
【請求項4】
前記分離チャンバ内に投射された光学トラップにより分離され、検出された独特の細胞を受容するための、前記分離チャンバに連通する付加的な容器と、
前記チャンバを監視して、所定の独特の細胞の存在を検出するように構成され、オペレータ警報に接続されている光学センサをさらに含む請求項１記載の血液成分分離システム。
【請求項5】
前記血液経路及び成分容器と連通し、血液成分を分離する遠心分離ボウルをさらに含む請求項１記載の血液成分分離システム。
【請求項6】
前記血液経路と連通する血液フィルタをさらに含む請求項１記載の血液成分分離システム。
【請求項7】
前記血液成分容器が、患者の血流と選択的に連通し、当該患者の血流に分離された成分を戻す出口を含む請求項１記載の血液成分分離システム。
【請求項8】
血液経路と、
前記血液経路と連通する静止した分離チャンバと、
前記血液経路との連通を維持したまま、前記静止した分離チャンバに収容されている血液の成分を能動的に分離するように構成されている成分分離手段とからなる高速血液分離システム。
【請求項9】
血液から個々の成分を分離する血液処理方法であって、
血液経路及び処理システムを含む血液成分分離システムを設け、該処理システムが、該血液経路と連通する分離チャンバと、該分離チャンバに光学トラップを投射する光学素子を有し、

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ヒトの血流に前記血液経路を接続し、
前記経路と前記分離チャンバを介する血液の流れを生じさせ、
前記分離チャンバを介して流れる血液に光学トラップを投射するように前記光学素子を操作し、
前記血液から少なくとも１つの形式の成分を分離し、前記血液経路と連通する成分容器
【発明の詳細な説明】からなる方法。
【技術分野】
【0001】
本発明は血液処理装置に関する。詳細には、本発明は、静止した分離チャンバを介して投射される光学トラップを利用して、血液から１つ又は複数の構成要素の成分を分離するためのシステム及び方法に関係する。
【背景技術】
【0002】
その構成要素の成分へ血液を分離するためのシステム及びプロセスは公知である。連続した流れ工程において大量の血液を迅速に処理するための市販のシステムが、マサチューセッツ、ブレーントリーのHaemonetics Corporationから入手可能である。詳細には、Haemoneticsから入手可能なCell Saver（登録商標）5システム及び装置のMCS（登録商標）ラインのような装置は、患者又はドナーから直接血液を受容し、血液処理チャンバーにその血液を移送し、血液から成分を分離し、後に患者に戻し又は利用するために分離された成分を個々の成分容器に導き、同時に連続したプロセスにおいて、未分離の成分とともに残った血液流を患者又はドナーに戻すように構成されている。
【0003】
上記のシステムのような高速血液処理装置の設計は、幾つかの要素により制限される。処理システムに異なるドナーからの血液が存在することにより示される内在する生物学的有害物質は、システムが複数のドナー又は患者に対して商業的に使用可能であるために、血液が接触する全ての表面及び構成要素、血液経路が経済的かつ使い捨てであることを要求する。その結果として、分離チャンバ、成分収集容器、それらを接続しドナーと接続する管類のような血液処理器の血液経路からなる構成要素は、プラスチックのような安価な材料から製造され、それにより、各収集手順の後装置から取り外され、殺菌された新しい血液経路の構成要素と置き換えることが可能である。
【0004】
連続した流れ工程と両立する高速での血液からの成分分離は、分離チャンバを機械的に操作し動作させ、液体血液から所望の細胞又は粒子を積極的に分離する必要がある。概して、遠心分離法がそのような分離を達成するために使用されている。上記の従来技術のシステムでは、ドナーからの血液により満たされた分離チャンバが回転し、血液内の種々の細胞及び成分に遠心力を作用させる。異なる成分の種々の質量が、それらを分離させ、同様の成分構造の層を形成する。層は、回転する分離チャンバ内で同心状の環として現れる。さらに、分離された成分の層は、ボウルから分離容器に引き出される。血液の効果的な遠心分離を達成するために、遠心ボウルとして構成されている分離チャンバが開発された。しかしながら、動く遠心ボウルとともに殺菌された流体経路を確実かつ経済的に維持することに依然として問題がある。
【0005】
回転する分離チャンバと血液経路の他の構成要素との間の殺菌された接続を維持するためのやり方には、Haemonetics Corporationにより製造されているレーサムボウルで採用されているような、経路を含むチャンバと管類の間の接合部に回転シールを組み込むことを含む。他のやり方は、スキップロープ技術を利用して、回転する分離チャンバに接続される経路管類のからみを回避することを必要とする。しかしながら、どちらのやり方も、市販可能であることを維持するために低価格設定及び拡大された信頼性が求められる使い捨て血液経路にコストを付加し、使い捨て血液経路の取付を複雑にする。
【0006】

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遠心分離技術を利用しない、その構成要素の成分へ血液を分離する代替的な方法は、大規模な血液分離工程の代替として利用することができない。例えば、細胞沈殿作用を利用して、重力により種々の構成要素の成分を分離することができる。しかしながら、そのような工程は、遅く、血液の沈滞の期間を必要とし、凝固の問題を増大させる。

【0007】

システムの殺菌された血液経路と安全に連通するとともに分離チャンバに容易に実装することができる成分分離技術を利用する高速血液成分分離システムを提供することが望まれている。さらに、連続した流れ工程に対して高効率、経済的であり、信頼性のある分離技術を使用するシステムを提供することが望まれている。そのようなシステムを提供することが本発明の目的に共通する。

【発明の開示】

【発明が解決しようとする課題】

【0008】

本発明は、光学トラップ技術を利用して、血液が殺菌された血液経路を介して流れる際に、血液の構成要素の成分を分離する血液成分分離システムを提供する。システムは、血液から単一の成分を分離するように構成され、又は複数の成分を分離して、後に使用するように個々の容器に導くように構成されている。

【課題を解決するための手段】

【0009】

システムは、血液経路への入口を含み、患者又はドナーの血流から血液を受容する。入口は、単一の針が接続され、ドナーの血流にアクセスできるように構成されている。血液経路は、ドナーからシステムに血液を流すことができるように寸法決めされている管類を含む。血液経路と相互作用するように構成されているドローポンプが、血液成分の分離に必要な流量で、入口から処理システムへの血液の流れを促進する。

【0010】

処理システムは、血液経路と流体が流れるように連通する分離チャンバを含む。処理システムは、さらに、分離チャンバを介して流れる血液に投射されるホログラフ的な光学トラップのような光学トラップを生成するように構成されている。分離チャンバの血液経路に投射される光学トラップが意図された場所に成分を分離して移動させ血液経路から回収するように動作するが、分離チャンバはシステム内で静止したままである。分離チャンバは、さらに、レーザーのような光学素子により生成される光エネルギーがチャンバを介して血液流に伝達される際に、干渉しないように構成されている。また、分離チャンバは、成分の光学トラップを助長する仕方で血液の流れを案内するように構成されている。さらに、分離チャンバは、ホログラフ的な光学トラップが、血液から分離された個々の成分を導く１つ又は複数の出口を含む。各出口は、分離された成分を保持するための容器に導かれるチャネルに接続されている。

【0011】

１つ又は複数の出口に続き、血液経路が、管類のような導管を介して分離チャンバから返血容器に連続する。今や分離された成分が取り除かれた処理された血液は、所定量が収集されてドナーに戻されるまで、返血容器に収集される。返血容器内に所定量が検出されると、血液が、返血ポンプにより管類を介して容器の出口を経て回収される。返血ポンプから、処理された血液は、返血のための所定の流量で、ドナーに向けて戻される。返血は、システムの入口を介して流れ、ドナーに挿入されている単一の針を介してドナーの血流に戻される。

【0012】

処理システム内の光学素子は、分離チャンバの流路にホログラフ的な光学トラップのアレイを生成するように構成されなければならない。光学素子は、レーザのような光線、回折光学素子、望遠鏡として機能する一対のレンズ、ビームスプリッタ及び対物レンズとして機能するダイクロイックミラーを含む。上記した構成要素からホログラフ的な光学トラップが如何に生成されるか、特に、如何に流体の流れにホログラフ的な光学トラップが伝

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達されて複数の粒子を捕捉するかの詳細については、米国特許第6,055,106号、米国特許第6,416,190号、米国特許出願第2003/0047676号、米国特許出願第2003/0119177号、米国特許出願第2004/0021949号、米国特許出願第2004/0089798号に開示されており、これらの文献は、参照することにより、その内容を全て本明細書に取り入れる。

【0013】

上記概説した基本的なシステムに加えて、付加的な構成要素を所与の手順のためにシステムに付加し、システムの性能を最適化することができる。抗凝固剤をシステムの入口に導入し、経路内の血液の凝固を防ぐばかりでなく、分離工程に対して血液の粘度を最適化することができる。抗凝固剤は、貯蔵バッグから管類のような導管を介して導入され、その流量は抗凝固剤ポンプにより制御される。代替的には、血漿又は生理食塩水のような、血液を希釈するのに適する他の剤が抗凝固剤の代わりに利用される。血漿のような血液製剤の場合には、患者又はドナー自身の血漿を利用することが好ましい。したがって、このようなシステムでは、血漿がシステムにより分離される成分の１つであり、また血漿容器が、血漿を導入するように血液経路に対して選択的に開口する導管に接続されている出口を有するように構成されている。

【0014】

さらに、処理システムより前に配置され、血液経路と連通する全血の緩衝容器がシステムに設けられている。緩衝容器の利用は、血液の有効処理に対して必要とされる流量対ドナーからシステムへの達成可能な最大流量によって決まる。処理システムが、ドナーからシステムへの達成可能な最大流量よりも少ない流量で動作されなければならない場合、システムの入口がドナーに血液を戻すのに利用され、流入が中断されるなどのときに、緩衝容器は、過剰の血液を、一時的に保持し、後に処理するように収集することを可能とする。移送ポンプは、導管を介して緩衝容器から処理システムへ血液を駆動する。本発明の他の形態では、光学トラップ要素が、血液試料内の有害な要素の存在を識別する目的で、病原体又は他の有害な汚染物質を付加的に同定し、血液から分離するように構成されている。有害な汚染物質又は病原体は有用な生成物として容器に導かれないが、分離チャンバは、汚染物質が導かれる出口又はチャネルを備えるように構成されている。さらに、導管に接続されている容器は汚染物質を受容し、光学センサのようなセンサが容器内の汚染物質の存在を検出する。センサは、システムコントローラの部分として統合されている警報システム及びユーザインタフェースと連通し、汚染物質の存在をオペレータに知らせる。

【0015】

本発明の他の形態では、追加の分離工程が、処理システム内で行われる主たる分離の前に、又は後にシステム内で実施される。詳細には、従来の遠心分離に基づく成分分離装置が、処理システムの前又は後のいずれかにおいて血液経路に接続され、赤血球又は血漿のような血液成分が取り除かれる。遠心分離に基づく分離装置に代えて、又は付加して、血液から汚染物質を分離するフィルタが、処理システムの前又は後のいずれかにおいて血液経路に付加される。

【0016】

本発明の他の形態では、全システムが、自己血回収配列において使用され、医療処置の間、患者に血液成分を戻す。自己血回収用のシステムは、分離された血液成分を収集するための容器が、システムに接続されている患者に隔離された成分を直接戻す返血導管とともに構成されている点を除いて、上記のシステムと同様に構成されている。

【0017】

本発明の目的は、光学トラップ技術を利用して、血液から構成要素の成分を分離する血液処理システム及び方法を提供することである。

【0018】

本発明のさらなる目的は、後に使用するために血液成分を収集し、並びに血液を分離して分離された血液が患者に戻される自己血回収のために血液成分を収集する場合のどちらにも寄与するに適した、光学トラップを利用する血液成分分離システム及び方法を提供することである。

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【0019】
本発明の他の目的は、患者又はドナーから収集される血液内の病原体又は汚染物質の存在を識別するシステム又は方法を提供することである。
【0020】
本発明の他の目的は、遠心分離及び/又は血液の沪過を含む付加的なシステム分離工程と組み合わせて光学トラップ技術を利用して、血液から個々の成分を分離するシステム及び方法を提供することである。
【0021】
本発明の他の形態は、静止した分離チャンバを利用して、複雑さ、コスト、血液経路における殺菌状態の喪失の危険性を低減する高速の血液成分分離システムを提供することである。
【発明を実施するための最良の形態】
【0022】
本発明の前述の及び他の目的及び利点を、添付の線図を参照して、以下のさらなる詳細な説明からより完全に明らかにする。
【0023】
図１は、光学トラップ技術を利用した血液成分分離システム10の構成要素及び配置を線図で示す。システムは、当該システムを血液が通過する際に、血液から１つ又は複数の構成要素の成分を分離するように構成されている。例えば、分離された成分には、赤血球、血漿、血漿を多く含む血小板が含まれる。加えて、光学トラップは、タンパク質、プリオン、ウィルス、バクテリア、他の汚染物質、システムを介して流れる血液からの粒子を分離するように構成されている。加えて、光学トラップは、疾病細胞（例えば鎌状細胞）又は感染細胞のような特異の細胞の存在、拒否されるべき献血試料を生じさせるものの存在を検出するように構成されている。種々の成分、細胞、細胞の部分、バクテリア、汚染物質の全てを、本明細書において、概して「成分」と呼ぶ。「成分」への言及が血液において見られる前述の要素の何れか１つ、さらに、上記に記していない何らかの他の識別される成分を表すことが理解されなければならない。
【0024】
図１に示すように、システム10は、血液が患者又はドナーから、システムの種々の構成要素へ移動する血液経路12からなる。血液経路は、経済的であり、生体適合性があり、殺菌された管類のような従来の導管を含む。血液経路及び、血液経路に沿った全ての関連するコネクタ、容器が、血液処理手順の間、殺菌状態を維持され、患者又はドナーに対する危険を排除し、後に使用することを意図して収集されて保存される成分に対する危険を排除することが重要である。経路は、経路の入口16に接続される単一の針14を介して、患者又はドナーの血流と連通するように配置されている。入口は、血液経路からの複数の管類を受容し、経路への血液の流れ及び、経路からの血液又は血液成分を患者又はドナーへ戻す流出のどちらをも取り扱うように構成されているマニホルドを含む。
【0025】
血液の流入は、患者から経路に入り、流入矢印20により示されているように、流入管18を介して進む。流入する血液の流量は、ドローポンプ22により制御される。ドローポンプ22、その上、本明細書で議論する全てのポンプを、管類の外側に作用して管類の中の血液を押し出す蠕動ポンプとすることができる。システム内の各ポンプの動作を、各容器内の血液又は成分の量も監視する中央コントローラにより電気的に監視して制御することができる。この仕方では、ポンプの速度は、最大の分離効率及び最小の処理時間の双方に対するシステムの各部分での理想的な血液の流速を維持する。
【0026】
基本的なシステムでは、血液は、図２に最もよく示すように、処理システム24内に先ず引き込まれる。処理システム24は、血液経路12と連通する分離チャンバ28内に、少なくとも１つの光学トラップを投射するように構成されている光学トラップ生成システム26を含む。おおよそ45ml/minの速さで移動する流れの所定の位置を通る大量の赤血球のような、

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血液の流れる場を通過する多数の成分の粒子を捕捉し、操作するために、ホログラフ的な光学トラップが有効である。血液が分離チャンバを介して流れるため、光学トラップ生成システムにより投射されるホログラフ的な光学トラップは、血液の流れの中の多数の同様成分の粒子を捕捉し、操作するように機能する。

【0027】

光エネルギーを利用して光学トラップの形式で分離チャンバ内で成分を分離することの利点は、チャンバ内に投射される光が成分を分離する全ての働きを担い、分離チャンバが静止したままであることにある。その結果として、遠心分離又はスキップロープ分離装置において必要とされるような、殺菌された血液経路に対して動く分離チャンバを接続することによる複雑な機構が、必要とされない。本発明の分離チャンバは、分離の間、静止状態を保ち、したがって、分離チャンバを容易に、確実に、血液経路と連通させて取り付けることができ、これにより経済的に製造することができ、しかも、より信頼性の高い殺菌状態が維持できる。

【0028】

図２を参照すると、血液が分離チャンバ内に投射されるホログラフ的な光学トラップを介して流れる際、光学トラップにより捕捉されるように予定されている目標成分が、操作されて、分離チャンバの１つ又は複数の出口に導かれる。図解することを目的として、３つの形式の成分を、図２において示す分離チャンバ28内の光線58によって操作されるように示す。赤血球を、出口32に導かれる円30として示す。出口は、血液収集バッグのような赤血球容器36に続くチャネル34に対して開口している。血小板を黒点38により示し、ホログラフ的な光学トラップは、血小板を操作して、赤血球の出口32から隔置されている出口40に導くように構成されている。出口40は、容器44に血小板を運ぶチャネル42に対して開口する。鎌状細胞のような疾病細胞を× 46により示し、ホログラフ的な光学トラップは、この例示では、特定の形式の疾病細胞を操作するように構成され、疾病細胞の出口48に疾病細胞46を導く。出口48は、疾病細胞容器52に疾病細胞を運ぶ疾病細胞チャネル50に対して疾病細胞を導く。

【0029】

疾病細胞46は再利用されないので、血液からそれらの疾病細胞を分離し、識別する目的は、血液試料内にそれらの存在を識別することにある。システムに疾病細胞の存在することをオペレータに警告するために、光学センサとすることができるセンサ54が、容器52内の何らかの疾病細胞の存在を検出するように構成されている。センサは、配線によりオペレータ警報に接続される。

【0030】

処理システムが、分離チャンバを通過する血液から１つの成分又は複数の成分を分離するように構成されていることを再度強調する。図１には、赤血球のような１つの成分を分離するように構成されている例示的なシステムを示し、そのシステムは１つの成分容器36を備えている。図２に示す処理システムの詳細な説明は、システムの他の実施形態を例証し、そのシステムでは、複数の成分が、分離チャンバを通過する血液から分離され、複数の対応する成分の容器36、44、52を必要とする。ホログラフ的な光学トラップにより分離される成分の数及び形式、処理システムの正確な構成は、適応性があり、システムの所望とされる使用目的に適合するように調整され得る。

【0031】

光学トラップ生成システム26は、レーザのような光線、光学素子、望遠鏡を作り出すレンズ、ダイクロイックミラー、対物レンズを含むホログラフ的な光学トラップを生成するのに必要な幾つかの光学素子からなる。光学素子を、ホログラムの形式を変化させるようにコンピュータ制御される動的光学素子とすることができる。それらの要素の動作させてホログラフ的な光学トラップを生成することについては、上記した特許及び特許出願において詳細に議論されており、それらの議論は、それらの文献を参照することにより、本明細書に全て取り込む。光学トラップ生成システム26から放射され、線58により示される結果生じるホログラフ的な光学トラップは、分離チャンバ28を介する血液の流れに投射され

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る。トラップを、成分の光学的な特性に基づいて、血液内の１つ又は複数の特定の成分を操作して捕捉するように調整することができる。動的な光学素子により、ホログラフ的なトラップを、所望の成分を出口に運ぶようにトラップの光線を動的に動かすことにより、所望の出口に捕捉された成分を移動させるように構成することができる。代替的には、静的なホログラフ的な光学トラップが、分離チャンバの血液経路にトラップの静的な場を生じる。血液がその静的な場を通過する際、各トラップは、選択された成分にのみ力を作用させ、それらの成分が選択された出口に向かう流れを生じさせる。

【0032】

光学トラップ生成システム26の１つの可能な構成は、また光ピンセットシステムとして公知であり、このシステムでは、図５－７に示すように、動的又は任意のアレイが形成されている。このシステムの配列は米国特許第6,416,190号に開示されており、この文献を参照することにより、その内容を全て本明細書に取り込むこととし、以下の説明はこの文献から取り込む。回折光学素子140は、平面142内に実質上配置され、対物レンズ120の後部開口124と共役をなす。回折された単一の出力ビームのみを明瞭に示すが、回折光学素子140によってそのようなビームを複数生成することが可能であることが理解されなければならないことに注意されたい。回折光学素子140に入射する入力光線112は、それぞれが点Ａから放射し、回折光学素子140の性質を特徴付ける出力ビーム144のパターンに分割される。したがって出力ビーム144は、また、先に開示した後続の光学素子の作用を受け、点Ｂを通過する。

【0033】

図５の回折光学素子140を、入力光線112に対して垂直であるように示すが、他の多様な配列が可能である。例えば、図６では、光線112が、光軸122に対して傾いた角度（β）で到達し、回折光学素子140に対して垂直ではない。この実施形態では、点Ａから放射される回折ビーム144が、イメージングボリューム132の焦点面152に光学トラップ150を形成する。光ピンセットシステム110のこの配列では、入力光線112の非回折部を、光ピンセットシステム110から取り出すことができる。したがって、この構成は、より少ない背景光で処理し、光学トラップの形成を効率及び有効性を改善する。

【0034】

回折光学素子140に、予め選択された所望のパターンに入力光線112を分割するコンピュータ処理ホログラムを含むことができる。そのようなホログラムと図５及び６の光学素子の残りを組み合わせることにより、任意のアレイを作り出すことができ、そのアレイでは、回折光学素子140が、独立して各回折ビームの波面を形成するのに利用される。したがって、光学トラップ150を、対物レンズ120の焦点面152のみならず、焦点面152の外にも位置させることができ、光学トラップ150の三次元配列が形成される。

【0035】

図５及び６の光ピンセットシステムでは、また、回折ビーム144を集束して光学トラップ150を形成するための、対物レンズ120（又はフレネルレンズのような機能面で同等の他の光学素子）のような集束光学素子を含む。さらに望遠鏡134、同等の他の転送光学素子が、先の後部開口124の中心点Ｂと共役の点Ａを作り出す。回折光学素子140は点Ａを含む平面内に配置されている。

【0036】

他の実施形態では、光学トラップ150の任意のアレイが、望遠鏡134を使用することなく作り出される。そのような実施形態では、回折光学素子140を点Ｂを含む平面内に直接配置することができる。

【0037】

光ピンセットシステム110では、静的な又は時間依存の回折光学素子140を利用することができる。動的な、すなわち時間依存する形態では、光学トラップ150の時間変化するアレイを作り出すことができ、そのアレイはそのような特徴を利用するシステムの一部分となる。加えて、それらの動的な光学素子140を利用して、粒子及びマトリックス媒体を互いに対して能動的に動かすことができる。例えば、回折光学素子140を、コンピュータ処

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理ホログラフパターンでつけられた変更を受ける液晶相のアレイとすることができる。
【0038】
図７に図解する他の実施形態では、システムを、光ピンセットトラップ150の連続的な並進を実施するように構成することができる。ジンバル搭載のミラー160が、点Ａをその回転中心として配置されている。光線112は、ミラー116の表面に入射し、点Ａを通過する軸を有し、後部開口124に放出される。ミラー116が角度可変であることにより、ミラー116に対する光線112の入射角を変化させることができ、この特徴は、結果生じる光学トラップ150を並進させるのに利用することができる。第２の望遠鏡162は、レンズL3及びL4から形成され、点Ａに対して共役である点Ａ’を作り出す。さらに、点Ａ’に配置されている回折光学素子140は、それぞれが点Ａを通過し、光ピンセットシステム110における光ピンセットトラップ150の１つを形成する回折ビーム164のパターンを作り出す。
【0039】
図７の実施形態の動作において、ミラー160は、１つの単位として、全体のピンセットアレイを移動させる。この手順は、わずかな振幅の素早い振動による変位を介して、静止した基板と光ピンセットアレイを正確に位置合わせし、光学トラップ150を動的に強化することに対して、及び任意の用途に対する一般的な移動性能の要求に対して有効である。
【0040】
また、光学トラップ150のアレイを、試料台を移動することにより、又は望遠鏡134を調節することにより、試料台（図示せず）に対して垂直方向に移動することができる。加えて、また、光学ピンセットアレイを、試料台を移動することにより、試料に対して横方向に移動することもできる。この特徴は、対物レンズの視野の範囲を超えて大きな範囲で移動する際に特に有効である。
【0041】
概して、細胞の操作は、複数のビームを利用することにより安全となる。複数のピンセットは、細胞のある特定の点に導入されるパワーがより小さくなることを確実とする。これにより、温点を排除することができ、損傷の危険性を低減することができる。吸収がレーザ出力の平方に比例するため、任意の破壊的な二光子過程は大いに利益をもたらす。まさに第２のピンセットを加えることにより、４倍だけ特定の点における二光子吸収が低減される。単一のトラップにパワーを投入することにより、細胞に対して迅速に損傷を与えることができる。例え単一の細胞の操作であっても、ホログラフ的な光学トラップを利用することによって能力が大いに強化される。本発明の光学トラップ生成システム26として使用可能なそのようなホログラフ的な光学トラップシステムは、米国特許出願第2004/0089798号に開示され、以下おいて、その出願の説明を記す。
【0042】
ホログラフ的な光学トラップ装置又はシステム200として構成されている光学トラップ生成システムを図８に図解する。光はレーザシステムから入射し、下向きの矢印により示すように、システム200に入り、システム200にパワーを供給する。位相をパターン化された光学素子201は、動的な表面を備えている動的な光学素子（DOE）であることが好ましく、また、日本国のHamamatsuにより製造されている「PAL-SLM series X7665」又は、コロラド州ラファイエットのBoulder Nonlinear Systemにより製造されている「SLM 512SA7」や「SLM 512SA15」のような相-単一空間光変換器（SLM）である。これらの動的な位相をパターン化された光学素子201は、コンピュータ制御され、媒体にエンコードされたホログラムによりビームレットを生成し、ホログラムは、ビームレットを生成し、及びビームレットの形態を選択するように変化する。図８の左下に生成されている位相パターン1-2は、右下に示すトラップ203を作り出し、トラップ203は、浮遊する直径１μmのシリカの球204が水205内に満たされている。したがって、システム200は、左側下に示す動的なホログラムにより制御されている。
【0043】
レーザビームは、レンズ206、207を介して、ダイクロイックミラー208に進む。ビームスプリッタ208は、ダイクロイックミラー、フォトニックバンドギャップミラー、無指向

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性ミラー、他の同様の素子から構成されている。ビームスプリッタ208は、光学トラップ203を形成するのに利用される波長の光を反射し、他の波長の光を伝達する。ビームスプリッタ208の領域から反射された光の部分は、さらに、集束（対物）レンズ209の平面的な後部開口と共役の平面に実質上配置されているエンコードされた位相のパターン化された光学素子の領域を通過する。

【0044】

ビームスプリッタ208を、静電場により制御される、すなわちコンピュータプログラムによって制御される本質的に液晶アレイである空間光変換器として構成することができる。液晶アレイは、適用された電場の強度に依存する異なる量によって、光の位相を遅らせる性質を有する。ネマチック液晶素子は、ディスプレイ用として、又は大きな位相-単一変換深さが必要とされる（2π又はそれより大きい）用途に対して利用される。ネマチック液晶分子は、通常、素子の表面に対して平行に位置し、液晶の複屈折性により最大の遅延特性を与える。電場が適用されると、分子は電場に対して平行に傾く。電圧が異常軸に沿った屈折率を増大させるので、したがって、複屈折が効果的に減少し、素子の遅延特性の減少が生じる。

【0045】

有用なレーザには、固体レーザ、ダイオード励起レーザ、気体レーザ、色素レーザ、アレキサンドライトレーザ、自由電子レーザ、VCSELレーザ、ダイオードレーザ、チタンサファイアレーザ、ドープYAGレーザ、ドープYLFレーザ、ダイオード励起YAGレーザ、フラッシュランプ励起YAGレーザが含まれる。10 mWと５Wの間で動作するダイオード励起Nd:YAGレーザが好ましい。生物学的材料を調査するアレイを形成するのに利用されるレーザビームの好ましい波長には、赤外、近赤外、可視赤色、緑色、可視青色波長が含まれ、約400 nmから約1060 nmの波長が最も好ましい。

【0046】

光学トラップ生成システム26の１つの配列は、図９（イリノイ州シカゴのArryx, inc.により販売されているBioRyx systemのような）に示す光学トラップシステム500である。このシステムには、ホログラフ的な光学トラップユニット505を利用する光学トラップを形成するマウントが配置されているNixon TE 2000 series顕微鏡501が含まれる。ハウジングを取り付けられるリボルバ502は、マウントを介して顕微鏡501に直接適合されている。結像のために、照明源503が対物レンズ504の上方に設けられ、試料506を照明する。

【0047】

光学トラップシステム200（図８及び９参照）には、光学素子に近接する第１の光チャネルの一方の端部、及び第１の光チャネルのもう一方の端部が含まれ、第１の光チャネルは、第１の光チャネルと垂直に形成されている第２の光チャネルと交差し、連通する。第２の光チャネルは、顕微鏡レンズ取付タレット又は「リボルバ」の基部内に形成されている。リボルバは、Nixon TE 2000 series顕微鏡内に適合するように適応されている。また第２の光チャネルと垂直な第３の光チャネルと、第２の光チャネルは連通する。第３の光チャネルは、リボルバの上部表面からリボルバの基部を介して、対物レンズ集束レンズ209と平行に横切る。集束レンズ209は、後部開口を形成する底部及び上部を有する。第２の光チャネルと集束レンズの後部開口の間の第３の光チャネルに、ダイクロイックミラービームスプリッタ208が介在されている。

【0048】

光学トラップを形成する光学トラップシステム内の他の構成要素には、第１の光チャネルを介して位相のパターン化された光学素子201から放射されたビームレットを反射する第１のミラー、第１の光チャネル内に配置され、第１のミラーによって反射されたビームレットを受容するように整列されている伝達光学素子の第１の組206、第１の光チャネル内に配置され、伝達レンズの第１の組を通過するビームレットを受容するように整列されている伝達光学素子の第２の組207、第１の光チャネルと第２の光チャネルの交点に位置し、伝達光学素子の第２の組及び第３の光チャネルを通過するビームレットを反射するように整列されている第２のミラー208が含まれる。

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【0049】
図９を参照すると、光学トラップを生成するために、レーザビームが、レーザ507（図５参照）から、コリメータを介して、光ファイバの端部508を経て方向付けられ、回折光学素子509の動的な表面で反射される。光ファイバのコリメータ端部を出た光ビームは、回折光学素子の動的な表面により複数のビームレットに回折される。各ビームレットの数、形式、方向は、動的な表面媒体のエンコードされたホログラムを変化することにより、制御し、変化させることができる。さらに、ビームレットは、第１のミラーで反射し、第１の光チャネルに後続する伝達光学素子の第１の組を介して、伝達光学素子の第２の組を介し、第２のミラーへ進み、ダイクロイックミラー509において対物レンズ504の後部開口に向けられ、対物レンズ504を介して集束され、それによって光学トラップを形成するのに必要な光学的な傾斜条件が実現される。ダイクロイックミラー509介して分割され、集束される光の部分は、光学的なデータの流れ（図８参照）を形成する第３の光チャネルの下側の部分を通過する。
【0050】
血液成分分離システムの分離チャンバ28は、ホログラフ的な光学トラップから得られるであろうトラップ力に基づき成分の効果的な光学トラップに資する仕方で血液の流れを方向付けるように構成されなければならない。さらに、分離チャンバは、光学トラップ生成システムが対向し、光学トラップが投射される少なくとも側壁29が、伝達される光の形態58に対して透明であるように構成されていなければならない。分離チャンバの配列は、使用されるホログラフ的なパターンの大きさを活用するように最適化されていなければならない。さらに、分離チャンバは、分離の効率を増大させるために、その範囲にわたって、一貫した流れを促進し、トラップの間、流速の変化を制限するように構成されていなければならない。表面に隣接した血液の速度を遅くし、流れが依然として速いチャンバの中央部と流れの速さに不均一を生じさせる、分離チャンバの内側表面への血液の凝固を防ぐように、その表面を被覆することができる。
【0051】
図１及び２に示すように、そこから分離されない成分を含む血液は分離チャンバ28を出た後、流れる矢印62により示されるように、血液経路を介して返血容器60へ導かれる。返血ポンプ64が処理された血液を返血ライン66を介して引き出し、入口16を介して及び針14を介して患者又はドナーの血流に送り出す所定量が収集されるまで、血液は返血容器に収集される。
【0052】
血液は、処理された後、容器60に収集されて保持され、システムの処理効率を増大させるために、患者又はドナーにバッチ式に返血される。患者又はドナーからの採血、及び患者又はドナーへの返血が単一のアクセスポイント、単一の針14のみを介して達成されるので、採血及び返血に要する時間は分担されなければならない。この時間分割は、短い時間で、大きな流速をもって、バッチ式に処理された血液を返血することによって達成される。したがって、容器60に保持される処理された血液の体積がシステムコントローラにより監視され、所定の体積が収集された場合にのみ、返血64ポンプがコントローラにより起動され、血液の流入が短時間中断される。返血ポンプがドナー又は患者に処理された血液を戻すように動作する際においても、ドローポンプ22は、システム内に血液を押し出し続けるように作動されたままである。両方のポンプの作動中、流入量から流出量を減じた量が、患者への流量又は患者からの流量を生じる。
【0053】
図１、３、４に示すシステムの他の変形形態では、抗凝固剤70の容器が血液経路に接続され、血液がシステムに入る際、抗凝固剤が選択的に導入される。抗凝固剤70の容器を、システムの入口16のマニホルドに接続されている導管72に接続され、抗凝固剤の液体で満たされている可撓性のバッグとすることができる。抗凝固剤は、システムの性能を最適化するように、血液に対する抗凝固剤の所望の比に対応する量の抗凝固剤を導入するように選択的に作動可能な抗凝固剤ポンプ74の動作により、システム内に導入される。概して、

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加えられる抗凝固剤の比は、システムを介する血液の動きに依存する。システムを介する血液の流れに多くの停滞する期間がある場合には、より多くの抗凝固剤が加えられ、経路内で血液が凝固することが防止される。

【0054】

本発明において使用される分離の光学トラップ方法では、抗凝固剤の正確な比を決定するために他の要素が意味を持つこととなる。抗凝固剤の比は、分離チャンバを通過する血液の理想的な速さが生じ、効率的な光学トラップが達成されるように加えられなければならない。血液の速さの調整は血漿又は生理食塩水を加えることによっても達成されることに注意されたい。分離の光学トラップ方法を利用するシステムは、従来の分離システムと比べて、より連続的な動きをもたらし、システムを介する血液の流量を維持するために必要とされる抗凝固剤の量を結果として減少させることができる。

【0055】

図３に示すようなシステムの他の実施形態では、患者又はドナーから採血される全血を収容する緩衝容器80がシステムに付加されている。緩衝容器は、ドローポンプ22によりシステム内に最初に引き出される血液に対する保持部として機能する。処理システムが、システム内への血液の最大引き出し流量よりも少ない血液の流量で、血液から成分を最適に分離する場合、さらに、血液は、処理可能となるまで、緩衝容器に収集されなければならない。

【0056】

移送ポンプ82は、移送ライン84を介して緩衝容器80を出る流量を調整する。例えば、最大達成可能流入流量が毎分80 mlであり、処理システム内で行われる血液からの成分の分離が、わずか毎分45mlの流量において最も効率的である場合、移送ポンプ82は、処理システム内への流れをわずか毎分45mlに調整するように、ある速度で作動されなければならない。システムに入る毎分80 mlのより速い流れは、緩衝容器80にバックアップされ、システム内の流量の必要とされる変動に適応される。緩衝容器80に収集された血液の体積は、光学的に又は重量により監視され、その容器が満たされると、返血ポンプ64が起動され、入口16に接続されている針14からなる単一のアクセスポイントを介して患者に処理された血液を戻す。処理された血液は入口16から流れ出るが、移送ポンプ82は、緩衝容器80内に蓄えられた血液を処理するように動作し続け、未処理の血液を消費する。返血容器60がすっかり排出されると、返血ポンプ64の動作は停止され、入口16は、患者又はドナーからシステムへの血液を再度受容する。

【0057】

本発明の他の形態では、経路12を運ばれる血液から成分を分離する追加の機構をシステムに付加することができる。図４に示すように、遠心分離に基づく分離チャンバ12又はボウル90を血液経路12に付加し、処理システム24で行われる主たる分離工程に先立ち、予備分離工程を実施することができる。付加的な分離ステップを利用して、赤血球のような血液の成分を予備的に取り除くことができ、その第１の分離ステップの後、血液内に依然残る他の分離された成分に対して光学トラップ分離工程が予定される。実際に、遠心分離ボウル90を緩衝容器80に続く流体経路に接続することができ、血液は遠心分離器ポンプ92により遠心分離ボウル内に引き込まれる。遠心分離ボウルは、血液成分を分離するために、従来公知の処理装置により機械的に回転され、所望の成分を導き、成分容器（図示せず）に直接接続する。さらに、残る血液成分は、移送ポンプ82の作動により遠心分離ボウルから出て移動され、光学トラップにより付加的な分離のための処理システムへと導かれる。処理システムの前に配置されるように、遠心分離ボウルを図４に例示的に示すが、患者又はドナーに返血する際、血液処理システムの後のような血液経路内の何れかに配置することができる。

【0058】

本システムに付加的な分離工程を設けるための他の機構は、血液フィルタ94の付加である。フィルタを、処理システムの前又は後の何れかの、血液経路内の任意の箇所に接続することができる。フィルタは、フィルタエレメントの細孔の寸法及び、汚染物質や粒子の

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寸法に基づき、汚染物質及び粒子を取り除くことができる。

【0059】

本発明の他の形態では、システムは、医療処置の間、患者から自己血液回収を行うように構成される。この状況において、システムを、上記議論したシステムと同様に構成することができる。しかしながら、赤血球又は血漿の多く含まれる血小板を収集するような成分容器は、システムに接続され、患者に成分を戻すように経路付けられている返血ラインを有するように構成されている。返血ラインは、選択的に開放され、ポンプを備えて構成され、患者へ収集された成分を戻すことができる。

【0060】

上記システムの動作において、容器に達した血液の体積を監視するセンサが、コントローラを含む集中制御システムに電気的に関連付けられ、利用されることに注意されたい。また、幾つかのポンプが制御システムに関連付けられ、システムの作業効率を維持するために、その動作は容器の容量に受容された情報と協調される。

【0061】

以上より、光学トラップ技術を利用し、分離を達成する実際の効果的な血液成分分離システムを示してきた。システムは、高速で成分を分離することができ、その上、経済的に製造され、使用において信頼性のある静止した分離チャンバを利用することができる。しかしながら、本発明の上記説明は、その例証のみを意図しており、他の変更、態様、同等物が、本発明の精神から逸脱することなく、当業者には明らかであることを理解されなければならない。

【0062】

したがって、本発明の開示は、添付の特許請求の範囲の記載により請求され、確保される。

【図面の簡単な説明】

【0063】

【図1】光学トラップ技術を利用した血液分離システムを示す線図である。

【図2】処理システムの詳細を示す線図である。

【図3】処理システムの前に全血の緩衝容器を含む、光学トラップを利用する血液分離システムを示す線図である。

【図4】血液経路に沿って処理システムの前に位置する付加的な血液遠心構成要素と、経路に沿って処理システムの後に配置されている血液フィルタとを有し、光学トラップを利用する血液分離システムを示す線図である。

【図5】光学トラップ生成システムを示す線図である。

【図6】入力光線に対して傾いた光学素子を利用する光学トラップ生成システムを示す線図である。

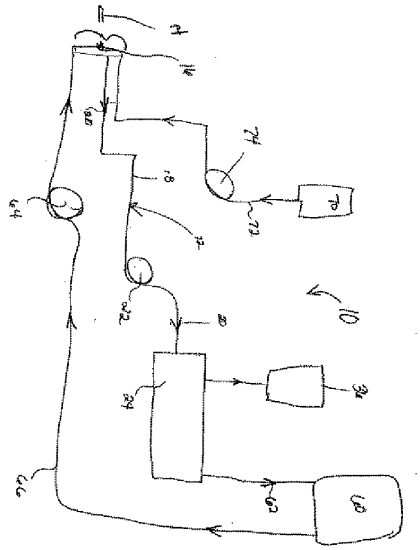
【図7】連続的に移動可能な光学トラップ生成システムを示す線図である。

【図8】ホログラフ的な光学トラップ生成システムを示す線図である。

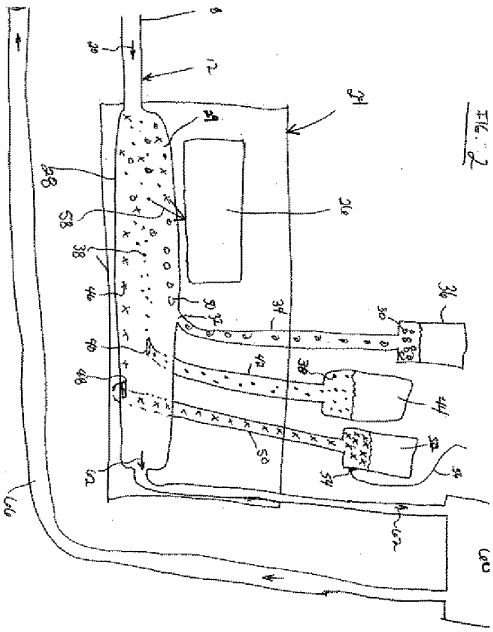
【図9】ホログラフ的な光学トラップ生成システムを示す線図である。

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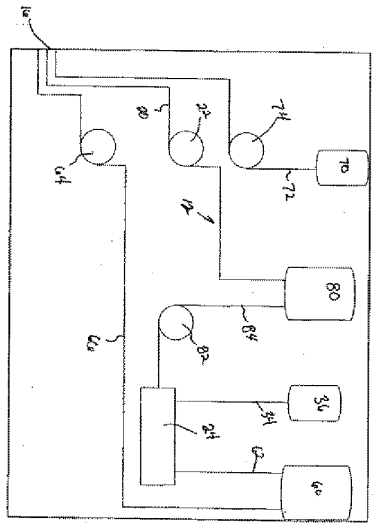
【図1】



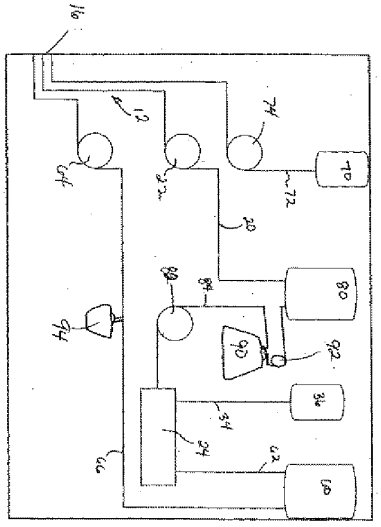
【図2】



【図3】

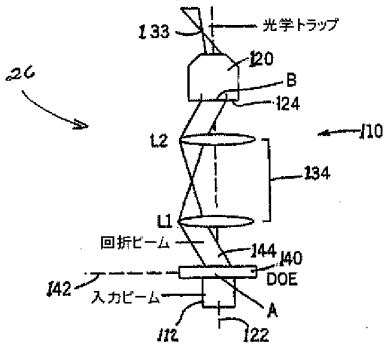


【図4】

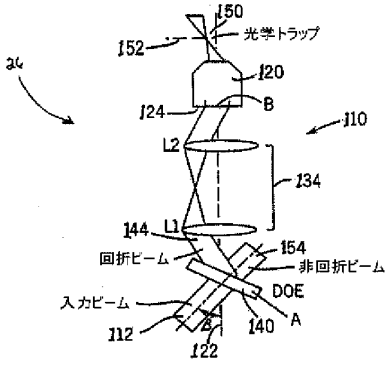


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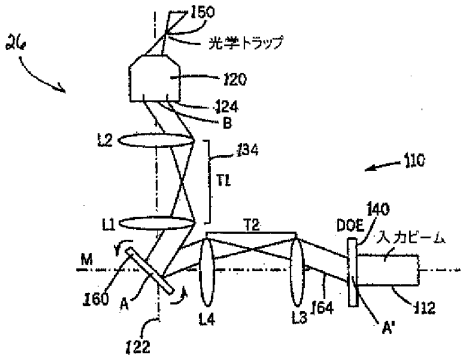
【図5】



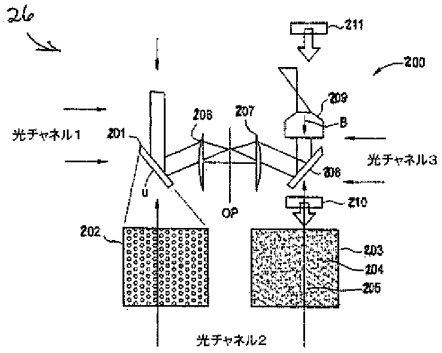
【図6】



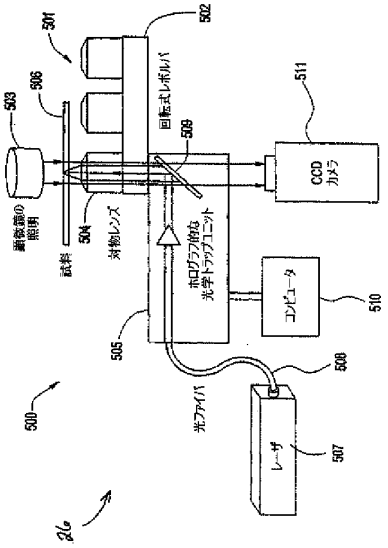
【図7】



【図8】



【図9】



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Petitioner Terumo Exhibit 1021-0534

60700800010

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/22608

A. CLASSIFICATION OF SUBJECT MATTER
IPC: A61M 37/00(2006.01);C02F 1/44(2006.01)

USPC: 604/5.01,6.01,6.08;210/645,646
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 604/5.01,6.01,6.08;210/645,646

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST BRS (optical, tweezers, separation, blood)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,649,903 A (DENIEGA et al) 22 July 1997 (22.07.1997), entire document.	2
Y	US 5,722,946 A (MUDLOFF et al) 03 March 1998 (03.03.1998), entire document.	1-9
X Y	US 5,868,936 A (OFSTHUN et al) 09 February 1999 (09.02.1999), entire document.	8 1-7,9
Y	US 2003/0007894 A1 (WANG et al) 09 January 2003 (09.01.2003), entire document.	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 July 2007 (17.07.2007)	13 SEP 2007
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Leslie R. Deak Telephone No. 571-272-2975

Form PCT/ISA/210 (second sheet) (April 2005)

06.12.2007

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0535

(81)指定国　　AP(BW,GH,GM,KE,LS,MW,MZ,NA,SD,SL,SZ,TZ,UG,ZM,ZW),EA(AM,AZ,BY,KG,KZ,MD,RU,TJ,TM),EP(AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IS,IT,LT,LU,MC,NL,PL,PT,RO,SE,SI,SK,TR),OA(BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG),AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BW,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,EG,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KM,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NA,NG,NI,NO,NZ,OM,PG,PH,PL,PT,RO,RU,SC,SD,SE,SG,SK,SL,SM,SY,TJ,TM,TN,TR,TT,TZ,UA,UG,US,UZ,VC,VN,YU,ZA,ZM,ZW

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Ｆターム(参考) 4C077 AA12 BB10 DD13 DD21 DD25 EE01 EE02 HH03 HH17 HH21
JJ03 JJ18 JJ24 JJ28 KK23 KK25 KK27 NN02 NN03 NN15

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Espacenet

Bibliographic data: JPH0775746 (A) — 1995-03-20

ROTATING SEALING MEMBER FOR CENTRIFUGAL SEPARATOR

Inventor(s): RON SHIIGAAZU; ROBAATO SUKAMERU ± (RON SHIIGAAZU, ; ROBAATO SUKAMERU)

Applicant(s): ELECTROMEDICS INC ± (EREKUTOROMEDEIKUSU INC)

Classification: - international: ***A61M1/02; B04B1/02; B04B15/02; B04B5/04; B04B9/12;*** (IPC1-7): A61M1/02; B04B1/02
- cooperative: **B04B15/02**; **B04B5/0442**; **B04B9/12**; B04B2005/0464

Application number: JP19930328065 19931224

Priority number (s): US19930043436 19930405

Also published as: EP0619145 (A2) EP0619145 (A3)

Abstract of JPH0775746 (A)

PURPOSE: To obtain a seal member which has stability, does not generate noises and has an excellent cooling effect by forming an annular rib and annular plate, the front surfaces of which delineate a seat for supporting a rotary seal ring to a home position, rotationally engaging the ring with a stationary seal ring and disposing choral vanes for cooling the rotary seal member. CONSTITUTION: This rotary seal member has the rotary seal ring 11 and the stationary seal ring 42. The seal ring hub 44 for supporting the rotary seal ring 11 has an annular hub plate 50 which delineates a central shaft receiving opening 51, the annular rib 54 which is an axially extending annular rib 54 arranged in spaced juxtaposition with respect to the opening 51 on the plate 50 and defines a seal ring supporting seat in proximity to the opening 51 together with the plate 50 and vanes 56 which are spaced-apart plural vanes 56 extending outwardly from the rib 54, stabilize the plate 50 at the time of rotation of the seal member and are adapted to fluidize cooling air at the circumference of the rotary seal member. Consequently, the rotary seal member which has stability, does not generate noises and has the excellent cooling effect is obtained.

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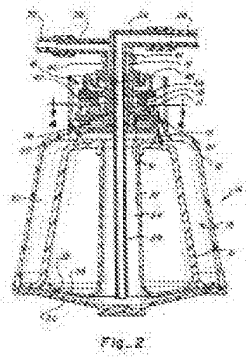


Fig. 2

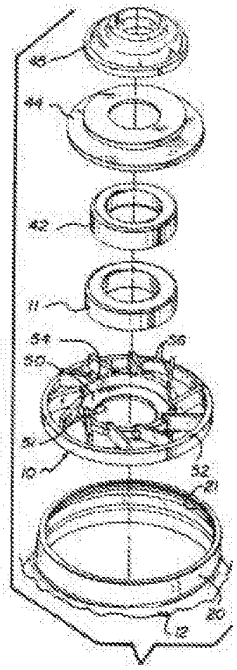


Fig. 5

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(19)日本国特許庁（ＪＰ）　(12) **公開特許公報（Ａ）**　(11)特許出願公開番号

特開平7－75746

(43)公開日　平成７年(1995)３月20日

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ	技術表示箇所
Ｂ０４Ｂ　1/02				
Ａ６１Ｍ　1/02		9052－4C		

審査請求　未請求　請求項の数４　ＯＬ　（全　５　頁）

(21)出願番号　特願平5－328065

(22)出願日　平成５年(1993)12月24日

(31)優先権主張番号　０４３４３６

(32)優先日　1993年４月５日

(33)優先権主張国　米国（ＵＳ）

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(72)発明者　ロバート　スカメル
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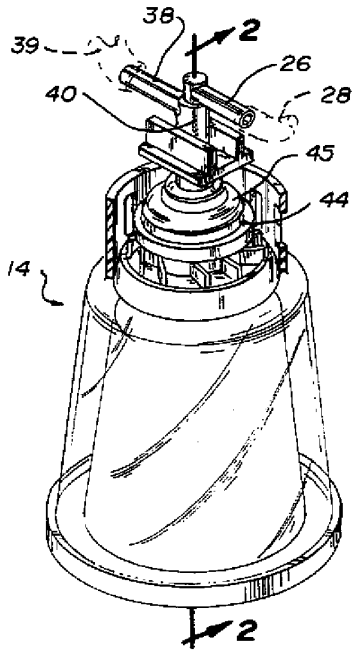
(74)代理人　弁理士　浅村　皓　（外３名）

(54)【発明の名称】　遠心分離機用回転密封部材

(57)【要約】

【目的】　血液処理遠心機ボウルに対する改良回転密封部材を提供する。

【構成】　無孔ボウルを有する遠心分離機において、回転密封リングおよび固定密封リングよりなる、回転密封部材の回転密封リングを支持するために密封リングハブを使用する。この密封リングハブは、中心軸受入孔を画定する環状ハブ板によって形成される。この板はその周囲に軸線方向に延びる環状舌片と、前記孔に対して並列的に隔置された、軸線方向に延びる環状リブとを有している。隔置されて弦状に延びる複数の羽根が、前記リブと舌片との間を延び、密封部材が回転する時に板を安定化し、かつ回転密封部材の周りの冷却空気を流動させる。



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【特許請求の範囲】
【請求項１】　中心軸の周りを回転し得る無孔ボウルを有する遠心分離機用回転密封部材において、回転密封リングおよび固定密封リングを有し、前記回転密封リングを支持するための密封リングハブが、中心軸受入孔を画定する環状ハブ板と、前記板の上を、前記孔に対して並列的に隔置され、かつ軸線方向に延びる環状リブで、前記板と共に前記孔に近接して密封リング支持座を画定する環状リブと、前記リブから外方に延びる、隔置された複数の羽根で、前記密封部材が回転する時に、前記板を安定化し、かつ前記回転密封部材の周囲において冷却空気を流動させるようになった羽根とを有することを特徴とする回転密封部材。
【請求項２】　中心軸の周りを回転し得る無孔ボウルを有する遠心分離機用回転密封部材において、回転密封リングおよび固定密封リングを有し、前記回転密封リングを支持するための密封リングハブが、中心軸受入孔を画定する環状ハブ板と、前記板の周囲において軸線方向に延びる環状舌片と、前記板の上を、前記孔に対して並列的に隔置され、かつ軸線方向に延びる環状リブで、前記舌片と平行に延び、前記板と共に前記孔に近接して、密封リング支持座を画定する環状リブと、前記リブおよび前記舌片の間を延びる、隔置された複数の羽根で、前記密封部材が回転する時に、前記板を安定化し、かつ前記回転密封部材の周囲において冷却空気を流動させるようになった羽根とを有する回転密封部材。
【請求項３】　中心軸の周りを回転し得る無孔ボウルを含む遠心分離機用回転密封部材の回転密封リングにおいて、前記回転密封部材が回転密封リングおよび固定密封リングよりなり、前記回転密封リングを支持するための密封リングハブが中心軸受入孔を画定する環状ハブ板と、該板の周囲において、軸線方向に延びる環状舌片と、前記板の上で前記孔に対し並列的に隔置されて軸線方向に延びる環状リブで、前記舌片と平行し、かつ前記板と共に前記孔に近接して密封リング支持座を画定する環状リブと、前記リブおよび前記舌片の間を延びる複数の隔置された弦状羽根で、前記舌片および前記リブを越えて軸線方向に延び、前記密封部材が回転する時に前記板を安定化し、かつ前記回転密封部材の周囲において冷却空気を流動させるようになっていた羽根とを有する回転密封リング。
【請求項４】　中心軸の周りを回転し得る無孔ボウルを含む遠心分離機用回転密封部材において、回転密封リングおよび固定密封リングよりなり、前記回転密封リングを支持するための密封リングハブが中心軸受入孔を画定する環状ハブ板と、該板の周囲において、軸線方向に延びる環状舌片と、前記板の上で前記孔に対して並列的に隔置されて軸線方向に延びる環状リブで、前記舌片と平行し、かつ前記板と共に前記孔に近接して密封リング支持座を画定する環状リブと、前記リブおよび前記舌片の間を延びる複数の隔置された弦状羽根で、前記リブおよび前記舌片を越えて軸線方向に延び、前記舌片の僅か手前で終わり、かつ前記リブに重なり、前記密封部材が回転する時に前記板を安定化し、かつ前記回転密封部材の周囲において冷却空気を流動させるようになった羽根とを有する回転密封部材。
【発明の詳細な説明】
【０００１】
【産業上の利用分野】本発明は無孔ボウル遠心機用回転密封部材に関する。本発明は特に血液処理用遠心分離機のボウルに対する回転密封部材に関する。
【０００２】
【従来の技術】回転密封部材を備えた遠心機ボウルは古くからあり、血液処理技術においては公知である。この技術においては血液は、全血をボウルに導入するための固定管状軸の周りを回転する無孔ボウルを備えた遠心機により、その赤血球成分と血漿成分とに分離され、血液部分、特に血漿および赤血球細胞が逐次ボウルから排出される。遠心装置の重要部分は、ボウルが回転する時に血液成分の漏洩を防止するために、固定軸と回転ボウルとの間に設けられる回転密封部材である。
【０００３】１９８７年５月２６日付、G. Reeder の米国特許第４，６６８，２１４号、赤血球洗浄方法には、回転ボウルと、該ボウルおよび固定軸間の回転密封部材とを含む血液処理遠心機が記載されている。この回転密封部材は管状金属板またはハブ内に装架された回転密封リングを有している。金属板は回転密封リングを冷却するための吸熱器として働く。１９８１年１１月１７日付、A. Latham の米国特許第４，３００，７１７号、回転遠心機密封部材には遠心機ボウルおよび該ボウルと固定軸との間に設けられた回転密封部材が記載されている。この回転密封部材は、固定軸に装着された金属アダプタリング内に支持されている上方固定密封リングと、回転無孔遠心機ボウルに装着された金属アダプタリング内に支持されている下方セラミック回転密封リングとよりなっている。密封リングから熱を導き出すために、この特許においては金属の如き、熱伝導の優れた材料よりなる回転密封リング構造が使用されており、この密封リングは固定リングおよび回転リング間の接触部分から熱を導き出す。さらに空気の流れを消散させるために外方シールド内にポートを設け、冷却を行うようになっている。この特許においてはなお、密封部材によって発生した熱を消散させるために、遠心機無孔ボウルの上部外表面に羽根が設けられている。
【０００４】市販のある種の血液処理遠心機ボウルおよび密封部材においては、密封リングを有する金属吸熱リングが使用され、これら両部材は遠心機ボウルに装着されたプラスチック板またはハブによって支持される。
【０００５】前述した在来技術による装置に伴う主なる問題は、冷却が効果的に行われないこと、回転密封リン

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グに騒音が発生することおよび支持ハブに高価な金属の使用を必要とすることである。

【０００６】

【発明が解決しようとする課題】本発明の主なる課題は血液処理遠心機ボウルに対する改良回転密封部材を提供することである。

【０００７】さらに特別の課題は前記の如き特性を有する改良回転密封部材で、安定性があり、騒音を発生せず、かつ優れた冷却効果を有する回転密封部材を提供することである。

【０００８】本発明の他の課題は前述の特性を有する回転密封部材で、在来の装置より安価であり、軽量であり、頑丈であり、作業を効果的に行うことができ、かつ低作動温度を維持し得る回転密封部材を提供することである。

【０００９】

【課題を解決するための手段】前記課題を解決するために、本発明においては回転密封部材の回転密封リングを支持するために、改良密封リングハブが使用される。遠心分離機で、その一部分として無孔ボウルを有する遠心分離機の回転密封部材は、回転密封リングおよび固定密封リングを含んでいる。密封リングハブは中心軸受入孔を画定する環状ハブ板と、その周囲を軸線方向に延びる環状舌片と、環状孔に対し並列的に隔置されて、軸線方向に延びる環状リブとよりなっている。前記リブは舌片と平行に延び、かつ板と共に孔に近接して密封リング支持座を画定する。隔置された弦状に延びる複数の羽根は、リブと舌片との間を延びている。これらの羽根は舌片およびリブを越えて軸線方向に延び、かつ舌片の僅か手前で終わり、かつリブに重なるようにされる。羽根は密封部材が回転する時に、板を安定化させる働きを有し、かつ回転密封部材の周囲の冷却空気を流動させる。

【００１０】

【実施例】本発明は回転密封リング１１を装架する支持板またはハブ１０を有するものとして実施され、該支持板は、血液および血液成分の処理および分離に適した遠心機１４の、無孔外方ボウル１２に装着されるようになっている。遠心機１４は固定軸組立体１６上に回転自在に装架されたボウル組立体１５を有し、かつ回転密封組立体１８を使用し、回転ボウル組立体１５および固定軸組立体１６間の、血液及び血液成分の漏洩を阻止するようになっている。

【００１１】遠心機組立体１４は図１および図２に示される如く、ベル形外方無孔ボウル１２よりなり、該ボウルは上孔２１を画定する上方スリーブ部分２０を有している。ボウル１２の底部は底板２２によって閉じられ、遠心機モータ（図示せず）に作動的に連結されるようになっている。ボウル１２および底板２２は中央空洞２４を画定し、該空洞の中には固定軸組立体１６の部分を形成する入口管２５が延びている。この管は空洞２４の下端に開口し、かつその上端には入口配管２８に連結された入口管２６を備え、該入口管は全血を分離機ボウルに押送するポンプ（図示せず）に延びている。

【００１２】外周分離室３０を形成するために、中央円錐形ボウルまたはコアー３１が外殻１２内に装架されている。この中央コアー３１は中央通路３２を有し、該通路を通って入口管２５が延びている。中央コアー３１は底板３４を備え、該底板は前記底板２２に近接して隔置され、それらの間に分離通路３５を画定するようになっており、この通路は外周分離室３０内に開口している。

【００１３】分離された血液成分を排出するために、分離室３０は遠心機ボウル組立体１４の上端において、外方ボウル１２のスリーブ部分２０と、密封リングハブまたは板１０との間に画定された出口室３６内に開口している。

【００１４】血液成分を、出口管３９に連結された出口導管３８に排出するために、固定スリーブ４０が、入口管２５と共に環状出口通路４１を画定している。固定スリーブ４０および入口管２５は固定軸を画定し、該固定軸は遠心機装架装置（図示せず）上に支持されている。

【００１５】固定軸組立体１６および回転遠心機ボウル組立体１５間を密封するために、回転密封組立体１８は固定密封リング４２を含み、該リングは回転密封リング１１と回転的に係合する。固定密封リング４２は固定ハブ４４内に支持され、該ハブは可撓性ダイヤフラム４５によって軸組立体１６に装架され、かつこれに対して密封されている。

【００１６】固定および回転密封リングの接触面はそれぞれ、遠心機の作動中に熱を発生するから、本発明においては改良された熱放散および密封リング安定化構造が設けられている。この目的のために密封リング装架ハブまたは板は環状板５０よりなり、該板はその外周縁に近接する点において、外方遠心機ハウジング１２の直立スリーブ部分２０に装着されている。環状ハブ板５０は固定軸を囲繞する中心軸受入孔５１を画定している。密封リングハブ５０はその上表面において、その外周面に近接して軸線方向に延びる環状舌片５２と、軸線方向に延びる環状リブ５４とを画定し、該環状リブは舌片５２と平行し、かつこれと同心であり、中央環状孔５１に対して並列的に隔置されている。リブ５４および環状板の上表面５５は回転密封リング１１を定位置に支持するための座を画定し、このリングを固定軸組立体１６に装着された固定密封リング４２と回転的に係合させるようになっている。密封リング１１、４２によって形成された回転密封部材を冷却するために、円周上に均等に隔置された複数の弦状羽根５６は、装架板またはハブ５０と共に一体的に装架され、かつ外方舌片５２および座画定リブ５４の間を延びている。図示の変型においては、羽根は内方リブ５４と重なっているが、環状舌片５２の僅か手前で終わっている。

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【００１７】羽根は回転密封部材を冷却すると共に、密封リング支持板５０を安定せしめ、密封リングのチャタリング、すなわち騒音の発生を阻止する。

【００１８】以上本発明の典型的な実施例について図示説明したが、これは本発明を特定の型に制限するものではない。本発明は特許請求の範囲を離れることなく種々の変型を行い得るものと解すべきである。

【図面の簡単な説明】

【図１】本発明の無孔ボウルおよび回転密封構造を有する血液処理遠心機の、一部切除せる透視図。

【図２】図１の線２－２に沿って取られた遠心機ボウル、密封および軸構造の拡大断面図。

【図３】図２に示された構造の拡大部分図で、特に本発明の密封楕を示す。

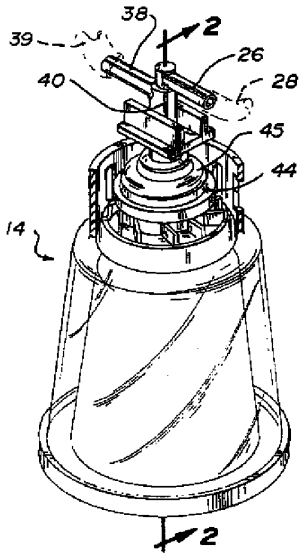
【図４】図２の線４－４に沿って取られた断面図。

【図５】図３に示された密封構造の透視展開図。

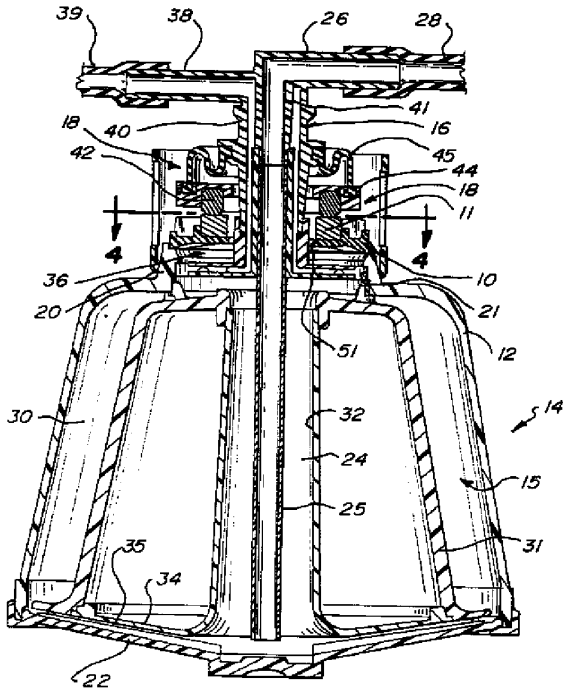
【符号の説明】

１０　支持板
１１　回転密封リング
１２　外方ボウル
１４　遠心機
１６　固定軸
１８　固定密封組立体
２０　上方スリーブ
２５　入口管
２６　入口管
３０　分離室
３１　中央コアー
３４　底板
３５　分離通路
３６　出口室
３９　出口管
４０　固定管
４４　固定ハブ
４５　ダイヤフラム
５１　受入孔
５２　環状舌片
５４　環状リブ
５６　羽根

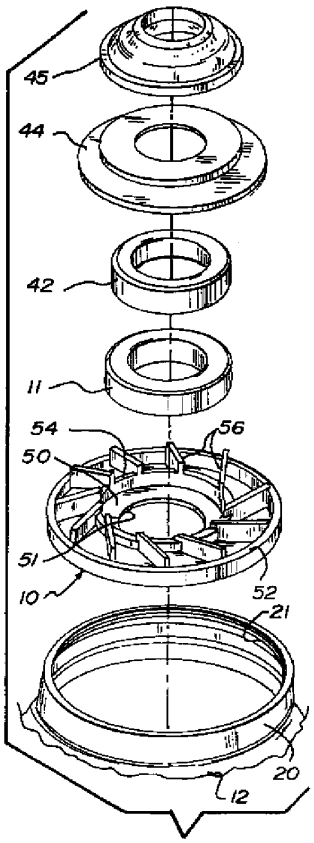
【図１】



【図２】

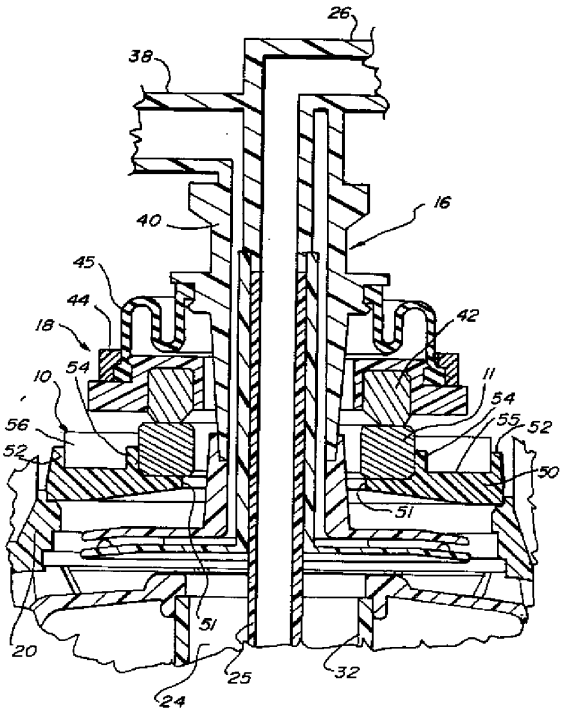


【図５】

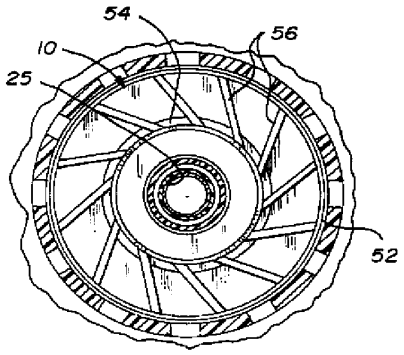


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【図３】



【図４】



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Espacenet

Bibliographic data: JPH08131539 (A) — 1996-05-28

BLOOD COMPONENT SEPARATING DEVICE, AND BLOOD PLATELET EXTRACTION METHOD

Inventor(s): KAWAZU SHUNJI; SUZUKI ATSUSHI ± (KAWAZU SHUNJI, ; SUZUKI ATSUSHI)

Applicant(s): TERUMO CORP ± (TERUMO CORP)

Classification: **- international:** ***A61K35/14; A61M1/02;*** (IPC1-7): A61K35/14; A61M1/02

- cooperative:

Application number: JP19940303043 19941111

Priority number (s): JP19940303043 19941111

Also published as: JP3715338 (B2)

Abstract of JPH08131539 (A)

PURPOSE: To improve a blood platelet yield of a separation device by supplying buffy coat among blood components centrifugally separated in a blood storing space to a buffy coat container, discharging the other components from the blood storing space to be transferred, returning buffy coat to the blood storing space, and performing centrifugal separation again for recovering blood plateles. CONSTITUTION: Blood in a blood bag 104 is introduced into a rotor 42 in a centrifugal bowl 4 through tubes 101, 103 to be centrifugally separated into plural blood components and collected in a blood storing space. A separated blood plasma layer is recovered from an upper part of the storing space to a blood plasma bag 21. Buffy coat is recovered from an outflow port 44 into a buffy coat bag 25. Next, a pump is inversely rotated to return red bood corpuscles left in the centrifugal bowl 4 into the blood bag 104. Buffy coat in the buffy coat 25 is then returned to the blood storing space, and it is processed with blood in the blood bag 104.

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(19)日本国特許庁（ＪＰ）　(12) **公開特許公報（Ａ）**　(11)特許出願公開番号

特開平8－131539

(43)公開日　平成８年(1996)５月28日

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ	技術表示箇所
Ａ６１Ｍ　1/02	５２０			
Ａ６１Ｋ　35/14		Ｚ　7431－4Ｃ		
		Ｃ　7431－4Ｃ		

審査請求　未請求　請求項の数７　ＦＤ　（全 16 頁）

(21)出願番号　特願平6－303043

(22)出願日　平成６年(1994)11月11日

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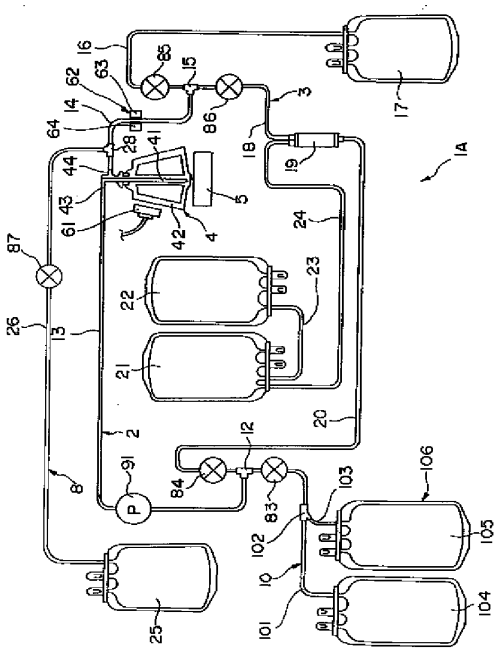
(74)代理人　弁理士　増田　達哉

(54)【発明の名称】　血液成分分離装置および血小板採取方法

(57)【要約】

【構成】血液成分分離装置１Ａは、遠心ボウル４と、その回転駆動装置５と、遠心ボウル４に血液および血漿を導入する第１のライン２と、遠心分離された血液成分を回収する第２のライン３と、バフィーコートバッグ２５と、バフィーコートを移送する第３のライン８と、光学センサー６１、６２と、制御手段と、血液貯留部１０６を有する第３のライン１０と、第１のライン２に設置されたポンプ９１とを有する。この装置１では、血液貯留部１０６から移送される血液を遠心ボウル４にて遠心分離し、得られたバフィーコートをバフィーコートバッグ２５に一旦貯留しておき、該バフィーコートを最後に貯血空間４６へ戻し、遠心分離しつつ下方より血漿を供給して血小板を浮上させ、該血小板を第２のライン３を介して血小板バッグ１７に回収する。

【効果】短い処理時間で白血球の除去率が高い高品質の血液製剤が得られる。



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【特許請求の範囲】
【請求項１】　血液を複数の血液成分に分離するとともに分離された血液成分を移送する血液成分分離装置であって、
内部に貯血空間を有する回転可能なローターと、前記貯血空間に連通する流入口および流出口とを有し、前記ローターの回転により前記流入口より導入された血液を前記貯血空間内で複数の血液成分に遠心分離する遠心分離器と、
前記流入口に接続された第１のラインと、
前記流出口に接続された第２のラインと、
バフィーコートを貯留する容器と、
一端が前記容器と接続され、他端が前記第１のラインおよび／または第２のラインに接続された第３のラインとを有し、
前記第１のラインを介して前記貯血空間に血液を導入するとともに前記ローターを回転し、前記血液を遠心分離して複数の血液成分に分離し、次いで、これにより得られたバフィーコートを前記第３のラインを介して前記容器へ移送するとともに、バフィーコート以外の血液成分を前記貯血空間から排出、移送し、その後、前記容器内のバフィーコートを前記第３のラインを介して前記貯血空間へ戻し、該バフィーコートを含む血液成分に対し再度遠心分離を施してバフィーコート中の血小板を前記第２のラインを介して回収するよう作動することを特徴とする血液成分分離装置。
【請求項２】　前記第３のラインは、前記第１のラインと接続されており、この接続部と前記流入口との間の前記第１のラインの途中にポンプが設置されている請求項１に記載の血液成分分離装置。
【請求項３】　前記第１のラインの途中および前記第３のラインの途中に、それぞれ、ポンプが設置されている請求項１に記載の血液成分分離装置。
【請求項４】　内部に貯血空間が形成されたローターを有する遠心分離器を用い、血液から血小板を分離し、採取する血小板採取方法であって、
前記貯血空間に血液を導入するとともに前記ローターを回転し、前記血液を遠心分離して複数の血液成分に分離する第１工程と、
前記第１工程で分離された各血液成分のうちのバフィーコートを前記貯血空間から排出し、容器に一旦貯留するとともに、バフィーコート以外の血液成分を前記貯血空間から排出し、他所へ移送する第２工程と、
前記容器内のバフィーコートを前記貯血空間に戻す第３工程と、
前記貯血空間内の前記バフィーコートを含む血液成分に対し、前記ローターを回転して遠心分離を施し、分離された血小板を回収する第４工程とを有し、
前記第１工程および前記第２工程を少なくとも１回行った後、前記第３工程および前記第４の工程を行うことを特徴とする血小板採取方法。
【請求項５】　前記第４工程において、前記ローターの回転下で前記貯血空間に下方より血漿を供給し、血小板を浮上させて回収する請求項４に記載の血小板採取方法。
【請求項６】　血漿の供給速度を１０～９０ml／min とする請求項５に記載の血小板採取方法。
【請求項７】　前記第３工程において、バフィーコートを前記貯血空間に戻した後、前記容器およびバフィーコートの流路を洗浄し、その洗浄に供された液を前記貯血空間に戻す請求項４ないし６のいずれかに記載の血小板採取方法。
【発明の詳細な説明】
【０００１】
【産業上の利用分野】本発明は、血液中から所定の血液成分を分離する血液成分分離装置および血液中から血小板を採取する血小板採取方法に関する。
【０００２】
【従来の技術】採血を行う場合、現在では、血液の有効利用および供血者の負担軽減などの理由から、採血血液を遠心分離などにより各血液成分に分離し、輸血者に必要な成分だけを採取し、その他の成分は供血者に返還する成分採血が行われている。
【０００３】このような成分採血において、血小板製剤を得る場合、供血者から採血した血液を血液成分分離回路に導入し、該血液成分分離回路に設置された遠心ボウルと呼ばれる遠心分離器により、血漿、白血球、血小板および赤血球の４成分に分離し、その内の血小板を容器に回収して血小板製剤とし、残りの血漿、白血球および赤血球は、供血者に返血することが行われる。そして、目標とする血小板数を確保するために、上記採血、採血血液の遠心分離、血小板の回収および返血よりなる一連の血液処理工程が複数回行われる。
【０００４】しかしながら、この方法では、白血球と血小板との比重がわずかな差であることから、これらの界面が明確ではなく、白血球と血小板とを含む一体のバフィーコート層として認識されるため、回収された血小板中の白血球（特にリンパ球）の除去率が低くなり、その結果、その血小板製剤を使用した場合に、肝炎、エイズ、ＧＶＨＤ等の感染の確率が高くなるという問題がある。
【０００５】そこで、遠心ボウルの下方より先に得られた血漿を供給して血小板を浮上させ、該血小板を回収する方法（サージ法）が提案されているが、１回の遠心分離で得られるバフィーコートの量が少なく、遠心ボウル内でのバフィーコート層の厚さが薄くなり、しかも、血漿の供給速度が比較的高速（２００ml／min 以上）であるため、やはり血小板中の白血球除去率が低く、上記問題が解決されていない。
【０００６】

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【発明が解決しようとする課題】本発明の目的は、遠心分離により得られた血小板の収率または該血小板中の白血球の除去率が高い血液成分分離装置および血小板採取方法を提供することにある。

【０００７】

【課題を解決するための手段】このような目的は、下記（１）～（11）の本発明により達成される。

【０００８】（１）　血液を複数の血液成分に分離するとともに分離された血液成分を移送する血液成分分離装置であって、内部に貯血空間を有する回転可能なローターと、前記貯血空間に連通する流入口および流出口とを有し、前記ローターの回転により前記流入口より導入された血液を前記貯血空間内で複数の血液成分に遠心分離する遠心分離器と、前記流入口に接続された第１のラインと、前記流出口に接続された第２のラインと、バフィーコートを貯留する容器と、一端が前記容器と接続され、他端が前記第１のラインおよび／または第２のラインに接続された第３のラインとを有し、前記第１のラインを介して前記貯血空間に血液を導入するとともに前記ローターを回転し、前記血液を遠心分離して複数の血液成分に分離し、次いで、これにより得られたバフィーコートを前記第３のラインを介して前記容器へ移送するとともに、バフィーコート以外の血液成分を前記貯血空間から排出、移送し、その後、前記容器内のバフィーコートを前記第３のラインを介して前記貯血空間へ戻し、該バフィーコートを含む血液成分に対し再度遠心分離を施してバフィーコート中の血小板を前記第２のラインを介して回収するよう作動することを特徴とする血液成分分離装置。

【０００９】（２）　前記第３のラインは、前記第１のラインと接続されており、この接続部と前記流入口との間の前記第１のラインの途中にポンプが設置されている上記）に記載の血液成分分離装置。

【００１０】（３）　前記第１のラインの途中および前記第３のラインの途中に、それぞれ、ポンプが設置されている上記（１）に記載の血液成分分離装置。

【００１１】（４）　少なくとも前記ポンプの作動を制御する制御手段を有する上記（２）または（３）に記載の血液成分分離装置。

【００１２】（５）　前記第１のライン、前記第２のラインおよび前記第３のラインのうちの少なくとも１つに、その流路を開閉し得る流路開閉手段が設置され、前記制御手段は、前記ポンプの作動とともに前記流路開閉手段の作動を制御する上記（４）に記載の血液成分分離装置。

【００１３】（６）　前記第１のラインの少なくとも一部は、前記貯血空間への血液の導入と血漿の導入とに兼用される上記（１）ないし（５）のいずれかに記載の血液成分分離装置。

【００１４】（７）　前記第２のラインは、それぞれ異なる血液成分を回収する複数の分岐ラインを有する上記（１）ないし（６）のいずれかに記載の血液成分分離装置。

【００１５】（８）　内部に貯血空間が形成されたローターを有する遠心分離器を用い、血液から血小板を分離し、採取する血小板採取方法であって、前記貯血空間に血液を導入するとともに前記ローターを回転し、前記血液を遠心分離して複数の血液成分に分離する第１工程と、前記第１工程で分離された各血液成分のうちのバフィーコートを前記貯血空間から排出し、容器に一旦貯留するとともに、バフィーコート以外の血液成分を前記貯血空間から排出し、他所へ移送する第２工程と、前記容器内のバフィーコートを前記貯血空間に戻す第３工程と、前記貯血空間内の前記バフィーコートを含む血液成分に対し、前記ローターを回転して遠心分離を施し、分離された血小板を回収する第４工程とを有し、前記第１工程および前記第２工程を少なくとも１回行った後、前記第３工程および前記第４の工程を行うことを特徴とする血小板採取方法。

【００１６】（９）　前記第４工程において、前記ローターの回転下で前記貯血空間に下方より血漿を供給し、血小板を浮上させて回収する上記（８）に記載の血小板採取方法。

【００１７】（10）　血漿の供給速度を１０～９０ml／min とする上記（９）に記載の血小板採取方法。

【００１８】（11）　前記第３工程において、バフィーコートを前記貯血空間に戻した後、前記容器およびバフィーコートの流路を洗浄し、その洗浄に供された液を前記貯血空間に戻す上記（８）ないし（10）のいずれかに記載の血小板採取方法。

【００１９】

【実施例】以下、本発明の血液成分分離装置および血小板採取方法を添付図面に示す好適実施例に基づいて詳細に説明する。

【００２０】図１は、本発明の血液成分分離装置の第１実施例を示す平面図、図２は、図１に示す血液成分分離装置の制御系を示すブロック図である。これらの図に示すように、血液成分分離装置１Ａは、遠心ボウル（遠心分離器）４と、その回転駆動装置５と、遠心ボウル４に血液および血漿を選択的に導入する第１のライン２（血液または血漿導入ライン）と、遠心ボウル４にて分離された血液成分を回収する第２のライン３（血液成分回収ライン）と、バフィーコートを貯留する容器であるバフィーコートバッグ２５と、該バフィーコートバッグ２５内のバフィーコートを遠心ボウル４へ導入する第３のライン８と、光学センサー６１、６２と、制御手段７と、血液貯留部１０６を有する第４のライン（供血者を想定した脱・返血ライン）１０と、第１のライン２に設置されたポンプ９１とを有する。

【００２１】図１に示すように、第４のライン１０は、

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主に、チューブ１０１と、チューブ１０１の途中にト字状の分岐コネクタ１０２を介して接続されたチューブ１０３と、チューブ１０１、１０３の先端にそれぞれ接続された血液バッグ１０４、１０５とで構成されている。両血液バッグ１０４、１０５により、血液貯留部１０６が構成されている。

【００２２】チューブ１０１の基端は、Ｔ字状の分岐コネクタ１２を介してチューブ１３および２０の一端と接続されている。チューブ１０１の途中には、チューブ１０１の内部流路を遮断・解放し得る流路開閉手段であるバルブ８３が設置されている。

【００２３】第１のライン２は、チューブ１３およびその一端に接続された分岐コネクタ１２により構成されている。チューブ１３の他端は、遠心ボウル４の流入口４３に接続され、チューブ１３の途中には、例えばローラポンプよりなる送液用のポンプ９１が設置されている。

【００２４】図３に示すように、遠心ボウル４は、上端に流入口４３が形成された鉛直方向に伸びる管体４１と、該管体４１の回りで回転し、上部４５に対し液密にシールされたローター４２とで構成されている。ローター４２の内部には、ローター周壁内面に沿って環状の貯血空間４６が形成されている。この貯血空間４６は、図３中下部から上部に向けてその内外径が漸減するような形状（テーパ状）をなしている。貯血空間４６の下部は、ローター４２の底部に沿って形成されたほぼ円盤状の流路４７を介して管体４１の下端開口と連通し、貯血空間４６の上部は、流路４８を介して流出口４４に連通している。また、このローター４２において、貯血空間４６の容積は、例えば、１００～３５０ml程度とされる。

【００２５】このようなローター４２は、回転駆動装置５により予め設定された所定の遠心条件（回転速度および回転時間）で回転される。この遠心条件により、ローター４２内の血液の分離パターン（例えば、分離する血液成分数）を設定することができる。本実施例では、図３に示すように、血液が貯血空間４６内で内層より血漿層３１、バフィーコート層３２および赤血球層３３に分離されるように遠心条件が設定される。

【００２６】回転駆動装置５は、図３に示すように、遠心ボウル４を収納するハウジング５１と、脚部５２と、駆動源であるモータ５３と、遠心ボウル４を保持する円盤状の固定台５５とで構成されている。

【００２７】ハウジング５１は、脚部５２の上部に載置、固定されている。また、ハウジング５１の下面には、ボルト５６によりスペーサー５７を介してモータ５３が固定されている。モータ５３の回転軸５４の先端部には、固定台５５が回転軸５４と同軸でかつ一体的に回転するように嵌入されており、固定台５５の上部には、ローター４２の底部が嵌合する凹部５５１が形成されている。また、遠心ボウル４の上部４５は、図示しない固定部材によりハウジング５１に固定されている。

【００２８】このような回転駆動装置５では、モータ５３を駆動すると、固定台５５およびそれに固定されたローター４２が、例えば、回転数３０００～６０００rpmで回転する。

【００２９】ハウジング５１の内壁には、ローター４２内の分離された血液成分の界面、すなわち、バフィーコート層３２と赤血球（濃厚赤血球）層３３との界面Ｂの位置を光学的に検出する光学センサー６１が、取付部材５８により設置、固定されている。この光学センサー６１としては、ローター４２の外周面に沿って上下方向に走査し得るラインセンサーが用いられる。すなわち、ＬＥＤのような発光素子とフォトダイオードのような受光素子とが列状に配置され、発光素子から発っせられた光の血液成分での反射光を受光素子により受光し、その受光光量を光電変換するように構成されている。分離されたバフィーコート層３２と赤血球層３３とで反射光の強度が異なるため、受光光量すなわち出力電圧が変化した受光素子に対応する位置が、界面Ｂの位置として検出される。

【００３０】図１に示すように、遠心ボウル４の流出口４４には、チューブ１４の一端が接続され、チューブ１４の他端は、Ｔ字状の分岐コネクタ１５を介してチューブ１６および１８の一端と接続されている。

【００３１】チューブ１６の他端は、血小板バッグ１７に接続され、チューブ１６の途中には、チューブ１６内の流路を開閉するバルブ８５が設置されている。また、チューブ１８の他端は、気泡除去用のチャンバー１９に接続され、チューブ１８の途中には、チューブ１８内の流路を開閉するバルブ８６が設置されている。

【００３２】一端が分岐コネクタ１２に接続されているチューブ２０の他端は、気泡除去用のチャンバー１９に接続され、チューブ２０の途中には、チューブ２０内の流路を開閉するバルブ８４が設置されている。

【００３３】空気貯留バッグ２２は、一連の処理後に血漿バッグ２１内からエアーを排出し、これを貯留するためのバッグであり、そのため、血漿バッグ２１および空気貯留バッグ２２は、チューブ２３により接続されてその内部同士が連通している。また、血漿バッグ２１には、チューブ２４の一端が接続され、チューブ２４の他端は、気泡除去用のチャンバー１９に接続されている。

【００３４】このような構成において、チューブ１４、１６、１８、２０、２３、２４、分岐コネクタ１５、チャンバー１９およびバッグ１７、２１、２２により、第２のライン３が構成されている。このうち、チューブ１８、チャンバー１９、チューブ２３、２４およびバッグ２１、２２は、血漿を回収するための血漿回収用分岐ラインを構成し、チューブ１４、１６および血小板バッグ１７は、血小板を回収するための血小板回収用分岐ラインを構成する。

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【００３５】なお、図示されていないが、血漿バッグ２１は、チューブ２４の接続側端部を上方または下方へ選択的に向けることができる装置（バッグ揺動装置）にセットされていてもよい。

【００３６】チューブ１４の流出口４４の近傍には、分岐コネクタ２８が設置され、この分岐コネクタ２８には、チューブ２６の一端が接続されている。また、チューブ２６の他端は、バフィーコートバッグ２５に接続され、チューブ２６の途中には、チューブ２６内の流路を開閉するバルブ８７が設置されている。このチューブ２６および分岐コネクタ２８により第３のライン８が構成されている。

【００３７】このようなバフィーコートバッグ２５は、複数個設置されていてもよく、その接続パターンも特に限定されない。また、バフィーコートバッグ２５の容量は、特に限定されないが、通常、合計容量が１００～８００ml程度が好ましく、４００～５００ml程度がより好ましい。なお、図示されていないが、バフィーコートバッグ２５は、前記と同様のバッグ揺動装置にセットされていてもよい。

【００３８】また、チューブ１４の途中には、チューブ１４内を流れる血液成分中の血小板の濃度を検出し得る光学センサー６２が設置されている。この光学センサー６２は、チューブ１４を介して対向配置された投光部（光源）６３および受光部（フォトダイオード）６４で構成されている。投光部６３から発せられた光（例えばレーザー光）は、チューブ１４を透過して受光部６４で受光され、その受光光量に応じた電気信号に変換されるが、チューブ１４内を流れる血液成分中の血小板濃度に応じて透過率が変化し、受光部６４での受光光量が変動するため、この変動を受光部６４からの出力電圧の変化として検出することができる。

【００３９】前記各バルブ８３～８７は、例えば、ソレノイド、電動モーター、またはシリンダ（油圧または空気圧）等の駆動源で作動し、該駆動源は、後述する制御手段７からの信号に基づいて作動する。なお、本発明において、流路開閉手段は、前記バルブ（コック）に限らず、例えば可撓性チューブを挟持してその内腔を閉塞し得るクレンメであってもよい。

【００４０】前記各バッグ１７、２１、２２、２５、１０４、１０５は、それぞれ、樹脂製の可撓性を有するシート材を重ね、その周縁部を融着（熱融着、高周波融着等）または接着して袋状にしたものである。

【００４１】各バッグ１７、２１、２２、２５、１０４、１０５を構成するシート材の構成材料としては、例えば、軟質ポリ塩化ビニルが好適に使用される。この軟質ポリ塩化ビニルにおける可塑剤としては、例えば、ジ（エチルヘキシル）フタレート（ＤＥＨＰ）、ジ－（ｎ－デシル）フタレート（ＤｎＤＰ）等が使用される。なお、このような可塑剤の含有量は、ポリ塩化ビニル１００重量部に対し、３０～７０重量部程度とするのが好ましい。

【００４２】また、各バッグ１７、２１、２２、２５、１０４、１０５のシート材の他の構成材料としては、ポリオレフィン、すなわちエチレン、プロピレン、ブタジエン、イソプレン等のオレフィンあるいはジオレフィンを重合または共重合した重合体を用いることができ、例えば、ポリエチレン、ポリプロピレン、エチレン－酢酸ビニル共重合体（ＥＶＡ）、ＥＶＡと各種熱可塑性エラストマーとのポリマーブレンド等、あるいは、これらを任意に組み合せたものが挙げられる。さらには、ポリエチレンテレフタレート（ＰＥＴ）、ポリブチレンテレフタレート（ＰＢＴ）、ポリ－１，４－シクロヘキサンジメチルテレフタレート（ＰＣＨＴ）のようなポリエステルや、ポリ塩化ビニリデンを用いることもできる。

【００４３】なお、血小板バッグ１７を構成するシート材は、血小板保存性を向上するために、ガス透過性に優れるものが好ましく、そのために、例えば、シート材として、前記ポリオレフィンやＤｎＤＰ可塑化ポリ塩化ビニル等を用いたり、また、シート材の厚さを比較的薄く（例えば、０．１～０．５㎜程度、特に、０．１～０．３㎜程度）するのが好ましい。

【００４４】血液バッグ１０４、１０５の少なくとも一方の内部には、予め血液が貯留されている。この血液中には、例えば、ＡＣＤ－Ａ液、ＣＰＤ液、ＣＰＤ－Ａ１液、ヘパリンナトリウム液等の抗凝固剤が添加されているのが好ましい。なお、血液貯留部１０６に設置される血液バッグの数は、１または３以上であってもよく、その接続方法、接続パターンも任意可能である。例えば、実開平６－２６８７７号公報等に記載されているチューブ接続装置により、１または２以上の血液バッグを無菌的に接続、交換して使用することもできる。また、血小板バッグ１７は、空の状態でもよいが、例えば、生理食塩水、ＧＡＣ、ＰＡＳ、ＰＳＭ－１のような血小板保存液が予め入れられていてもよい。

【００４５】チューブ１０１、１０３、１３、１４、１６、１８、２０、２３、２４、２６、２７の構成材料としては、例えば、ポリ塩化ビニル、ポリエチレン、ポリプロピレン、ＰＥＴやＰＢＴのようなポリエステル、エチレン－酢酸ビニル共重合体、ポリウレタン、ポリエステルエラストマー、スチレン－ブタジエン－スチレン共重合体等の熱可塑性エラストマー等が挙げられるが、その中でも特に、ポリ塩化ビニルが好ましい。各チューブがポリ塩化ビニル製であれば、十分な可撓性、柔軟性が得られるので取り扱いがし易く、また、クレンメ等による閉塞にも適するからである。また、分岐コネクタ１０２、１２、１５、２８、２９の構成材料についても、前記チューブの構成材料と同様のものを用いることができる。

【００４６】図２に示すように、血液成分分離装置１Ａ

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は、例えばマイクロコンピュータで構成される制御手段７を有し、該制御手段７には、前記ポンプ９１、バルブ８３～８７、光学センサー６１、６２および回転駆動装置５がそれぞれ電気的に接続されている。

【００４７】光学センサー６１からの検出信号（界面位置検出情報）および光学センサー６２からの検出信号（血小板濃度情報）は、それぞれ、制御手段７へ随時入力される。制御手段７は、光学センサー６１、６２からの各検出信号に基づき、ポンプ９１の回転／停止、回転方向（正転／逆転）および回転数を制御するとともに、必要に応じ、各バルブ８３～８７の開閉および回転駆動装置５の作動を制御する。

【００４８】以上のような遠心ボウル４を用いた血液成分分離装置１Ａでは、バッグ内で血液を遠心分離する方法に比べ、回収された血小板のペレット化（塊状となること）が極めて少ないという利点がある。

【００４９】次に、図１に示す血液成分分離装置１Ａを用いた本発明の血小板採取方法の好適な実施例について説明する。以下の各工程におけるバルブ８３～８７、ローター４２およびポンプ９１の作動状態を、下記表１に示し、該表１を参照しつつ説明する。

【００５０】

【表１】

表　１　　（血液成分分離装置１Ａ）

工　程	バルブ開閉パターン	バルブ 83	84	85	86	87	ローター 42	ポンプ 91
[1a] [2a]	(1)	○	×	○	×	×	回転	正転
[3a]	(2)	○	×	×	○	×	回転	正転
[4a]	(3)	○	×	×	×	○	回転	正転
[5a]	(4)	○	×	○	×	×	停止	逆転
[6a]	(5)	×	○	×	○	×	停止	正転
[7a] [8a]	(6)	○	×	○	×	×	停止	逆転
[9a]	(7)	×	○	×	×	○	回転	逆転
[10a]	(8)	○	×	×	○	×	回転	正転
[11a]	(9)	○	×	×	×	○	回転	正転
[12a]	(10)	×	○	×	×	○	回転	逆転
[13a]	(11)	×	○	○	×	×	回転	正転
[14a]	(12)	○	×	×	○	×	回転	正転
[15a]	(13)	×	○	○	×	×	回転	正転
[16a]	(14)	○	×	×	○	×	停止	逆転
[17a]	(15)	×	○	×	○	×	停止	正転
[18a]	(16)	○	×	○	×	×	停止	逆転

バルブ○：開放　　ポンプ正転：液の流れは遠心ボウル方向
バルブ×：閉鎖　　ポンプ逆転：液の流れは血液貯留部方向

【００５１】［１ａ］　血液バッグ１０４、１０５内には、それぞれ、例えば４００mlの採血血液が充填されており、チューブ１０３をクレンメで閉塞し、バルブ開閉パターンを表１中の（１）として、ポンプ９１を作動（正転）する。これにより、血液バッグ１０４内の血液は、チューブ１０１および１３を介して移送され、遠心ボウル４の流入口４３より管体４１を経てローター４２内に導入される。なお、ポンプ９１の回転速度は、血液吐出量（血液供給速度）が例えば３０～８０ml／min 程度となるように設定される。

【００５２】［２ａ］　また、前記工程［１ａ］の血液移送と同時に、回転駆動装置５を作動して、ローター４２を好ましくは３０００～６０００rpm （例えば、４８００rpm ）で回転する。管体４１の下端開口より流出した血液は、ローター４２の回転による遠心力により、流路４７を外周方向へ向けて放射状に流れ、貯血空間４６に集められ、該貯血空間４６において内層より血漿層３１、バフィーコート層３２および赤血球層３３に分離さ

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れる。

【００５３】［３ａ］　前記工程［１ａ］、［２ａ］を継続しつつ、血漿層３１が貯血空間４６の上部に到達したら、バルブ開閉パターンを（２）とする。これにより、ローター４２内の血漿が流出口４４よりオーバーフローし、チューブ１４、１８、チャンバー１９、チューブ２４を介して血漿バッグ２１内に回収される。

【００５４】［４ａ］　ローター４２内からの血漿の排出に伴い、バフィーコート層３２と赤血球層３３との界面Ｂも徐々に上昇する。この界面Ｂは、光学センサー６１により随時検出されており、界面Ｂが所定レベル、すなわち流出口４４からバフィーコートが流出し始める程度のレベルに到達したことが検出されると、制御手段７は、その検出信号（界面位置検出情報）に基づき、バルブ開閉パターンを（３）とするよう制御する。これにより、以後、流出口４４から流出したバフィーコートは、チューブ１４、２６を介してバフィーコートバッグ２５へ移送、回収される。

【００５５】［５ａ］　光学センサー６１により、界面Ｂが所定レベル、すなわち貯血空間６４からほぼ全てのバフィーコートが排出される程度のレベルに到達したことが検出されると、制御手段７は、その検出信号（界面位置検出情報）に基づき、回転駆動装置５を停止し、バルブ開閉パターンを（４）とし、ポンプ９１を逆回転するよう制御する。これにより、遠心ボウル４内に残った赤血球が、管体４１、チューブ１３、１０１を介して、血液バッグ１０４内に返血される。

【００５６】［６ａ］　バルブ開閉パターンを（５）とし、ポンプ９１を作動（正転）して、血漿バッグ２１内の血漿の全部または一部をチューブ２４、チャンバー１９、チューブ２０、１３を介してローター４２内に入れる。

【００５７】［７ａ］　続いて、バルブ開閉パターンを（６）とし、ポンプ９１を逆回転して、血漿バッグ２１から移送した遠心ボウル４内の血漿を、管体４１、チューブ１３、１０１を介して、血液バッグ１０４内に返血する。

【００５８】［８ａ］　分岐コネクタ１０２と血液バッグ１０４との間のチューブ１０１の途中を例えば融着により封止し、さらにこの封止部を切断、分離する。これにより、返血用乏血小板血液入りの血液バッグ１０４が得られる。血液バッグ１０４内の乏血小板血液は、必要に応じ、供血者に返血される。

【００５９】なお、処理する血液バッグ数がｎ個（ｎ＝３以上の整数）である場合、ｎ－１個までの血液バッグに対し、前記工程［１ａ］～［８ａ］を繰り返し行い、ｎ個目の血液バッグに対し、以下の工程を行う。

【００６０】［９ａ］　回転駆動装置５を作動してローター４２を例えば３０００～６０００rpm で回転するとともに、バフィーコートバッグ２５のチューブ２６の接続側端部を下方へ向けた状態で、バルブ開閉パターンを（７）とし、ポンプ９１を逆回転する。これにより、バフィーコートバッグ２５内に貯留されているバフィーコートは、チューブ２６、１４、流出口４４、流路４８を介して貯血空間４６内に戻される。

【００６１】［１０ａ］　クレンメによるチューブ１０３の閉塞を解除し、バルブ開閉パターンを（８）とし、ポンプ９１を前記工程［１ａ］と同条件で作動（正転）する。これにより、血液バッグ１０５内の血液は、チューブ１０３、１０１および１３を介して移送され、遠心ボウル４の流入口４３より管体４１を経てローター４２内に導入され、貯血空間４６において血液が内層より血漿層３１、バフィーコート層３２および赤血球層３３に分離される。

【００６２】この場合、バフィーコート層３２は、複数回の採血に相当する複数の血液バッグ（図示の構成では血液バッグ１０４、１０５）内の合計の血液より得られる量のバフィーコートで構成されるため、その層厚が厚くなり、後述するサージ工程において、血小板の浮上、濃縮がより明確に行われ、血小板の収率および回収された血小板中の白血球の除去率が向上する。

【００６３】［１１ａ］　流出口４４より血漿が流出したら、まず、バルブ開閉パターンを（９）とする。これにより、流出口４４より流出した血漿が、チューブ１４、２６を介してバフィーコートバッグ２５内に導入され、チューブ１４、２６の流路およびバフィーコートバッグ２５の内部が洗浄される。このとき、バフィーコートバッグ２５を揺動させると、その内部の洗浄効果が高まり、好ましい。

【００６４】［１２ａ］　バフィーコートバッグ２５のチューブ２６の接続側端部を下方へ向けた状態で、バルブ開閉パターンを（10）とし、ポンプ９１を逆回転する。これにより、バフィーコートバッグ２５内等の洗浄に供された血漿（洗浄液）が、チューブ２６、１４、流出口４４、流路４８を介して貯血空間４６内に戻される。なお、バフィーコートバッグ２５を高所へ置き、必要に応じ所定のエアー抜きを設け、落差によりバフィーコートバッグ２５内の洗浄液を貯血空間４６へ移送してもよく、あるいは、バフィーコートバッグ２５を例えば一対の加圧板等により挟持、圧迫して洗浄液を排出、移送してもよい。

【００６５】このような、バフィーコートバッグ２５内等の洗浄およびその洗浄液の貯血空間４６への回収を行うことにより、血小板をバフィーコートバッグ２５内等に残存せず、血小板の収率が向上する。

【００６６】［１３ａ］　バルブ開閉パターンを（11）とし、ポンプ９１を作動（正転）する。これにより、血漿バッグ２１内の血漿が、チューブ２４、チャンバー１９、チューブ２０、１３および管体４１を介してローター４２内に供給され、さらにチューブ１４、１６を流

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れ、サージ回路が血漿でプライミングされる。
【００６７】［１４ａ］　次いで、バルブ開閉パターンを（12）とする。これにより、ローター４２内の血漿が流出口４４より流出し、チューブ１４、１８、チャンバー１９、チューブ２４を介して血漿バッグ２１内に回収される。
【００６８】［１５ａ］　光学センサー６１により、界面Ｂが所定のサージ開始レベル、すなわち貯血空間４６の容積に対する貯血空間４６内に存在する赤血球層３３の体積の比率が好ましくは７０～９６％、より好ましくは８５～９４％に達したときのレベルに到達したことが検出されると、制御手段７は、その検出信号（界面位置検出情報）に基づき、バルブ開閉パターンを（13）とするよう制御する。これにより、血漿バッグ２１内の血漿が、チューブ２４、チャンバー１９、チューブ２０、１３および管体４１を介してローター４２内に供給される。管体４１の下端開口より流出した血漿は、ローター４２の回転による遠心力により、流路４７を外周方向へ向けて放射状に流れ、貯血空間４６の下部を経て貯血空間４６内を上昇する。これにより、バフィーコート層３２中の血小板が遠心力に抗して浮上し（舞い上がり）、流路４８を経て流出口４４より流出し、チューブ１４および１６を介して血小板バッグ１７内に回収される（サージ工程）。なお、血小板の流出は、光学センサー６２による血小板濃度の上昇により検知される。
【００６９】このサージ工程において、制御手段７は、ポンプ９１の回転速度（血漿吐出量）を制御することにより、ローター４２内への血漿の供給速度を好ましくは１０～９０ml／min 、より好ましくは１０～７０ml／min に設定する。血漿供給速度が１０ml／min 未満では、血小板の回収に長時間を要し、９０ml／min を超えると、血小板とともに白血球の浮上量が増え、回収された血小板中の白血球の除去率が低下するからである。
【００７０】また、血小板の回収中において、血漿の供給速度は、１０～９０ml／min の範囲内で適宜変更してもよい。例えば、最初に血漿を所定速度で供給し、次いでそれより低速で供給するサイクルを少なくとも１回行うような方法が挙げられる。このような場合、血漿の最大供給速度は、２５～９０ml／min 、特に３０～７０ml／min とするのが好ましい。このような血漿供給速度の変更は、例えば、制御手段７に内蔵されるタイマーに基づいて、あるいは光学センサー６２により検出される血小板濃度情報に応じて行うことができる。
【００７１】［１６ａ］　光学センサー６２により検出される血小板濃度が予め設定された基準値以下となったら、血小板バッグ１７への血小板の回収が終了したものとみなし、制御手段７は、その検出信号（血小板濃度情報）に基づき、回転駆動装置５を停止し、バルブ開閉パターンを（14）とし、ポンプ９１を逆回転するよう制御する。これにより、遠心ボウル４内に残った赤血球、白血球および血漿が、管体４１、チューブ１３、１０１を介して、血液バッグ１０５内に返血される。
【００７２】［１７ａ］　バルブ開閉パターンを（15）とし、ポンプ９１を作動（正転）して、血漿バッグ２１内に残った血漿をチューブ２４、チャンバー１９、チューブ２０、１３を介してローター４２内に入れる。
【００７３】［１８ａ］　続いて、バルブ開閉パターンを（16）とし、ポンプ９１を逆回転して、血漿バッグ２１から移送した遠心ボウル４内の血漿を、管体４１、チューブ１３、１０１を介して、血液バッグ１０５内に返血する。
【００７４】［１９ａ］　チューブ１０３の途中を例えば融着により封止し、さらにこの封止部を切断、分離する。これにより、返血用乏血小板血液入りの血液バッグ１０５が得られる。血液バッグ１０５内の乏血小板血液は、必要に応じ、供血者に返血される。
【００７５】［２０ａ］　血小板バッグ１７付近のチューブ１６を例えば融着により封止し、さらにこの封止部を切断、分離することにより、血小板製剤入りの血小板バッグ１７が得られる。
【００７６】以上のように、本発明では、複数の血液バッグ（図示の構成では血液バッグ１０４、１０５）内の合計の血液より得られる量のバフィーコートを集め、これに対し一度にサージ工程を行うため、サージの際の貯血空間４６内におけるバフィーコート層３２の層厚が厚くなり、よって、バフィーコート層３２中からの血小板の浮上、濃縮がより明確に行われ、血小板の収率および回収された血小板中の白血球の除去率が向上する。
【００７７】特に、サージ工程において、血漿の供給速度を１０～９０ml／min とすることにより、血小板の浮上を最適に調整し、よって、白血球の除去率が極めて高い高品質の血小板製剤が得られる。しかも、光学センサー６１により、分離された血液成分の界面を検出し、それに基づいて血漿供給の開始（血液供給の終了）のタイミングを制御するため、自動化とともにより高精度の制御が可能となり、血小板の回収率および回収された血小板中の白血球の除去率がさらに向上する。このようなことから、該血小板製剤を用いた場合、肝炎、エイズ、ＧＶＨＤ等の感染をより高い確率で防止することができ、安全性が高い。また、サージ工程が１回でよいため、全体の処理時間を短縮することができる。
【００７８】図４は、本発明の血液成分分離装置の第２実施例の構成を模式的に示す平面図である。同図に示す血液成分分離装置１Ｂは、第３のライン８の構成が異なる以外は、前記血液成分分離装置１Ａと同様である。
【００７９】血液成分分離装置１Ｂにおいて、バフィーコートバッグ２５には、２本のチューブ２６、２７の一端が接続されている。チューブ２６の他端は、前記と同様、分岐コネクタ２８を介してチューブ１４の途中に接続されており、チューブ２７の他端は、分岐コネクタ２

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９を介してチューブ１３のポンプ９１と流入口４３との間に接続されている。また、チューブ２６の途中には、チューブ２６内の流路を開閉するバルブ８７が設置されている。これらのチューブ２６、２７および分岐コネクタ２８、２９により第３のラインが構成されている。

【００８０】このような血液成分分離装置１Ｂを用いた血小板採取方法は、次の通りであり、工程［１２ａ］以外は、基本的に前記血液成分分離装置１Ａによる血小板採取方法と同様である。

【００８１】［１ｂ］～［１１ｂ］　チューブ２７をクレンメで閉塞した状態で、前記［１ａ］～［１１ａ］と同様の工程を行う。

【００８２】［１２ｂ］　ポンプ９１の作動（正転）下で、バルブ８３および８６を開放、その他のバルブを閉鎖した状態とする。さらに、チューブ２７のクレンメによる閉塞を解除し、バフィーコートバッグ２５を高所へ置き、かつそのチューブ２６の接続側端部を下方へ向け、落差によりバフィーコートバッグ２５内の洗浄液をチューブ２７を介して第１のライン２へ供給する。これにより、洗浄液は、分岐コネクタ２９内において、ポンプ９１より送液されて来る血液と混合され、チューブ１３、流入口４３および管体４１を介して貯血空間６４へ移送される。

【００８３】［１３ｂ］～［２０ｂ］　チューブ２７をクレンメで再び閉塞した状態で、前記［１３ａ］～［２０ａ］と同様の工程を行う。

【００８４】このような血小板採取方法では、工程［１２ｂ］における洗浄液（血小板を含む）の返送を、血液貯留部１０６からローター４２内への血液の移送を停止することなく行うことができるので、全体の処理時間を短縮することができるという利点がある。

【００８５】図５は、本発明の血液成分分離装置の第３実施例の構成を模式的に示す平面図である。同図に示す血液成分分離装置１Ｃは、ポンプ９１の位置が異なる以外は、前記血液成分分離装置１Ｂと同様である。

【００８６】すなわち、血液成分分離装置１Ｃにおいて、ポンプ９１は、チューブ１３の分岐コネクタ２９と流入口４３との間に設置されている。このような血液成分分離装置１Ｃを用いた血小板採取方法は、次の通りである。各工程におけるバルブ８３～８７、ローター４２およびポンプ９１の作動状態を、下記表２に示し、該表２を参照しつつ説明する。

【００８７】

【表２】

表　２　　（血液成分分離装置１Ｃ）

工　程	バルブ開閉パターン	バルブ 83	84	85	86	87	ローター 42	ポンプ 91
[1c] [2c]	(1)	○	×	○	×	×	回転	正転
[3c]	(2)	○	×	×	○	×	回転	正転
[4c]	(3)	○	×	×	×	○	回転	正転
[5c]	(4)	○	×	○	×	×	停止	逆転
[6c]	(5)	×	○	×	○	×	停止	正転
[7c] [8c]	(6)	○	×	○	×	×	停止	逆転
[9c] [10c]	(8)	○	×	×	○	×	回転	正転
[11c]	(9)	○	×	×	×	○	回転	正転
[12c]	(10)	○	×	×	○	×	回転	正転
[13c]	(11)	×	○	○	×	×	回転	正転
[14c]	(12)	○	×	×	○	×	回転	正転
[15c]	(13)	×	○	○	×	×	回転	正転
[16c]	(14)	○	×	×	○	×	停止	逆転
[17c]	(15)	×	○	×	○	×	停止	正転
[18c]	(16)	○	×	○	×	×	停止	逆転

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バルブ×：閉鎖　　ポンプ逆転：液の流れは血液貯留部方向

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【００８８】［１ｃ］～［８ｃ］　チューブ２７をクレンメで閉塞した状態で、前記［１ａ］～［８ａ］と同様の工程を行う。

【００８９】［９ｃ］　回転駆動装置５を作動してローター４２を所定の回転数で回転するとともに、クレンメによるチューブ１０３の閉塞を解除し、バルブ開閉パターンを表２中の（８）とし、ポンプ９１を前記工程［１ａ］と同条件で作動（正転）する。これにより、血液バッグ１０５内の血液は、チューブ１０３、１０１および１３を介して移送され、遠心ボウル４の流入口４３より管体４１を経てローター４２内に導入され、貯血空間４６において血液が内層より血漿層３１、バフィーコート層３２および赤血球層３３に分離される。

【００９０】［１０ｃ］　前記工程［９ｃ］と同時に、バフィーコートバッグ２５のチューブ２６の接続側端部を下方へ向けた状態で、チューブ２７のクレンメによる閉塞を解除する。これにより、バフィーコートバッグ２５内に貯留されているバフィーコートは、ポンプ９１の作動によりチューブ２７を介して第１のライン２へ供給され、分岐コネクタ２９内において、血液貯留部１０６側から送液されて来る血液と混合され、チューブ１３、流入口４３および管体４１を介して貯血空間６４へ移送され、遠心分離に供される。バフィーコートバッグ２５からバフィーコートのほぼ全量が排出されたら、再びチューブ２７をクレンメで閉塞する。

【００９１】貯血空間４６においては、血液バッグ１０５からの血液とバフィーコートバッグ２５からのバフィーコートとが混合され、遠心分離が施されるが、分離されたバフィーコート層３２は、複数回の採血に相当する複数の血液バッグ（図示の構成では血液バッグ１０４、１０５）内の合計の血液より得られる量のバフィーコートで構成されるため、その層厚が厚くなり、サージ工程において、血小板の浮上、濃縮がより明確に行われ、血小板の収率および回収された血小板中の白血球の除去率が向上する。

【００９２】［１１ｃ］　流出口４４より血漿が流出したら、バルブ開閉パターンを（９）とする。これにより、流出口４４より流出した血漿が、チューブ１４、２６を介してバフィーコートバッグ２５内に導入され、チューブ１４、２６の流路およびバフィーコートバッグ２５の内部が洗浄される。このとき、バフィーコートバッグ２５を揺動させると、その内部の洗浄効果が高まり、好ましい。

【００９３】［１２ｃ］　バフィーコートバッグ２５のチューブ２６の接続側端部を下方へ向けた状態で、バルブ開閉パターンを（10）とし、再びクレンメによるチューブ２７の閉塞を解除する。これにより、バフィーコートバッグ２５内等の洗浄に供された血漿（洗浄液）が、前記工程［１０ｃ］と同様の経路で貯血空間４６内に戻される。

【００９４】このような、バフィーコートバッグ２５内等の洗浄およびその洗浄液の貯血空間４６への回収を行うことにより、血小板をバフィーコートバッグ２５内等に残存せず、血小板の収率が向上する。

【００９５】［１３ｃ］～［２０ｃ］　チューブ２７をクレンメで再び閉塞した状態で、前記［１３ａ］～［２０ａ］と同様の工程を行う。

【００９６】このような血小板採取方法では、工程［１０ｃ］におけるバフィーコートの返送および工程［１２ｃ］における洗浄液（血小板を含む）の返送を、血液貯留部１０６からローター４２内への血液の移送中に行うことができ、特に、バフィーコートおよび洗浄液の返送をポンプ９１の駆動により確実かつ迅速に行うことができるので、全体の処理時間をさらに短縮することができる。

【００９７】図６は、本発明の血液成分分離装置の第４実施例の構成を模式的に示す平面図である。同図に示す血液成分分離装置１Ｄは、チューブ２７の途中にポンプ９２を設置した以外は、前記血液成分分離装置１Ｂと同様である。ポンプ９２としては、例えばローラポンプが用いられ、図２中の制御手段７によりその駆動が制御される。このポンプ９２は、一方向のみ回転可能なものであればよい。この構成では、ポンプ９２が停止しているときには、チューブ２７の流路は、閉塞されているが、チューブ２７の途中に別途前記と同様のバルブ（図示せず）を設けてもよい。

【００９８】このような血液成分分離装置１Ｄを用いた血小板採取方法は、次の通りである。各工程におけるバルブ８３～８７、ローター４２およびポンプ９１、９２の作動状態を、下記表３に示し、該表３を参照しつつ説明する。

【００９９】

【表３】

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表　３　　（血液成分分離装置１Ｄ）

工　程	バルブ開閉パターン	バルブ 83	84	85	86	87	ローター 42	ポンプ 91	ポンプ 92
［１ｄ］［２ｄ］	(1)	○	×	○	×	×	回転	正転	停止
［３ｄ］	(2)	○	×	×	○	×	回転	正転	停止
［４ｄ］	(3)	○	×	×	×	○	回転	正転	停止
［５ｄ］	(4)	○	×	○	×	×	停止	逆転	停止
［６ｄ］	(5)	×	○	×	○	×	停止	正転	停止
［７ｄ］［８ｄ］	(6)	○	×	○	×	×	停止	逆転	停止
［９ｄ］［10ｄ］	(8)	○	×	×	○	×	回転	正転	正転
［１１ｄ］	(9)	○	×	×	×	○	回転	正転	停止
［１２ｄ］	(10)	○	×	×	○	×	回転	正転	正転
［１３ｄ］	(11)	×	○	○	×	×	回転	正転	停止
［１４ｄ］	(12)	○	×	×	○	×	回転	正転	停止
［１５ｄ］	(13)	×	○	○	×	×	回転	正転	停止
［１６ｄ］	(14)	○	×	×	○	×	停止	逆転	停止
［１７ｄ］	(15)	×	○	×	○	×	停止	正転	停止
［１８ｄ］	(16)	○	×	○	×	×	停止	逆転	停止

バルブ○：開放　　ポンプ正転：液の流れは遠心ボウル方向
バルブ×：閉鎖　　ポンプ逆転：液の流れは血液貯留部方向

【０１００】［１ｄ］～［８ｄ］　ポンプ９２を停止した状態で、前記［１ａ］～［８ａ］と同様の工程を行う。

【０１０１】［９ｄ］　回転駆動装置５を作動してローター４２を所定の回転数で回転するとともに、クレンメによるチューブ１０３の閉塞を解除し、バルブ開閉パターンを表３中の（８）とし、ポンプ９１を前記工程［１ａ］と同条件で作動（正転）する。これにより、血液バッグ１０５内の血液は、チューブ１０３、１０１および１３を介して移送され、遠心ボウル４の流入口４３より管体４１を経てローター４２内に導入され、貯血空間４６において血液が内層より血漿層３１、バフィーコート層３２および赤血球層３３に分離される。

【０１０２】［１０ｄ］　前記工程［９ｄ］と同時に、バフィーコートバッグ２５のチューブ２６の接続側端部を下方へ向けた状態で、ポンプ９２を作動（正転）する。これにより、バフィーコートバッグ２５内に貯留されているバフィーコートは、チューブ２７を介して第１のライン２へ供給され、分岐コネクタ２９内において、血液貯留部１０６側から送液されて来る血液と混合され、チューブ１３、流入口４３および管体４１を介して貯血空間６４へ移送され、遠心分離に供される。バフィーコートバッグ２５からバフィーコートのほぼ全量が排出されたら、ポンプ９２を停止する。

【０１０３】［１１ｄ］　流出口４４より血漿が流出したら、まず、バルブ開閉パターンを（９）とする。これにより、流出口４４より流出した血漿が、チューブ１４、２６を介してバフィーコートバッグ２５内に導入され、チューブ１４、２６の流路およびバフィーコートバッグ２５の内部が洗浄される。このとき、バフィーコートバッグ２５を揺動させると、その内部の洗浄効果が高まり、好ましい。

【０１０４】［１２ｄ］　バフィーコートバッグ２５のチューブ２６の接続側端部を下方へ向けた状態で、バルブ開閉パターンを（10）とし、ポンプ９２を作動（正転）する。これにより、バフィーコートバッグ２５内等の洗浄に供された血漿（洗浄液）が、前記工程［１０ｄ］と同様の経路で貯血空間４６内に戻される。このような操作により、前記と同様、血小板が回路に残存せず、その収率が向上する。

【０１０５】［１３ｄ］～［２０ｄ］　ポンプ９２を停止した状態で、前記［１３ａ］～［２０ａ］と同様の工程を行う。

【０１０６】このような血小板採取方法では、工程［１

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０ｄ］におけるバフィーコートの返送および工程［１２ｄ］における洗浄液（血小板を含む）の返送を、血液貯留部１０６からローター４２内への血液の移送中に行うことができ、特に、バフィーコートおよび洗浄液の返送をポンプ９２の駆動により確実かつ迅速に行うことができるので、全体の処理時間をさらに短縮することができる。

【０１０７】なお、血液成分分離装置１Ｄにおいて、チューブ２０の一端を分岐コネクタ１２と接続せず、図示しない分岐コネクタを用いてチューブ２７の途中に接続した構成としてもよい。次に、本発明を具体的実施例に基づいてさらに詳細に説明する。

【０１０８】（実施例１）図１および図２に示す構成の血液成分分離装置１Ａを用い、前述した工程［１ａ］～［２０ａ］により、貯血量４００mlの血液バッグ５個に対し血液処理を行い、血小板製剤の作製を行った。各工程での条件を下記表４に示す。

【０１０９】

【表４】

表　４

使用血液	ヘマトクリット値　４８．４　％		
	血小板数　２７×１０⁴　個／μｌ		
	合計処理量　２０００　ｍｌ		
ローター回転数	工程	［１ａ］～［４ａ］	４８００　rpm
		［９ａ］～［１４ａ］	４８００　rpm
		［１５ａ］	４８００　rpm
ポンプ91吐出量	工程	［１ａ］～［７ａ］	６０　ｍｌ／分
		［９ａ］～［１４ａ］	６０　ｍｌ／分
		［１５ａ］（２０秒）	４０　ｍｌ／分
		［１５ａ］（８０秒）	１４　ｍｌ／分
		［１６ａ］～［１８ａ］	８０　ｍｌ／分

【０１１０】（実施例２）図５および図２に示す構成の血液成分分離装置１Ｃを用い、前述した工程［１ｃ］～［２０ｃ］により、貯血量４００mlの血液バッグ５個に対し血液処理を行い、血小板製剤の作製を行った。対応する各工程での条件は、上記表４に示す条件と同様とした。

【０１１１】（実施例３）図６および図２に示す構成（ただし、ポンプ９２は制御手段７に接続）の血液成分分離装置１Ｄを用い、前述した工程［１ｄ］～［２０ｄ］により、貯血量４００mlの血液バッグ５個に対し血液処理を行い、血小板製剤の作製を行った。対応する各工程での条件を上記表５に示す条件と同様とした。

【０１１２】

【表５】

表　５

使用血液	ヘマトクリット値　４８．４　％		
	血小板数　２７×１０⁴　個／μｌ		
	合計処理量　２０００　ｍｌ		
ローター回転数	工程	［１ｄ］～［４ｄ］	４８００　rpm
		［９ｄ］～［１４ｄ］	４８００　rpm
		［１５ｄ］	４８００　rpm
ポンプ91吐出量	工程	［１ｄ］～［７ｄ］	６０　ｍｌ／分
		［９ｄ］～［１４ｄ］	６０　ｍｌ／分
		［１５ｄ］（２０秒）	４０　ｍｌ／分
		［１５ｄ］（８０秒）	１４　ｍｌ／分
		［１６ｄ］～［１８ｄ］	８０　ｍｌ／分
ポンプ92吐出量	工程	［９ｄ］～［１０ｄ］	６０　ｍｌ／分
		［１２ｄ］	６０　ｍｌ／分

【０１１３】（比較例）図１に示す装置において、バフィーコートバッグ２５および第３のライン８を有さない構成の回路を用い、貯血量４００mlの血液バッグ５個のそれぞれを処理する毎に、サージ工程を行い、サージ５回分の血小板を集め血小板製剤とした。なお、各サージ工程における血漿供給は、ポンプ吐出量（血漿供給速度）２２０ml／min で４０秒とした。

【０１１４】［評価］実施例１～３および比較例で得られた血小板製剤について、回収量、血小板数、白血球数、血小板回収率および処理時間を求めた。その結果を下記表６に示す。なお、血小板数は、血球計数装置（東亜電子社製、Sysmex K-2000 型）を用いてカウントし、白血球数は、Negeotteチャンバー法により測定した。

【０１１５】

【表６】

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表　６

	実施例１	実施例２	実施例３	比較例
濃厚血小板血漿回収量（ｍｌ）	２１０	２２０	２１５	２３０
血小板数　（個／μｌ）	150×10^4	167×10^4	163×10^4	122×10^4
白血球数　（個／μｌ）	５００	６００	３００	１１００
血小板回収率　（％）	５８．０	６８．０	６５．０	５２．０
合計処理時間　（分）	６４	６２	５９	６７

【０１１６】上記表６に示すように、実施例１～３は、比較例に比べ、いずれも、血小板の回収率および回収された血小板中の白血球の除去率が高く、しかも、合計処理時間も短い。

【０１１７】以上、本発明を各実施例に基づいて説明したが、本発明の装置および方法に用いられる回路構成等は、図示のものに限定されず、例えば、前記第４のライン１０は、供血者の血管に穿刺する穿刺針を有する脱・返血ラインであってもよい。また、前記血漿回収用分岐ラインおよび前記血小板回収用分岐ラインのいずれか一方がない構成であってもよい。また、バルブのような流路開閉手段が、チューブ１３または２４の途中に設けられていてもよい。また、第２のライン３または第４のライン１０にポンプが設けられていてもよい。

【０１１８】なお、バフィーコートを一旦貯留する容器は、図示のごときバッグに限らず、例えばボトルのような硬質の容器であってもよい。また、本発明の血小板採取方法において、上記各工程のうちの所定の工程の順序が異なっていてもよく、任意の工程が追加されてもよく、また所定の工程（例えば、バフィーコートバッグの洗浄および洗浄液の返送工程）が省略されていてもよい。

【０１１９】バフィーコートバッグ等の洗浄は、別途容易された例えば生理食塩水等の洗浄液により行ってもよい。この場合、予め洗浄液が貯留された容器がバフィーコートバッグに連通するよう例えば第３のラインの途中に接続されていてもよい。なお、本発明の血液成分分離装置および血小板採取方法は、前述した血小板製剤の製造に使用される場合に限らないことは、言うまでもない。

【０１２０】

【発明の効果】以上述べたように、本発明の血液成分分離装置および血小板採取方法によれば、複数の血液成分への分離および血液成分の移送を行うに際し、より高精度の分離、移送が可能となり、特に、成分採血に適用した場合、血小板の回収率が高く、回収された血小板中の白血球（特にリンパ球）の除去率が極めて高い高品質の血液製剤が得られる。その結果、肝炎、エイズ、ＧＶＨＤ等の感染をより高い確率で防止することができ、安全性が高い。また、本発明では、血小板の回収を一度で行うため、全体の処理時間を短縮することができる。

【０１２１】また、第４工程において、貯血空間の下方より血漿を供給して血小板を浮上させて回収する方法を採用した場合、特に血漿供給速度を１０～９０ml／minとした場合には、血小板の回収率および白血球の除去率がさらに向上する。また、バフィーコートを貯留する容器を洗浄し、その洗浄に供された液を貯血空間に戻す場合には、血小板が残存せず、血小板の回収率がさらに向上する。

【図面の簡単な説明】

【図１】本発明の血液成分分離装置の第１実施例の構成を模式的に示す平面図である。

【図２】本発明の血液成分分離装置の制御系を示すブロック図である。

【図３】本発明における遠心ボウルおよび回転駆動装置の構成例を示す部分断面正面図である。

【図４】本発明の血液成分分離装置の第２実施例の構成を模式的に示す平面図である。

【図５】本発明の血液成分分離装置の第３実施例の構成を模式的に示す平面図である。

【図６】本発明の血液成分分離装置の第４実施例の構成を模式的に示す平面図である。

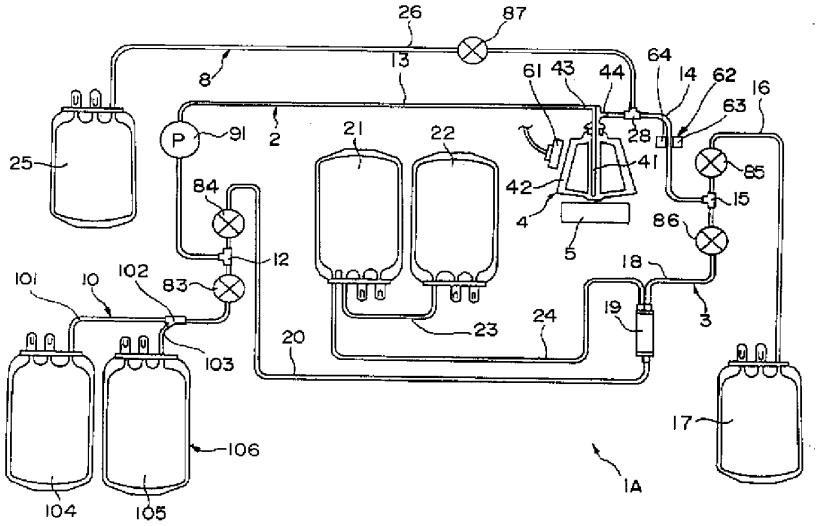
【符号の説明】

１Ａ～１Ｄ	血液成分分離移送装置
２	第１のライン
３	第２のライン
４	遠心ボウル
４１	管体
４２	ローター
４３	流入口
４４	流出口
４５	上部
４６	貯血空間
４７、４８	流路

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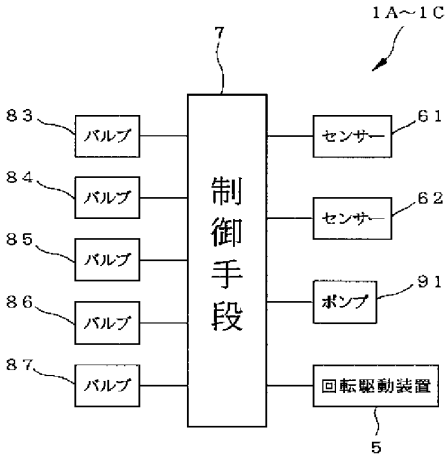
５	回転駆動装置
５１	ハウジング
５２	脚部
５３	モータ
５４	回転軸
５５	固定台
５５１	凹部
５６	ボルト
５７	スペーサー
５８	取付部材
６１、６２	光学センサー
６３	投光部
６４	受光部
７	制御手段
８	第３のライン
８３～８７	バルブ
９１、９２	ポンプ
１０	第４のライン
１０１	チューブ
１０２	分岐コネクタ
１０３	チューブ
１０４、１０５	血液バッグ
１０６	血液貯留部
１２	分岐コネクタ
１３、１４	チューブ
１５	分岐コネクタ
１６	チューブ
１７	血小板バッグ
１８	チューブ
１９	チャンバー
２０	チューブ
２１	血漿バッグ
２２	空気貯留バッグ
２３、２４	チューブ
２５	バフィーコートバッグ
２６、２７	チューブ
２８、２９	分岐コネクタ
３１	血漿層
３２	バフィーコート層
３３	赤血球層
Ｂ	界面

【図１】

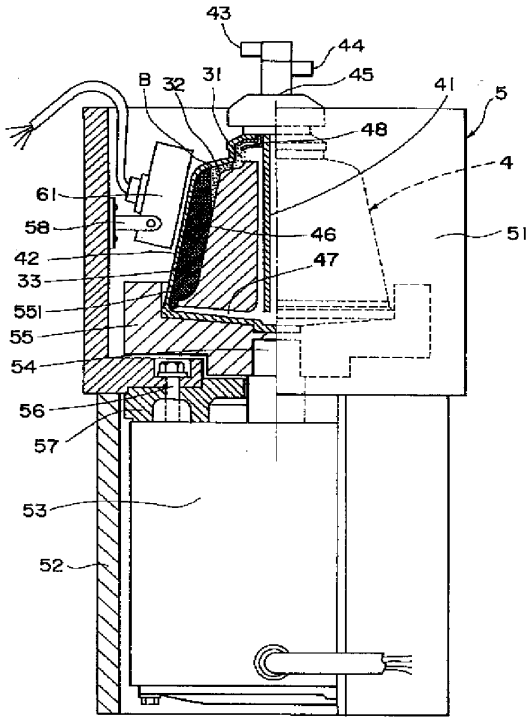


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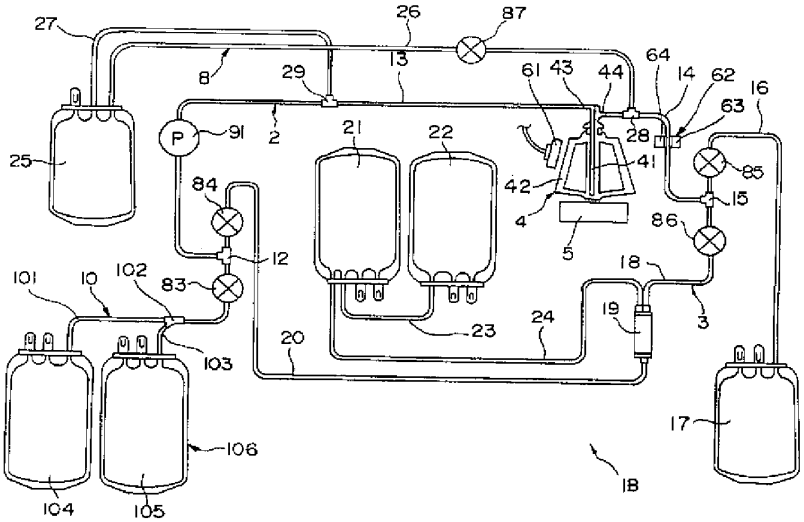
【図２】



【図３】

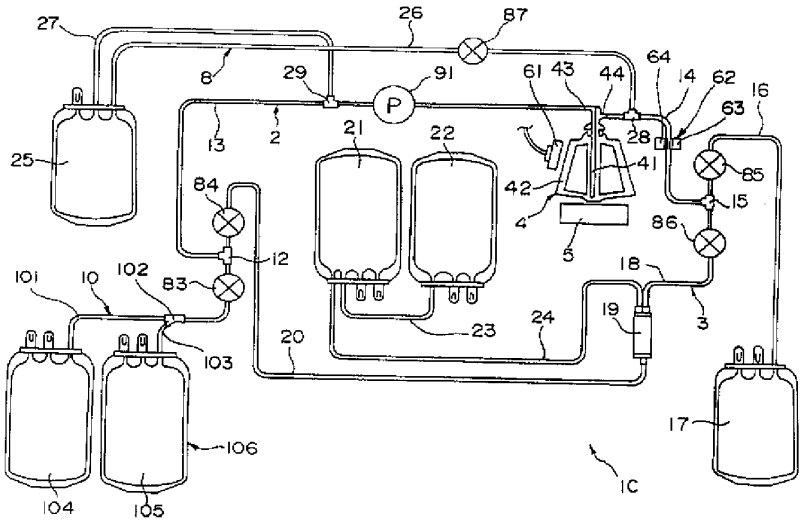


【図４】

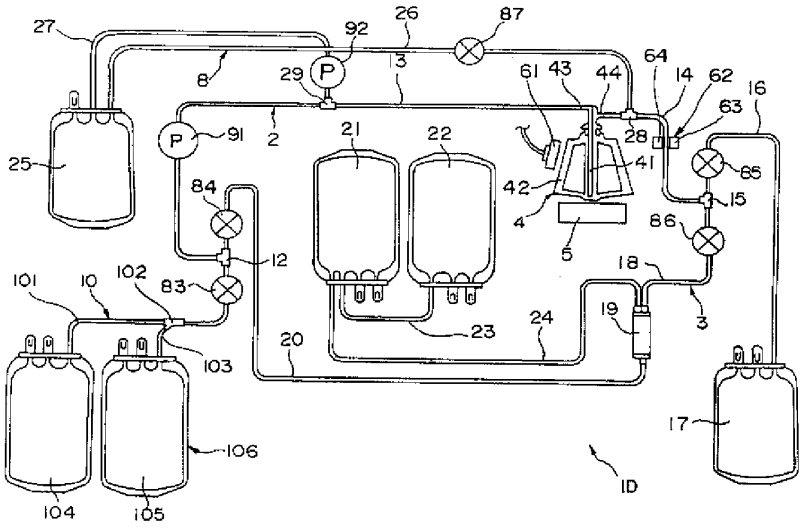


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【図５】



【図６】



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Petitioner Terumo Exhibit 1021-0560

Espacenet

Bibliographic data: JPH09192215 (A) — 1997-07-29

CENTRIFUGAL BOWL

Inventor(s): NAKANE TAKAHARU ± (NAKANE TAKAHARU)

Applicant(s): NAKANE TAKAHARU ± (NAKANE TAKAHARU)

Classification: **- international:*A61M1/02; B04B5/04;*** (IPC1-7): A61M1/02
- cooperative: **A61M1/3693**; **A61M1/3696**; **B04B5/0442**; A61M2202/0415; A61M2202/0429; B04B2005/0464

Application number: JP19960024587 19960117

Priority number (s): JP19960024587 19960117

Abstract of JPH09192215 (A)

PROBLEM TO BE SOLVED: To provide a centrifugal bowl for use in an intermittent blood flow centrifugal type blood component separating device, in which out-of-body circulation time is reduced along with the amount of blood that circulates outside the body and measures are taken to prevent leakage from a rotary seal member. SOLUTION: Inside a centrifugal bowl 1B, a first sampling space 53 into which erythrocytes flow, a second sampling space 52 into which plasmas flow, and a third sampling space 54B into which buffy coats flow are provided in positions oriented to a rotation axis P1 from a separating space 51, and are communicated to the separating space 51 so that the erythrocytes, the plasmas, and the buffy coats are sampled separately without stopping of rotation of the centrifugal bowl 1B. Also, compressed, sterilized air is supplied to a supply port provided in a port member 5B, so as to force leaks from mechanical seal 9 out from inside a centrifugal bowl main body.

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Ａ６１Ｍ　1/02	５２０		Ａ６１Ｍ　1/02	５２０	

審査請求　未請求　請求項の数５　ＦＤ　（全 17 頁）

(21)出願番号　特願平8－24587

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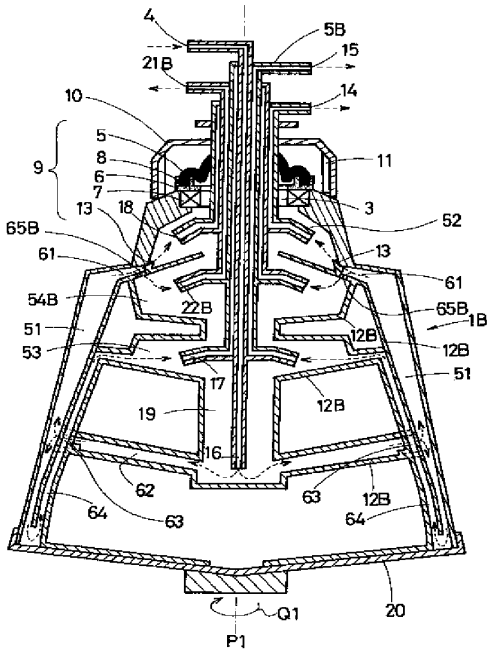
(74)代理人　弁理士　富澤　孝　（外２名）

(54)【発明の名称】　遠心ボウル

(57)【要約】

【課題】　間欠血流遠心方式の血液成分分離装置で使用する遠心ボウルにおいて、体外循環時間を短縮するとともに体外循環血液量を少なくし、また、回転シール部材の漏洩対策がなされた遠心ボウルを提供すること。

【解決手段】　遠心ボウル１Ｂの内部において、赤血球１０１が流入する第１採取空間５３と、血漿１０２が流入する第２採取空間５２と、バフィーコート１０３が流入する第３採取空間５４Ｂとを、分離空間５１から回転軸Ｐ１に向かった位置に設け、分離空間５１と連通させることにより、遠心ボウル１Ｂの回転を停止することなく、赤血球１０１、血漿１０２、バフィーコート１０３を分離採取する。また、ポート部材５Ｂに設けられた供給ポート１４０に加圧滅菌空気を供給して、メカニカルシール９における漏れを、遠心ボウル本体２の内部から外部に向かって流出させる。



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【特許請求の範囲】
【請求項１】　上側に向かって次第に狭くなる中空状の遠心ボウル本体の頂部に、前記遠心ボウル本体の軸線と同心である開口を設け、流入ポートを設けたポート部材を前記開口から前記遠心ボウル本体の内部に遊挿して回転シール部材で取り付けることにより、前記遠心ボウル本体を密封しながら前記軸線を回転軸として回転させ、前記軸線と平行若しくは上側に向かって漸近する面と前記遠心ボウル本体の内周面とで形成される分離空間に、前記分離空間と流通する前記流入ポートから流入する血液を、前記分離空間で遠心力により比重の異なる血液成分に分離する遠心ボウルにおいて、
前記遠心ボウル本体に、前記流入ポートが前記分離空間に流通する位置の下側から前記軸線に向かって前記分離空間と連通する第１採取空間と、前記開口に隣接するとともに前記分離空間の上側から前記軸線に向かって前記分離空間と連通する第２採取空間とを形成し、
前記ポート部材に、前記第１採取空間と流通する第１流出ポートと、前記第２採取空間と流通する第２流出ポートとを設けることにより、
前記遠心ボウルを回転させている間に、前記分離空間の下側に滞留する比重の重い第１血液成分を、前記第１採取空間を介して前記第１流出ポートから流出させる一方、前記分離空間の上側に滞留する比重の軽い第２血液成分を、前記第２採取空間を介して前記第２流出ポートから流出させることを特徴とする遠心ボウル。
【請求項２】　請求項１に記載する遠心ボウルにおいて、
前記分離空間と前記第２採取空間とは前記軸線の方向に狭いチャンネルを介して連通されており、前記チャンネルの下側において形成された間隙により、前記分離空間の上側から前記軸線に向かって前記分離空間と連通する第３採取空間を前記遠心ボウル本体に形成し、
前記ポート部材に、前記第３採取空間と流通する第３流出ポートを設けることにより、
前記遠心ボウルを回転させている間に、前記第２血液成分の次に比重が軽い第３血液成分を、前記間隙から前記第３採取空間に流入させて前記第３流出ポートから流出させることを特徴とする遠心ボウル。
【請求項３】　請求項１または２に記載する遠心ボウルにおいて、
コア部材を前記遠心ボウル本体に内装することにより、前記分離空間、前記第１採取空間、前記第２採取空間、前記第３採取空間、及び前記チャンネルを形成し、前記コア部材は前記遠心ボウル本体と一体となって回転することを特徴とする遠心ボウル。
【請求項４】　請求項１、２、または３に記載するいずれか１つの遠心ボウルにおいて、
前記ポート部材に前記第２採取空間と流通する供給ポートを設けることにより、
前記供給ポートから前記第２採取空間に加圧空気が供給されることを特徴とする遠心ボウル。
【請求項５】　請求項４に記載する遠心ボウルにおいて、
前記回転シール部材がメカニカルシールであることを特徴とする遠心ボウル。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】本発明は、間欠血流遠心方式の血液成分分離装置に使用する遠心ボウルに関し、さらに詳細には、体外循環時間を短縮するとともに体外循環血液量を少なくし、また、回転シール部材の漏洩対策がなされた遠心ボウルに関するものである。
【０００２】
【従来の技術】以前、輸血は血液を漫然と輸血する形で施行されてきた。しかし、現在においては、真に患者が必要とする血液成分のみを与え、不要な血液成分はなるべく与えない成分輸血が急速に発展している。その血液成分とは、基質となる血漿と細胞成分の血球とに大別され、さらに、かかる血球は、赤血球、白血球および血小板に区別される。成分輸血が急速に発展してきた理由には、患者に不要な血液成分を輸注して臓器に負担をかけたり、副作用を起こしたり、新しい抗体が産出されたりすることを防止するという医学的要請等による。かかる成分輸血を施行するためには、必要とされる血液成分を血液から選択的に分離する「血液成分分離」を行なわなければならない。
【０００３】現在における「血液成分分離」では、供血者から血液を採血し、採血した血液から必要とされる血液成分のみを分離採取し、残りの血液を同一の供血者に返血している。一般に、供血者から採血される血液の大部分（例えば、赤血球を含んだ血漿）は返血されることから、採血された血液の全てを提供する「献血」と比べて、供血者にかかる負担は少ない。採血・分離採取・返血の一連の動作からなる「血液成分分離」は、種々の血液成分分離装置により約３０分から９０分かけて行なわれている。
【０００４】かかる血液成分分離装置は、血液の成分を分離する方式によりいくつかに分類することができるが、その中の一つに、間欠血流遠心方式の血液成分分離装置がある。供血者の片側の静脈を確保して、一定量の血液を抗凝固剤を混合しながら採血し、採血された血液を遠心分離により必要とされる血液成分を採取した後に、残りの血液を返血する操作を交互に６～８回繰り返す方式で、いわゆるバッチ方式と呼ばれるものである。以下に、間欠血流遠心方式の血液成分分離装置の原理について、図面を用いて簡単に説明する。
【０００５】図１０、１１に、間欠血流遠心方式の血液成分分離装置１５０における、乏血小板血漿（少量の血小板を含んだ血漿）を分離採取する際のフロー図を示

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す。図１０は採血（及び分離採取）時のものであり、図１１は返血時のものである。尚、かかる血液成分分離装置１５０のモーターや開閉弁等の一連の操作はマイクロコンピュータにより制御されるが、自動制御に関する記述等は説明の便宜上省略する。

【０００６】採血（及び分離採取）時において、採血針１５１を介して供血者の静脈から採られたばかりの血液は、採血針１５１を離れるとすぐに抗凝固処理される。抗凝固処理は、容器１５２に入っている抗凝固剤１５３が、ローラー形の抗凝固剤用ポンプ１５４の回転によって、除菌フィルター１６６を介して容器１５２に接続されている管１５５を通り、採血針１５１に供給されることにより行なわれる。抗凝固処理された血液は、静脈圧力により管１５６を通って、気泡検出室１５７の底部に流れ込む。

【０００７】そして、気泡検出室１５７を満たした血液は、ローラー形の血液用ポンプ１５８の回転により管１５９、１６０を通って、遠心ボウル１６１の流入ポート１８１（図１２、１３、１４参照）に送られる。血液が送られた遠心ボウル１６１は、図示しないモーターにより回転する。この回転により、遠心ボウル１６１内の血液は遠心分離されて、乏血小板血漿と非乏血小板血漿（赤血球等を多量に含んだ血漿）とに分けられる。分離された乏血小板血漿は、周辺ポート１８２（図１２、１３、１４参照）から流出され、管１６２、１６３を通って、血漿用容器１６４に送られる。

【０００８】ここで、血液成分分離装置１５０に使用される遠心ボウル１６１の構造について、図面を用いて簡単に説明する。図１２に遠心ボウル１６１の外観図を示す。また、図１３に遠心ボウル１６１の断面図を示す。

【０００９】血液が送られる流入ポート１８１を設けたポート部材１８０には、そのほかに周辺ポート１８２と上部スカート１８３が設けられている。また、ポート部材１８０には供給管ステム１８４が挿嵌されており、ポート部材１８０の内部は二重管の構造となっている。かかる二重管の構造では、（供給管ステム１８４の）内側は流入ポート１８１と連通しており、（供給管ステム１８４の）外側は周辺ポート１８２と連通している。また、下部スカート１８５が供給管ステム１８５に嵌挿されて、上部スカート１８３との間に周辺ポート１８２と連通する採取口１８６を形成している。一方、中空状の遠心ボウル本体１８７の頂部には、遠心ボウル本体１８７の軸線Ｐ２と同心である開口２００が設けられており、かかる開口２００にポート部材１８０が遊挿されて、供給管ステム１８５と採取口１８６が遠心ボウル本体１８７の内部に位置している。

【００１０】かかる遠心ボウル本体１８７は、上側に向かって次第に狭くなる所謂円錐台の形状をしており、その遠心ボウル本体１８７の内部には、同じく円錐台の形状をした上部コア１８８が内装されて、遠心ボウル本体１８７の内周面と上部コア１８８の外周面との間に分離空間２０１を形成し、さらに、遠心ボウル本体１８７の開口２００と上部コア１８８の頂部との間に採取空間２０２を形成している。かかる採取空間２０２に、上述した採取１８６が介在することにより、周辺ポート１８２と採取空間２０２とが流通する。また、上部コア１８８の頂部中央に形成された遊挿口に下部コア１８９の円管部１８９Ａを嵌着し、上部コア１８８の下側端部に下部コア１８９の円板部１８９Ｂを嵌着することにより、上部コア１８８と下部コア１８９とを一体化している。かかる下部コア１８９の円管部１８９Ａには、上述した供給管ステム１８５が挿入されており、下部コア１８９の円管部１８９Ａの内部も二重管の構造をしている。

【００１１】そして、遠心ボウル本体１８７の下側に底部材１９０を固着することにより、上部コア１８８の頂部に形成された数個の爪部１８８Ａを遠心ボウル本体１８７の内側に当接させ、上部コア１８８の下側端部に形成された数個の爪部１８８Ｂを底部材１９０の上側に当接させて、一体化された上部コア１８８と下部コア１８９とを、遠心ボウル本体１８７の内部において固定している。これにより、下部コア１８９の円板部１８９Ｂの下側と底部材１８３の上側との間に底部チャンネル２０３が形成され、遠心ボウル本体１８７の頂部と上部コア１８８の頂部との間に採取チャンネル２０４が形成されている。

【００１２】ポート部材１８０と遠心ボウル本体１８７との装着に用いられる回転シール部材は、弾性ベローズ１９１、カーボンリング１９２、セラミック環１９３および押えリング１９４からなるメカニカルシール１９５が用いられ、矢印Ｑ２の方向に軸Ｐ２を回転軸として回転可能に取り付けられている。尚、遠心ボウル１６１が回転する時は、管１６０等が接続されるポート部材１８０等は血液成分分離装置１５０に固定されており、血液が流入する遠心ボウル本体１８７や上部コア１８８等が回転する。

【００１３】血液成分分離装置１５０においては、血液を採血時の状態で維持するために、遠心ボウル本体１８７の内部を密封することにより、空気の漏洩を最小に防ぐ必要があるが、遠心ボウル１６１（即ち、メカニカルシール１９５）に関しては、以下のようにして、空気の漏洩を最小に防いでいる。

【００１４】遠心ボウル１６１が血液成分分離装置１５０に装着されていない時は、弾性ベローズ１９１によりポート部材１８０が上側に押し上げられるが、ポート部材１８０に設けられた上部スカート１８３が遠心ボウル本体１８７の内面と当接することにより、ポート部材１８０が上部へ抜けることを防止するとともに、弾性ベローズ１９１の歪んだ状態が保持されて、弾性ベローズ１９１がカーボンリング１９２をセラミック環１９３に押えつけることができ、メカニカルシール１９５の摺動面

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（カーボンリング１９２とセラミック環１９３との接触面）における、空気の漏洩を最小に防いでいる。

【００１５】一方、遠心ボウル１６１が血液成分分離装置１５０に装着されている時は、ポート部材１８０が下側に押し下げられて固定される。これにより、前者と比べてより強い弾性力をもって、弾性ベローズ１９１がカーボンリング１９２をセラミック環１９３に押えつけることができ、遠心ボウル１６１の回転時におけるメカニカルシール１９５の摺動面の空気の漏洩を最小に防いでいる。

【００１６】また、ポート部材１８０には、メカニカルシール１９５を覆うようにヘッダーシールド１９６が設けてあり、メカニカルシール１９５が外部に露出しないようにしている。また、ヘッダーシールド１９６の爪部１９６Ａが、遠心ボウル本体１８７の頂部と当接することにより、ポート部材１８０が下側に押し下げ過ぎることがないようにしている。

【００１７】次に、かかる遠心ボウル１６１によって、血液が乏血小板血漿と非乏血小板血漿とに遠心分離される原理について、図面を用いて説明する。図１４は、遠心分離の原理図である。回転している遠心ボウル１６１に、管１６０を通して流入ポート１８１に送られてきた血液は、供給管ステム１８４により底部材１９０の中央部にまで運ばれる。そして、遠心ボウル１６１の回転によって血液に遠心力が作用し、血液が底部チャンネル２０３を通って分離空間２０１に移動する。さらに、血液が遠心ボウル１６１に送り続けられると、分離空間２０１、採取チャンネル２０４、採取空間２０２等の遠心ボウル１６１の空間は、血液で満たされていく（全量２２５ｍｌ）。

【００１８】このとき、血液成分の比重の差と遠心力等から、図１４に示す相が分離空間２０１に形成される。分離空間２０１の外側には、血球の中で最も比重の重い赤血球（比重１．０９３～１．０９６）を多量に含んだ血漿（以下、単に「赤血球」という）の相２１１が形成される。赤血球の相２１１の内側には、赤血球の次に比重が重い白血球２１３が存在し、さらに、その内側には白血球の次に比重が重い血小板２１２（比重１．０４０）が存在する。

【００１９】白血球２１３と血小板２１２は、血液において占める割合が極端に低いので、赤血球の相２１１の厚さに比べて、白血球２１３または血小板２１２を多量に含んだ血漿の相の厚さは薄いため、白血球２１３および血小板２１２を多量に含んだ血漿の相２１４をまとめて「バフィーコート」と呼んで扱われることが多い。バフィーコートの相２１４の内側には、採取チャンネル２０４、採取空間２０２に渡って、血漿（比重１．０９３～１．０９６）の相２１５が形成される。

【００２０】但し、上述した相２１１、２１４、２１５の形成具合いは、血液に供給される抗凝固剤１５３の比率（以下、「抗凝固剤：血液」の比率で表記する）や遠心速度等に左右される。また、相２１１、２１４、２１５の境界が明確に形成されることはなく、例えば、血漿の相２１５における境界付近には、血小板２１２が混入している領域がかなりの幅をもって存在している。

【００２１】図１４に示すような相を分離空間２０１に形成するには、抗凝固剤１５３を１：９～１０の比率で供給し、遠心速度を４８００ｒｐｍに設定する必要があるとされる。また、乏血小板血漿と非乏血小板血漿とを分離するには、抗凝固剤１５３を１：１６の比率で供給し、遠心速度を５６５０ｒｐｍに設定する必要があるとされ、このような条件に設定すると、バフィーコートの相２１４は、赤血球を多量に含んだ血漿の相２１１に含まれる状態となり、血漿の相２１５に混入する血小板２１２がより少なくなって、血漿の相２１５を乏血小板血漿として扱うことができる。

【００２２】そして、さらに血液が遠心ボウル１６１に供給されると、分離空間２０１の上側（の内側）に滞留する血漿の相２１５の乏血小板血漿が、周辺ポート１８２から流出して血漿用容器１６４に採取される。一方、分離空間２０１の下側（の外側）に滞留する赤血球を多量に含んだ血漿の相２１１は、分離空間２０１内において体積を次第に増しながら残留する。

【００２３】その後において、赤血球を多量に含んだ血漿の相２１１が分離空間２０１を満たしたら、かかる相２１１（非乏血小板血漿であり、以下、「残留血液」という）を供血者に返血する（図１１参照）。返血時においては、遠心ボウル１６１の回転を止めるとともに、血液用ポンプ１５８の回転を反転させる。同時に、抗凝固剤用ポンプ１５４の回転を止めて、抗凝固剤１５３の供給を中止する。回転が止められた遠心ボウル１６１では、残留血液が底部に向かって貯められる。かかる残留血液が、血液用ポンプ１５８の汲み上げ作用によって、流入ポート１８１から流出して管１６０、１５９を通り、気泡検出室１５７に流入する。気泡検出室１５７においては、残留血液が沪過されるとともに、残留血液に気泡が包含されていないことを確認する。確認された残留血液は、管１５６と採血針１５１を介して、供血者に返血される。

【００２４】このようにして、間欠血流遠心方式の血液成分分離装置１５０では、断続的に血液成分の分離を行うことによって、採血と返血の操作を交互に６～８回繰り返している。ところで、遠心分離の原理を用いた血液成分分離装置装置には、間欠血流遠心方式のほかに連続血流遠心方式のものがある。連続血流遠心方式の血液成分分離装置装置では、供血者の２本の静脈を確保して、一方の静脈から採血した血液に対し連続的に血液成分の分離を行いながら他方の静脈へ返血するので、採血針と返血針の間に血液の連続流を形成する必要があり、装置の仕組みや操作が複雑になる傾向がある。即ち、間欠血

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流遠心方式の血液成分分離装置１５０は、連続血流遠心方式のものと比べて、装置の仕組みが単純であり、操作が簡便である利点を持つ。

【００２５】

【発明が解決しようとする課題】しかしながら、従来の遠心ボウル１６１を使用した間欠血流遠心方式の血液成分分離装置１５０では、以下のような問題点があった。（１）採血（及び分離採取）時においては供血者に全く返血されることがないので、返血される血液のうち、供血者から最初の頃に採血されたものについては、供血者の体外から出て再び供血者の体内に戻るまでに要する時間（以下、「体外循環時間」という）が相当に長くなり、返血される血液（ひいては、供血者）にかなりの負担をかけていた。かかる観点から言えば、採血と返血を同時に行う連続血流遠心方式の血液成分分離装置装置を使用することが望ましいが、かかる装置は仕組みや操作が複雑なので、仕組みが単純であり操作が簡便である間欠血流遠心方式の血液成分分離装置１５０において、連続的に血液成分の分離を行って採血と返血を同時に行うことができる技術の開発が待たれていた。

【００２６】（２）分離空間２０１の下側（の外側）に残留する赤血球の相２１１が、分離空間２０１内において体積を次第に増加させて、分離空間２０１の上側（の内側）に滞留する血漿の相２１５である乏血小板血漿を、分離空間２０１から周辺ポート１８２へ押し出すようにして、分離された乏血小板血漿を血漿用容器１６４に採取するので、血液中の赤血球の占める割合であるヘマトクリット値（以下、「Ｈｔ値」という）が低い供血者にとっては、血液を分離採取するために必要な供血者から採血される血液量（以下、「体外循環血液量」という）が多くなり、低体重でありＨｔ値の低い供血者にかなりの負担をかけていた。最近の装置においては、供血者安全対策の充実により、体外循環血液量をプログラムによって自動制御できるものもあるが、装置の仕組みが複雑になる上に、供血者のＨｔ値や体重等を予め計測して体外循環血液量を予測する必要があり、供血者に対する安全管理が確実であるとは言えなかった。

【００２７】（３）回転する遠心ボウル１６１を密封するために、メカニカルシール１９５により空気の漏洩を最小に防いでいたが、メカニカルシール１９５では空気の漏洩を完全に防止することはできないので、外部から菌が侵入する可能性は否定できず、また、メカニカルシール１９５が不良であるか否かは外見からは発見できない場合もあり得るので、供血者や成分輸血される者に対する安全管理が確実であるとは言えなかった。

【００２８】そこで、本発明は、上述した問題点を解決するためになされたものであり、間欠血流遠心方式の血液成分分離装置に使用する遠心ボウルにおいて、連続的に血液成分分離を行うことにより、体外循環時間を短縮するとともに体外循環血液量を少なくし、また、遠心ボウルの内圧を外圧より高圧にすることにより、回転シール部材の漏洩対策がなされた遠心ボウルを提供することを目的とする。

【００２９】

【課題を解決するための手段】この目的を達成するため本発明の遠心ボウルは、上側に向かって次第に狭くなる中空状の遠心ボウル本体の頂部に、前記遠心ボウル本体の軸線と同心である開口を設け、流入ポートを設けたポート部材を前記開口から前記遠心ボウル本体の内部に遊挿して回転シール部材で取り付けることにより、前記遠心ボウル本体を密封しながら前記軸線を回転軸として回転させ、前記軸線と平行若しくは上側に向かって漸近する面と前記遠心ボウル本体の内周面とで形成される分離空間に、前記分離空間と流通する前記流入ポートから流入する血液を、前記分離空間で遠心力により比重の異なる血液成分に分離する遠心ボウルを有する遠心ボウルであって、前記遠心ボウル本体に、前記流入ポートが前記分離空間に流通する位置の下側から前記軸線に向かって前記分離空間と連通する第１採取空間と、前記開口に隣接するとともに前記分離空間の上側から前記軸線に向かって前記分離空間と連通する第２採取空間とを形成し、前記ポート部材に、前記第１採取空間と流通する第１流出ポートと、前記第２採取空間と流通する第２流出ポートとを設けることにより、前記遠心ボウルを回転させている間に、前記分離空間の下側に滞留する比重の重い第１血液成分を、前記第１採取空間を介して前記第１流出ポートから流出させる一方、前記分離空間の上側に滞留する比重の軽い第２血液成分を、前記第２採取空間を介して前記第２流出ポートから流出させることを特徴とする。

【００３０】また、前記分離空間と前記第２採取空間とは前記軸線の方向に狭いチャンネルを介して連通されており、前記チャンネルの下側において形成された間隙により、前記分離空間の上側から前記軸線に向かって前記分離空間と連通する第３採取空間を前記遠心ボウル本体に形成し、前記ポート部材に、前記第３採取空間と流通する第３流出ポートを設けることにより、前記遠心ボウルを回転させている間に、前記第２血液成分の次に比重が軽い第３血液成分を、前記間隙から前記第３採取空間に流入させて前記第３流出ポートから流出させることを特徴とする。また、コア部材を前記遠心ボウル本体に内装することにより、前記分離空間、前記第１採取空間、前記第２採取空間、前記第３採取空間、及び前記チャンネルを形成し、前記コア部材は前記遠心ボウル本体と一体となって回転することを特徴とする。

【００３１】さらに、前記ポート部材に前記第２採取空間と流通する供給ポートを設けることにより、前記供給ポートから前記第２採取空間に加圧空気が供給されることを特徴とする。また、前記回転シール部材がメカニカルシールであることを特徴とする。

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【００３２】このような構成を有する本発明の遠心ボウルでは、遠心ボウル本体の軸線上に、回転シール部材を介して、ポート部材が取り付けられている。かかるポート部材を血液成分分離装置に固定させることにより、遠心ボウル本体の軸線を回転軸として遠心ボウルを回転させることができ、また、回転する遠心ボウルに対して血液の流入・流出を安定して行うことができる。回転する遠心ボウルの内部にポート部材の流入ポートから血液が流入すると、血液が回転軸から遠心ボウル本体の内周面に向かって遠心力により移動して、流入ポートと流通する分離空間に集められる。

【００３３】分離空間に集められた血液は、遠心力が作用する方向（回転軸から遠心ボウル本体の内周面）に向かって、血液成分の比重の軽い順（即ち、第２血液成分、第３血液成分、血液、第１血液成分）に、回転軸と平行な相を分離空間に形成して滞留する。しかしながら、本発明に係る遠心ボウルの分離空間は、回転軸（即ち、軸線）と平行若しくは上側に向かって漸近するコア部材の面と、上側に向かって次第に狭くなる遠心ボウル本体の内周面により形成されているので、かかる分離空間は上側に向かって次第に回転軸に近づいていく。従って、分離空間のうち下側の空間については、回転軸から最も遠くなって、比重の最も重い第１血液成分である赤血球が滞留する。また、分離空間のうち上側の空間については、回転軸から最も近くなって、比重の最も軽い第２血液成分である血漿が滞留する。

【００３４】そして、さらに血液が流入ポートから回転する遠心ボウルの内部に流入されると、分離空間の下側に滞留する第１血液成分である赤血球は、分離空間の下側から連通する第１採取空間に押し出される。流入ポートが分離空間に流通する位置の下側において、分離空間が第１採取空間と連通するので、流入ポートから分離空間に流入した血液のうち、第１血液成分である赤血球より比重の軽い第２血液成分である血漿等が、第１採取空間に押し出されることはない。第１採取空間に押し出された第１血液成分である赤血球は、第１採取空間と流通する第１流出ポートから遠心ボウル本体の外部に流出して採取される。

【００３５】また、分離空間の上側に滞留する第２血液成分である血漿は、分離空間の上側から連通する第２採取空間に、狭いチャンネルを介して押し出される。流入ポートが分離空間に流通する位置の上側において、分離空間が第２採取空間と連通するので、流入ポートから分離空間に流入した血液のうち、第２血液成分である血漿より比重の重い第１血液成分である赤血球が、第２採取空間に押し出されることはない。第２採取空間に押し出された第２血液成分である血漿は、第２採取空間と流通する第２流出ポートから遠心ボウル本体の外部に流出して採取される。また、チャンネルの下側に形成された間隙を介して、分離空間と第３採取空間が連通している場合でも、チャンネルを介して第２採取空間に向かう第２血液成分である血漿は、遠心力の作用によりチャンネルの下側にある間隙から第３採取空間に向かうことはない。

【００３６】第３血液成分であるバフィーコートを採取する場合には、第１流出ポートと第２流出ポートを閉じて、分離空間に滞留する血液が、第３流出ポートのみから遠心ボウル本体の外部に流出できるようにする。このような状態において、血液が流入ポートから分離空間に流入すると、分離空間の上側に滞留する第２血液成分である血漿は、分離空間の上側と連通するチャンネルに押し出される。第２流出ポートは閉じられていることから、第２採取空間に流入することができる量に限界が生じ、第２採取空間に流入することができない第２血液成分である血漿は、チャンネルの下側にある間隙から第３採取空間に流入する。第３採取空間に流入した第２血液成分である血漿は、第３採取空間と流通する第３流出ポートから遠心ボウル本体の外部に流出する。

【００３７】その後に、さらに血液が流入ポートから分離空間に流入すると、分離空間に滞留する第３血液成分であるバフィーコートがチャンネルに押し出されるが、遠心力が作用することによって、第２血液成分である血漿より比重の軽い第３血液成分であるバフィーコートは、チャンネルと比べて回転軸により近い位置にある第２採取空間に、既に流入した第２血液成分である血漿と入れ換わって流入することはできない。従って、チャンネルの下側にある間隙から第３採取空間に流入する。このとき、回転軸に平行で厚さの薄い相を分離空間に形成しているバフィーコートは、回転軸（即ち、軸線）の方向に狭いチャンネルに押し出されることから、バフィーコートはチャンネルに残留することなく、第３採取空間に効率よく流入させることができる。第３採取空間に流入した第３血液成分であるバフィーコートは、第３採取空間と流通する第３流出ポートから遠心ボウル本体の外部に流出して採取される。

【００３８】尚、第３血液成分であるバフィーコートを第３流出ポートから流出している際にも、流入ポートから分離空間に血液が流入しているので、かかる血液のうち第２血液成分である血漿も、第３血液成分であるバフィーコートと一緒に、第３流出ポートから流出されることになるが、第２血液成分である血漿は血液の基質であって、第３血液成分であるバフィーコートに当然に含まれるので問題はない。

【００３９】また、第１採取空間、第２採取空間、第３採取空間は、分離空間から軸線に向かった位置（即ち、遠心ボウル本体の内周面に対し内側）に設けられており、分離空間で分離された第１血液成分、第２血液成分、第３血液成分は、遠心力が作用する方向とは逆の方向に向かって徐々に押し出される。これは、分離空間から第１血液成分、第２血液成分、第３血液成分が、例え

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ば遠心力等によって急激に押し出されて、分離空間に形成される第１血液成分、第２血液成分、第３血液成分等の相の状態を破壊することを防止する。

【００４０】また、供給ポートから加圧空気を供給して、遠心ボウル本体の開口に隣接した第２採取空間に加圧空気を供給すると、遠心ボウル本体の内部の圧力が遠心ボウル本体の外部の圧力より高くなる。従って、遠心ボウル本体（の開口）を密封している回転シール部材のシール性能が不良になった場合には、回転シール部材における漏れが遠心ボウル本体の内部から外部に向かって流出するので、遠心ボウル本体の外部から内部に空気が侵入することを防ぐ。

【００４１】

【発明の実施の形態】以下、本発明を具体化した一実施の形態である遠心ボウル１Ａ、１Ｂを、図面を用いて詳細に説明する。図１、３に、かかる血液成分分離装置５０で使用する遠心ボウル１Ａ、１Ｂの構造を示す。尚、遠心ボウル１Ａ、１Ｂの外観は、ポート部材５Ａ、５Ｂに設けられるポートの数を除いては、従来の遠心ボウル１６１（図１２参照）と同様な形状をしている。

【００４２】図１は、３つのポート４、１４、１５をもつ遠心ボウル１Ａの構造を示した断面図である。上側に向かって次第に狭くなる中空状の遠心ボウル本体２の頂部には、かかる遠心ボウル本体２の軸線Ｐ１と同心である開口３が設けられている。流入ポート４を設けたポート部材５Ａが、かかる開口３から遠心ボウル本体２の内部に遊挿されており、回転シール部材であるメカニカルシール９で取り付けられている。メカニカルシール９は、弾性ベローズ５、カーボンリング６、セラミック環７および押えリング８等からなり、遠心ボウル本体２を密封しながら軸線Ｐ１を回転軸（以下、「回転軸」に対しても符号Ｐ１を用いる）として回転させることができる。尚、回転方向はどちらの方向でもよいが、説明の便宜上、矢印Ｑ１の方向とする。

【００４３】また、ポート部材５Ａには、メカニカルシール９を覆うようにヘッダーシールド１０が設けて、外部にメカニカルシール９が露出しないようにしており、さらに、ヘッダーシールド１０の爪部１１が、遠心ボウル本体１Ａの頂部と当接することにより、ポート部材５Ａが下側に押し下げ過ぎることがないようにしている。

【００４４】ポート部材５Ａには、血液１００（図６、７、８、９、１０参照）が送られる流入ポート４のほかに、第１流出ポート１４と第２流出ポート１５が設けられている。また、ポート部材５Ａの内部は三重管の構造となっていて、流入ポート４は流出口１６と、第１流出ポート１５は第１採取流入口１７と、第２流出ポート１４は第２採取流入口１８と、それぞれ連通している。尚、流出口１６は管の切口であるが、第１採取流入口１７と第２採取流入口１８は円形のスカート状である。

【００４５】遠心ボウル本体２の内部には、軸線Ｐ１と上側に向かって漸近するコア部材１２Ａ（いわゆる円錐台の形状をしている）の外周面と、遠心ボウル本体２の内周面との間に、分離空間５１が環状に形成されている。また、コア部材１２Ａの頂部と、遠心ボウル本体２の開口３との間に、第２採取空間５２が形成されている。さらに、コア部材１２Ａの爪部１３が遠心ボウル本体２の内面に当接することにより、軸線Ｐ１の方向に狭いチャンネル６１が環状に形成されている。かかるチャンネル６１により、第２採取空間５２は、分離空間５１の上側から軸線Ｐ１の方向に向かって、分離空間５１と連通している。

【００４６】さらに、コア部材１２Ａの内部の上部には第１採取空間５３が、底部には円板状の底部チャンネル６２が、それぞれ形成されている。また、コア部材１２Ａには、その頂部から底部にかけて、第１採取空間５３を貫き底部チャンネル６２にまで達する遊挿口１９が、ポート部材５Ａを遊挿するために設けてあり、ポート部材５Ａを開口３から遊挿口１９に遊挿して、流出口１６を底部チャンネル６２の中央の上部に介在させている。同時に、第１採取流入口１７を第１採取空間５３に、第２採取流入口１８を第２採取空間５２に、それぞれ介在させている。これにより、第１流出ポート１５が第１採取流入口１７を介して第１採取空間５３と流通し、第２流出ポート１４が第２採取流入口１８を介して第２採取空間５２と流通することができる。

【００４７】また、コア部材１２Ａの外周面が底部チャンネル６２と接続する位置には、スリット６３が円形状に形成されている。これにより、流入ポート４は、流出口１６、底部チャンネル６２、スリット６３を介して、分離空間５１と流通することができる。スリット６３によりコア部材１２Ａの外周面は上下に分断されるが、かかる外周面の内側に上下方向に沿って形成された内部チャンネル６４等により保持される。

【００４８】ここで、遠心ボウル本体２を底部チャンネル６２（切断線Ａ－Ｂ－Ｃ）において切断した（水平）断面図である図２を用いて、スリット６３近辺の構造を説明すると、管状の４本の内部チャンネル６４が円板状の底部チャンネル６２を貫いており、かかる内部チャンネル６４がコア部材１２Ａの外周面の内側に沿って形成されることにより、スリット６３により上下に分断されるコア部材１２Ａの外周面を保持する。尚、スリット６３を断続的に設けることにより、コア部材１２Ａの外周面が上下に分断されることを防止してもよい。

【００４９】また、内部チャンネル６４は、下側で分離空間５１と、上側で第１採取空間５３と連通している。これにより、第１採取空間５３は、分離空間５１の下側から軸線Ｐ１の方向に向かって、分離空間５１と連通することができる。分離空間５１等の各空間やチャンネル６１等の各チャンネルを形成しているコア部材１２Ａは、底部材２０が遠心ボウル本体２に固着されることに

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より、遠心ボウル本体２の内部において固定され、遠心ボウル本体２と一体となって回転する。

【００５０】ここで、３つのポート４、１４、１５をもつ遠心ボウル１Ａにおける血液１００に流れについて、簡単に説明する。流入ポート４に流入した血液１００は流出口１６から流出され、底部チャンネル６２の中央部に運ばれる。底部チャンネル６２の中央部に運ばれた血液１００は、遠心力の作用によって、底部チャンネル６２とスリット６３を介して分離空間５１に移動する（図２参照）。

【００５１】分離空間５１に移動した血液１００は、２つのルートを通って、遠心ボウル１Ａの外部に流出する。一方のルートは、分離空間５１の下側より内部チャンネル６４、第１採取空間５３、第１採取口１７を介して、第１流出ポート１４から遠心ボウル１Ａの外部に流出するルートである。他方のルートは、分離空間５１の上側よりチャンネル６１、第２採取空間５２、第２採取口１８を介して、第２流出ポート１５から遠心ボウル１Ａの外部に流出するルートである。尚、分離空間５１において、連続的に行われる血液成分分離の説明は、後述する。

【００５２】次に、４つのポート４、１４、１５、２１Ｂをもつ遠心ボウル１Ｂの構造について、説明する。尚、遠心ボウル１Ｂの構造のうち、上述した遠心ボウル１Ａと共通する構造については、遠心ボウル１Ａの構造の説明を参照することとし、遠心ボウル１Ａと異なる構造について、以下に取り上げて説明する。図３は、遠心ボウル１Ｂの構造を示した断面図である。ポート部材５Ｂには、第３流出ポート２１Ｂが設けられている。また、ポート部材５Ｂの内部は四重管の構造となっていて、第３流出ポート２１Ｂは第３採取流入口２２Ｂと連通している。尚、第３採取流入口２２Ｂは円形のスカート状である。

【００５３】また、コア部材１２Ｂの内部の上部には第３採取空間５４Ｂが形成されおり、かかるコア部材１２Ｂには、その頂部から底部にかけて、第３採取空間５４Ｂと第１採取空間５３を貫き底部チャンネル６２にまで達する遊挿口１９が、ポート部材５Ｂを遊挿するために設けてあり、ポート部材５Ｂを開口３から遊挿口１９に遊挿することにより、第３採取流入口２２Ｂを第３採取空間５４Ｂに介在させている。これにより、第３流出ポート２１Ｂが第３採取流入口２２Ｂを介して第３採取空間５４Ｂと流通することができる。さらに、チャンネル６１の下側には断続的に間隙６５Ｂが設けてあり、かかるチャンネル６１と間隙６５Ｂにより、第３採取空間５４Ｂは、分離空間５１の上側から軸線Ｐ１の方向に向かって、分離空間５１と連通することができる。

【００５４】４つのポート４、１４、１５、２１Ｂをもつ遠心ボウル１Ｂにおける血液１００に流れについては、上述した遠心ボウル１Ａの２つのルートのほかに、分離空間５１の上側よりチャンネル６１、間隙６５Ｂ、第３採取空間５４Ｂ、第３採取口２２Ｂを介して、第３流出ポート２１Ｂから遠心ボウル１Ｂの外部に流出するルートがある。

【００５５】次に、遠心ボウル１Ｂを用いた血液成分分離装置５０の血液成分分離について、図面を用いて説明する。図５に、両腕法における血液成分分離装置５０のフロー図を示す。

【００５６】採血針１２０Ｒを介して供血者の一方の腕７０Ｒの静脈から採られたばかりの血液１００は、採血針１２０Ｒを離れるとすぐに抗凝固処理される。抗凝固処理は、抗凝固剤用容器１１０に入っている抗凝固剤１０５が、ローラー形の抗凝固剤用ポンプ７１の回転によって、除菌フィルター３９を介して抗凝固剤用容器１１０に接続されている管８０を通り、圧力モニター４０に監視されながら採血針１２０Ｒに供給されることにより行なわれる。抗凝固処理された血液１００は、静脈圧力により管８１を通って、気泡検出室４１の底部に流れ込む。

【００５７】そして、気泡検出室４１を満たした血液１００は、ローラー形の供給用ポンプ７２の回転により管８２、８３を通って、エアーセンサー４２により血液１００に気泡が包含していないことを確認しながら、遠心ボウル１Ｂの流入ポート４に送られる。血液１００が送られた遠心ボウル１Ｂは、図示しないモーターにより回転する。この回転により、遠心ボウル１Ｂ内の血液１００は遠心分離されて、第１血液成分である赤血球１０１と、第２血液成分である血漿１０２と、第３血液成分であるバフィーコート１０３の血液成分に分離される（図６、７、８、９、１０参照）。以下に、遠心ボウル１Ｂによって、血液１００の各血液成分が分離採取される原理について、図面を用いて説明する。

【００５８】図６は、供血者から採血された血液１００から、第１血液成分である赤血球１０１と、第２血液成分である血漿１０２とが採取される際の血液成分分離装置５０のフロー図を示す。赤血球１０１と血漿１０２を採取する際には、バルブ３０（図５参照）、３５、３６は開いておき、バルブ３１、３２、３３、３４、３７、３８は閉じておく。尚、血液成分分離装置５０で使用されるバルブ３０～３８はいわゆるピンチバルブであり、弾力性を有する管８１～９７をクランプすることにより、バルブ３０～３８の開閉は行なわれる。

【００５９】回転する遠心ボウル１Ｂの内部に流入ポート４から流入した血液１００は、回転軸Ｐ１から遠心ボウル本体２の内周面に向かって作用する遠心力によって、底部チャンネル６２とスリット６３を通って、分離空間５１に集められる。分離空間５１に集められた血液１００は、遠心力が作用する方向（回転軸Ｐ１から遠心ボウル本体２の内周面）に向かって、血液成分の比重の軽い順（即ち、第２血液成分である血漿１０２、第３血

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液成分であるバフィーコート１０３、血液１００、第１血液成分である赤血球１０１）に、回転軸Ｐ１と平行な相を分離空間５１に形成して滞留する。本発明に係る遠心ボウル１Ｂの分離空間５１は、上側に向かって次第に回転軸Ｐ１に近づいていくことから、分離空間５１の下側に比重の最も重い第１血液成分である赤血球１０１が滞留する。また、分離空間５１の上側に比重の最も軽い第２血液成分である血漿１０２が滞留する。

【００６０】そして、さらに血液１００が回転する遠心ボウル１Ｂの内部に流入ポート４から流入すると、分離空間５１の下側に滞留する第１血液成分である赤血球１０１は、分離空間５１の下側から連通する第１採取空間５３に、内部チャンネル６３を介して押し出される。第１採取空間５３が分離空間５１と連通する位置は、血液１００が分離空間５１に流入するスリット６３より下側だから、流入ポート４から分離空間５１に流入した血液１００のうち、第１血液成分である赤血球１０１より比重の軽い第２血液成分である血漿１０２等が、第１採取空間５３に押し出されることはない。第１採取空間５３に押し出された第１血液成分である赤血球１０１は、第１採取口１７を介して第１流出ポート１５から流出し、管８６を通って、計量器４５により監視される赤血球用容器１１３に採取される。

【００６１】第１血液成分である赤血球１０１を返血する場合には、赤血球用容器１１３に第１血液成分である赤血球１０１が一定量を採取したことを計量器４５により確認した後に、バルブ３７を開くとともにローラー形の返血用ポンプ７３を回転させて、同一の供血者に返血する。赤血球用容器１１３に採取された第１血液成分である赤血球１０１は、管８８、９０、９１、９２を通って、エアーセンサー４７により気泡を包含してないことを確認されながら気泡検出室４８に流入し、管９３と採血針１２０Ｌを介して、同一の供血者の他方の腕７０Ｌの静脈に返血される。このようにして、第１血液成分である赤血球１０１を採取（採血）しながら、返血を同時に行うことができ、もって、血液成分分離に要する時間を短縮できる。

【００６２】また、分離空間５１の上側に滞留する第２血液成分である血漿１０２は、分離空間５１の上側から連通する第２採取空間５２に、狭いチャンネル６１を介して押し出される。第２採取空間５２が分離空間５１と連通する位置は、血液１００が分離空間５１に流入するスリット６３より上側だから、流入ポート４から分離空間５１に流入した血液１００のうち、第２血液成分である血漿１０２より比重の重い第１血液成分である赤血球１０１等が、第２採取空間５２に押し出されることはない。また、遠心力が作用することにより、第２血液成分である血漿１０２が、チャンネル６１の下側の間隙６５Ｂを介して、第３採取空間５４Ｂに向かうこともない。第２採取空間５２に押し出された第２血液成分である血漿１０２は、第２採取口１８を介して第２流出ポート１４から流出し、管８５を通って、計量器４６により監視される血漿用容器１１４に採取される。

【００６３】第２血液成分である血漿１０２を返血する場合には、血漿用容器１１４に第２血液成分である血漿１０２が一定量を採取したことを計量器４６により確認した後に、バルブ３８を開くとともにローラー形の返血用ポンプ７３を回転させて、同一の供血者に返血する。血漿用容器１１４に採取された第２血液成分である血漿１０２は、管８９、９０、９１、９２を通って、エアーセンサー４７により気泡を包含してないことを確認さらながら気泡検出室４８に流入し、管９３と採血針１２０Ｌを介して、同一の供血者の他方の腕７０Ｌの静脈に返血される。このようにして、第２血液成分である血漿１０２を採取（採血）しながら、返血を同時に行うことができ、もって、血液成分分離に要する時間を短縮できる。

【００６４】尚、液層光学センサー４９Ａ、４９Ｂで監視することにより、分離空間５１に形成されるバフィーコート１０３の相の位置を調節し、かかるバフィーコート１０３や血液１００等が血漿用容器１１４に流入することを防止して、連続的に血液成分分離を行うことを確保している。具体的には、液層光学センサー４９Ａがバフィーコート１０３を検知したときに、バルブ３４、３６、３８を開くとともに返血用ポンプ７３を回転させることにより、血漿用容器１１４に採取された血漿１０２を、遠心ボウル１Ｂの流入ポート４に流入する血液１００と合流させて、遠心ボウル１Ｂに再び流入させる。同時に、遠心ボウル１Ｂの流入ポート４に流入する血液１００の量を常に一定に保つため、供給用ポンプ７２の回転を減速させてもよい。これにより、液層光学センサー４９Ａがバフィーコート１０３を検知する以前と比べて、遠心ボウル１Ｂの流入ポート４へ流入する血液１００における赤血球１０１の占める割合が少なくなり、分離空間５１で分離される赤血球１０１よりも第１流出ポート１５から流出する赤血球１０１の量が多くなって、赤血球１０１の相の位置が分離空間５１の下側に移動し、ひいては、バフィーコート１０３の相の位置も分離空間５１の下側に移動する。この状態は、液層光学センサー４９Ｂがバフィーコート１０３を検知するまで維持され、液層光学センサー４９Ｂがバフィーコート１０３を検知した場合には、バルブ３４、３６、３８を閉じるとともに返血用ポンプ７３の回転を停止させ、同時に供給用ポンプ７２の回転を通常時の回転に戻して、通常の血液成分分離の状態に戻す。

【００６５】次に、第３血液成分であるバフィーコート１０３の分離採取について説明する。図７は、供血者から採血された血液１００から、第３血液成分であるバフィーコート１０３が採取される際の血液成分分離装置５０のフロー図を示す。第３血液成分であるバフィーコー

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ト１０３を採取する際は、液層光学センサー４９Ａがバフィーコート１０３を検知した後に、閉じていたバルブのうちバルブ３３を開き、開いていたバルブのうちバルブ３５、３６、３７、３８を閉じる。

【００６６】そして、さらに血液１００が流入ポート４から回転する遠心ボウル１Ｂの内部に流入すると、分離空間５１の上側に滞留する第２血液成分である血漿１０２は、分離空間５１の上側と連通するチャンネル６１に押し出される。バルブ３６は閉じられて第２流出ポート１４から流出することができないことから、第２採取空間５２に流入することができる量に限界が生じて、第２採取空間５２に流入することができない第２血液成分である血漿１０２が、チャンネル６１の下側にある間隙６５Ｂから第３採取空間５４Ｂに流入する。第３採取空間５４Ｂに流入した第２血液成分である血漿１０２は、第３採取口２２Ｂを介して第３流出ポート２１Ｂから流出し、管８４を通って、バフィーコート用容器１１２に採取される。

【００６７】その後に、さらに血液１００が流入ポート４から分離空間５１に流入すると、分離空間５１に滞留する第３血液成分であるバフィーコート１０３がチャンネル６１に押し出されるが、第２血液成分である血漿１０２より比重の重い第３血液成分であるバフィーコート１０３は、遠心力が作用することによって、チャンネル６１と比べて回転軸Ｐ１により近い位置にある第２採取空間１０２に、既に流入した第２血液成分である血漿１０２と入れ換わって流入することはできず、チャンネル６１の下側にある間隙６５Ｂから第３採取空間５４Ｂに流入する。

【００６８】分離空間５１に滞留していたときは、回転軸Ｐ１と平行で厚さの薄い相を形成していたバフィーコート１０３（図６参照）が、回転軸Ｐ１の方向に狭いチャンネル６１に押し出されることから、バフィーコート１０３がチャンネル６１に残留することなく、第３採取空間５４Ｂに効率よく流入することができる。第３採取空間５４Ｂに流入した第３血液成分であるバフィーコート１０３は、第３採取口２２Ｂを介して第３流出ポート２１Ｂから流出し、管８４を通って、バフィーコート用容器１１２に採取される。

【００６９】第３血液成分であるバフィーコート１０３の採取の終了は、管８４を通るバフィーコート１０３を監視するカラーセンサー４３により行う。遠心ボウル本体２の内部で分離されたバフィーコート１０３のほとんどがバフィーコート用容器１１２に採取されると、第３採取空間５４Ｂは血液１００により占有された状態となり、かかる血液１００の一部がバフィーコート１０３に混ざって、管８４を通ってバフィーコート用容器１１２に向かって移動し始める。これをカラーセンサー４３が検出すると、バルブ３３を閉じてバフィーコート１０３の採取を終了する。バフィーコート１０３の採取が終了した時の遠心ボウル１Ｂの断面は、後述する図８に示したものと同じである。

【００７０】尚、第３血液成分であるバフィーコート１０３がバフィーコート用容器１１２に採取される以前には、第２血液成分である血漿１０２がバフィーコート用容器１１２に採取され、また、第３血液成分であるバフィーコート１０３を第３流出ポート２１Ｂから流出している際には、流入ポート４から分離空間５１に血液１００が流入しているので、かかる血液１００のうち第２血液成分である血漿１０２も、第３血液成分であるバフィーコート１０３と一緒に、第３流出ポート２１Ｂから流出されてバフィーコート用容器１１２に採取されることになるが、第２血液成分である血漿１０２は血液１００の基質であって、第３血液成分であるバフィーコート１０３（白血球１０３Ａと血小板１０３Ｂを含む血漿１０２）に当然に含まれるので問題はない。

【００７１】また、第１血液成分である赤血球１０１が押し出される第１採取空間５３、第２血液成分である血漿１０２が押し出される第２採取空間５２、第３血液成分であるバフィーコート１０３が押し出される第３採取空間５４Ｂは、分離空間５１から回転軸（即ち、軸線）Ｐ１に向かった位置に設けられていることから、分離空間５１で分離された赤血球１０１、血漿１０２、バフィーコート１０３は、遠心力に逆らうこととなり、徐々に押し出されることになる。これによって、血液１００、赤血球１０１、血漿１０２、バフィーコート１０３が、遠心力によって急激に分離空間５１から押し出されて、分離空間５１に形成される血液１００、赤血球１０１、血漿１０２、バフィーコート１０３の相の状態を破壊することを防止することができる。

【００７２】さらに、上述した実施の形態では、４つのポート４、１４、１５、２１Ｂをもつ遠心ボウル１Ｂを用いて、供血者から採取した血液１００を、第１血液成分である赤血球１０１と、第２血液成分である血漿１０２と、第３血液成分であるバフィーコート１０３に血液成分分離していたが、３つのポート４、１４、１５をもつ遠心ボウル１Ａを用いた場合にも、遠心ボウル１Ｂを用いたときと同様にして、供血者から採取した血液１００を、第１血液成分である赤血球１０１を赤血球用容器１１３に、第２血液成分である血漿１０２を血漿用容器１１４に、それぞれ採取することができる。

【００７３】次に、片腕法における血液成分分離装置５０のフローについて説明する。上述した両腕法との大きな違いは、供血者の一方の腕７０Ｒのみを拘束する点と、以下に説明する返血方法にある。図８に、第１血液成分である赤血球１０１が供血者に返血される際の血液成分分離装置５０のフロー図を示す。尚、図８に示す遠心ボウル１Ｂの断面は、第３血液成分であるバフィーコート１０３の採取が終了した時のものである。また、片腕法の場合には、管９２、９３、エアーセンサー４７、

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気泡検出室４８、返血針１２０Ｌは、血液成分分離装置５０から外される。

【００７４】両腕法と同様にして、第１血液成分である赤血球１０１を赤血球用容器１１３に、第２血液成分である血漿１０２を血漿用容器１１４に、第３血液成分であるバフィーコート１０３をバフィーコート用容器１１２に、それぞれ採取したら、以下の手順で返血を行う。

【００７５】第１血液成分である赤血球１０１を返血する際には、バルブ３０、３２、３５、３７を開き、バルブ３１、３３、３６、３８を閉じておく。そして、供給用ポンプ７２を停止するとともに返血用ポンプ７３を回転させて、赤血球用容器１１３に採取された赤血球１０１を同一の供血者に返血する。かかる赤血球１０１は、管８８、９１、９４、９６を介して、エアーセンサー４２により気泡を包含してないことを確認されながら気泡検出室４１に流入し、管８１と採血針１２０Ｒを介して、同一の供血者の腕７０Ｒの静脈に返血される。このようにして、遠心ボウル１Ｂの回転を停止することなく返血を行うことができ、もって、血液成分分離に要する時間を短縮できる。

【００７６】また、第２血液成分である血漿１０２を返血する際には、バルブ３０、３２、３６、３８を開き、バルブ３１、３３、３５、３７を閉じておく。そして、供給用ポンプ７２を停止するとともに返血用ポンプ７３を回転させて、血漿用容器１１４に採取された血漿１０２を同一の供血者に返血する。かかる血漿１０２は、赤血球１０１と同様にして、同一の供血者の腕７０Ｒの静脈に返血されて、遠心ボウル１Ｂの回転を停止することなく返血を行うことができ、もって、血液成分分離に要する時間を短縮できる。

【００７７】また、遠心ボウル本体２の内部に残留している赤血球１０１等を返血する際には、生理食塩水１０６を遠心ボウル本体２の内部に流入することにより行なわれる。図９に、遠心ボウル本体２の内部に残留している赤血球１０１が供血者に返血される際の血液成分分離装置５０のフロー図を示す。かかる際には、バルブ３１、３５を開き、バルブ３０、３２、３３、３４、３６、３７、３８を閉じておく。そして、供給用ポンプ７２の回転により、生理食塩水用容器１１１の生理食塩水１０６を、流入ポート４から回転する遠心ボウル１Ｂの内部に流入させる。遠心ボウル１Ｂの内部に流入した生理食塩水１０６は、回転軸Ｐ１から遠心ボウル本体２の内周面に向かって作用する遠心力によって、底部チャンネル６２とスリット６３を通り、分離空間５１に集められる。

【００７８】そして、さらに回転する遠心ボウル１Ｂの内部に生理食塩水１０６が流入ポート４から流入すると、分離空間５１の下側に滞留する第１血液成分である赤血球１０１は、分離空間５１の下側から連通する第１採取空間５３に、内部チャンネル６３を介して押し出される。また、生理食塩水１０６の比重は各血液成分に比べて最も軽いことから、分離空間５１、第２採取空間５２、第３採取空間５４Ｂにそれぞれ滞留している血液１００、血漿１０２と入れ換わることができ、これらの血液１００等は分離空間５１の下側から連通する第１採取空間５３に、内部チャンネル６３を介して押し出される。第１採取空間５３に押し出された赤血球１０１等は、第１採取口１７を介して第１流出ポート１５から流出し、管８６を通って、計量器４５により監視される赤血球用容器１１３に採取される。このようにして、赤血球用容器１１３に採取されたものは、第１血液成分である赤血球１０１を返血する場合と同様にして、同一の供血者の腕７０Ｒの静脈に返血される。

【００７９】次に、遠心ボウル本体２の外部から内部に空気が侵入することを防いだ遠心ボウル１Ａについて説明する。図４に、かかる遠心ボウル１Ａの構造と、血液成分分離装置５０のフローの一部を示す。図１に示す遠心ボウル１Ａのポート部材５Ａに、供給ポート１４０が設けられており、ポート部材５Ａの内部は四重管の構造となっていて、供給ポート１４０は供給口１４１と連通している。また、供給ポート１４０が供給口１４１を介して第２採取空間５２と流通することができる。

【００８０】供給ポート１４０には、加圧および滅菌された空気（以下、「加圧滅菌空気」という）が充填された加圧ボンベ１３３が、管１３０を介して接続されている。かかる管１３０には圧力調節弁１３１が設けてあり、加圧滅菌空気の加圧圧力を圧力センサー１３２に基づいて２０ｍｍＨｇ（最大１２０ｍｍＨｇ）に調節して、遠心ボウル本体２の内部に加圧滅菌空気を供給することができる。供給ポート１４０から供給された加圧滅菌空気が、遠心ボウル本体２の開口３に隣接した第２採取空間５２に流入すると、遠心ボウル本体２の内部の圧力を遠心ボウル本体２の外部の圧力より高くなり、遠心ボウル本体２（の開口３）を密封しているメカニカルシール９のシール性能が不良になった場合には、メカニカルシール９の摺動面における漏れが遠心ボウル本体２の内部から外部に向かって流出するので、遠心ボウル本体２の外部から内部に空気が侵入することを防ぐことができる。

【００８１】尚、上記の実施の形態では、３つのポート４、１４、１５をもつ遠心ボウル１Ａに対して、供給ポート１４０と供給口１４１とを設けて、メカニカルシール９の漏洩対策を行なっているが、４つのポート４、１４、１５、２１Ｂをもつ遠心ボウル１Ｂに対しても、供給ポート１４０と供給口１４１とを設けて、ポート部材５Ｂの内部を五重管の構造とし、供給ポート１４０が供給口１４１を介して第２採取空間５２と流通することができるようにすれば、同様にしてメカニカルシール９の漏洩対策を行なうことができる。

【００８２】以上詳細に説明したように、本実施の形態

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による遠心ボウル１Ａ、１Ｂを用いた血液成分分離装置５０によれば、供血者から採取された血液１００が流入ポート４から遠心ボウル１Ａ、１Ｂの内部に流入すると、回転する遠心ボウル１Ａ、１Ｂの遠心分離の作用により、血液１００が赤血球１０１と血漿１０２とバフィーコート１０３とに分離空間５１において遠心分離され、さらに血液１００が遠心ボウル１Ａ、１Ｂの内部に流入すれば、分離空間５１の下側に滞留する赤血球１０１が、分離空間５１の下側より第１採取空間５３等を介して、第１流出ポート１４から遠心ボウル１Ａ、１Ｂの外部に流出し、また、分離空間５１の上側に滞留する血漿１０２が、分離空間５１の上側よりチャンネル６１、第２採取空間５２等を介して、第２流出ポート１５から遠心ボウル１Ａ、１Ｂの外部に流出し、さらに、分離空間５１に滞留するバフィーコート１０３が、分離空間５１の上側よりチャンネル６１、間隙６５Ｂ、第３採取空間５４Ｂ等を介して、第３流出ポート２１Ｂから遠心ボウル１Ｂの外部に流出するので、遠心ボウル１Ａ、１Ｂの回転を停止することなく、分離空間５１において血液１００から各血液成分に分離された赤血球１０１、血漿１０２、バフィーコート１０３を採取することができ、採取された赤血球１０１または血漿１０２については、遠心ボウル１Ａ、１Ｂが回転している時でも同一の供血者に返血することができるので、採血と返血を同時に行うことが可能となり、もって、体外循環時間を短縮することができ、また、血液１００から血液成分分離された赤血球１０１と血漿１０２は、遠心ボウル１Ａ、１Ｂの外部に連続的に流出することによって、赤血球１０１が分離空間５１に蓄積することはないので、各血液成分に分離するために必要な分離空間５１の容量を従来の２２５ｍｌから１００ｍｌ以下に減少させることが可能となり、もって、体外循環血液量を少なくすることができる遠心ボウル１Ａ、１Ｂを提供することができる。

【００８３】さらに、ポート部材５Ａ、５Ｂに設けられた供給ポート１４０に加圧滅菌空気を供給して、遠心ボウル１Ａ、１Ｂの内圧を外圧より高圧にすることにより、回転シール部材であるメカニカルシール９の漏洩対策がなされた遠心ボウル１Ａ、１Ｂを提供することができる。

【００８４】尚、本発明は上記実施の形態に限定されるものでなく、その趣旨を逸脱しない範囲で様々な変更が可能である。例えば、第２流出ポート１５から流出する血漿１０２を再び遠心ボウル１Ａ、１Ｂに流入させ、循環する血漿１０２の流れを形成させることができれば、いわゆるサージ効果を利用して、白血球１０３Ａの混入が少なく血小板１０３Ｂを多く含んだ血漿１０２（以下、「高純度血小板濃厚液」という）を、第２流出ポート１５より流出させることができ、もって、本発明に係る遠心ボウル１Ａ、１Ｂにより、高純度血小板濃厚液を採取することもできる。

【００８５】また、第１流出ポート１５と第３流出ポート２１Ｂを閉じ、流入ポート４へ血液１００を流入させて血液成分分離を行うことにより、分離空間５１で分離される赤血球１０１を、内部チャンネル６４や第１採取空間５３に押し出されることなく、分離空間５１に滞留させ、所定量の赤血球１０１が分離空間５１に滞留したら、流入ポート４への血液１００の流入を中止するとともに第１流出ポート１５に生理食塩水を流入させて、分離空間５１の下側から生理食塩水を分離空間５１に供給させることにより、分離空間５１に滞留する赤血球１０１に生理食塩水を通過させて、分離空間５１に存在する遊離ヘモグロビンや抗凝固剤に含まれるヘパリンなどを、生理食塩水と一緒に第２流出ポート１４から流出させ、その後に、第２流出ポート１４から空気を送り込むことによって、遊離ヘモグロビンやヘパリンなどが洗いながされた赤血球１０１（以下、「濃縮洗浄赤血球液」という）を、第１流出ポート１５から流出させることができ、もって、本発明に係る遠心ボウル１Ａ、１Ｂにより、濃縮洗浄赤血球液を採取することもできる。

【００８６】

【発明の効果】以上説明したことから明かなように、本発明の遠心ボウル１Ａ、１Ｂを使用する血液成分分離装置によれば、供血者から採取された血液が流入ポートから遠心ボウルの内部に流入すると、回転する遠心ボウルの遠心分離の作用により、血液が赤血球と血漿とバフィーコートとに分離空間において遠心分離され、さらに血液が遠心ボウルの内部に流入すれば、分離空間の下側に滞留する赤血球が、分離空間の下側より第１採取空間等を介して、第１流出ポートから遠心ボウルの外部に流出し、また、分離空間の上側に滞留する血漿が、分離空間の上側よりチャンネル、第２採取空間等を介して、第２流出ポートから遠心ボウルの外部に流出し、さらに、分離空間に滞留するバフィーコートが、分離空間の上側よりチャンネル、間隙、第３採取空間等を介して、第３流出ポートから遠心ボウルの外部に流出するので、遠心ボウルの回転を停止することなく、分離空間において血液から各血液成分に分離された赤血球、血漿バフィーコートを採取することができ、採取された赤血球または血漿については、遠心ボウルが回転している時でも同一の供血者に返血することができるので、採血と返血を同時に行うことが可能となり、もって、体外循環時間を短縮することができ、また、血液から血液成分分離された赤血球と血漿は、遠心ボウルの外部に連続的に流出することによって、赤血球が分離空間に蓄積することはないので、各血液成分に分離するために必要な分離空間の容量を従来の２２５ｍｌから１００ｍｌ以下に減少させることが可能となり、もって、体外循環血液量を少なくすることができる遠心ボウルを提供することができる。

【００８７】さらに、ポート部材に設けられた供給ポートに加圧滅菌空気を供給して、遠心ボウルの内圧を外圧

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より高圧にすることにより、回転シール部材であるメカニカルシールの漏洩対策がなされた遠心ボウルを提供することができる。

【図面の簡単な説明】

【図１】３つのポートもつ遠心ボウルの構造を示した断面図である。

【図２】遠心ボウル本体を底部チャンネルにおいて切断した断面図である。

【図３】４つのポートをもつ遠心ボウルの構造を示した断面図である。

【図４】メカニカルシールの漏洩対策がなされた遠心ボウルの構造と、血液成分分離装置のフローの一部を示した図である。

【図５】両腕法における血液成分分離装置のフロー図を示す。

【図６】両腕法において赤血球と血漿とが採取される際の血液成分分離装置のフロー図を示す。

【図７】両腕法においてバフィーコートが採取される際の血液成分分離装置のフロー図を示す。

【図８】片腕法において赤血球を返血する際の血液成分分離装置のフロー図を示す。

【図９】片腕法において残留した赤血球等を返血する際の血液成分分離装置のフロー図を示す。

【図１０】従来の遠心ボウルを用いた血液成分分離装置の、乏血小板血漿を分離採取する際における、採血及び分離採取時のフロー図である。

【図１１】従来の遠心ボウルを用いた血液成分分離装置の、乏血小板血漿を分離採取する際における、返血時のフロー図である。

【図１２】遠心ボウルの外観図である。

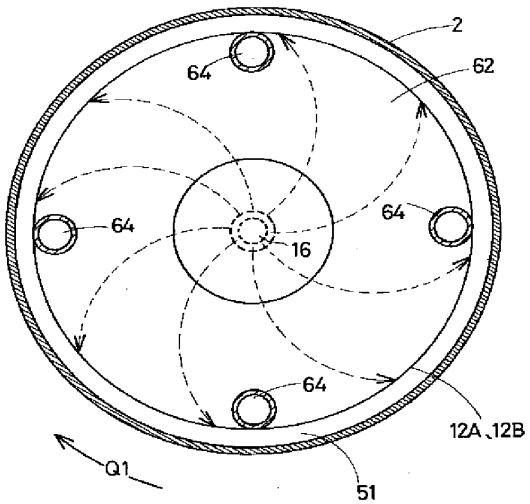
【図１３】従来の遠心ボウルの構造を示す断面図である。

【図１４】従来の遠心ボウルにおける遠心分離の原理図である。

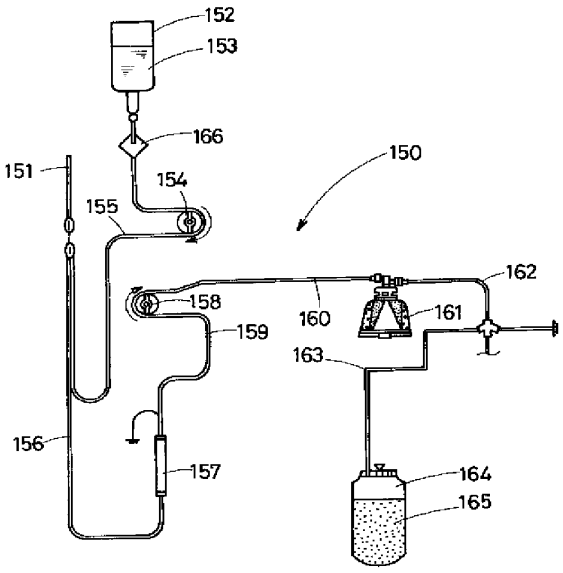
【符号の説明】

１Ａ、１Ｂ	遠心ボウル
２	遠心ボウル本体
３	開口
４	流入ポート
５Ａ、５Ｂ	ポート部材
９	メカニカルシール
１２Ａ、１２Ｂ	コア部材
１４	第２流出ポート
１５	第１流出ポート
２１Ｂ	第３流出ポート
５０	血液成分分離装置
５１	分離空間
５３	第１採取空間
５２	第２採取空間
５４Ｂ	第３採取空間
６１	チャンネル
６５Ｂ	間隙
１００	血液
１０１	赤血球
１０２	血漿
１０３	バフィーコート
１４０	供給ポート
Ｐ１	遠心ボウル本体の軸線

【図２】

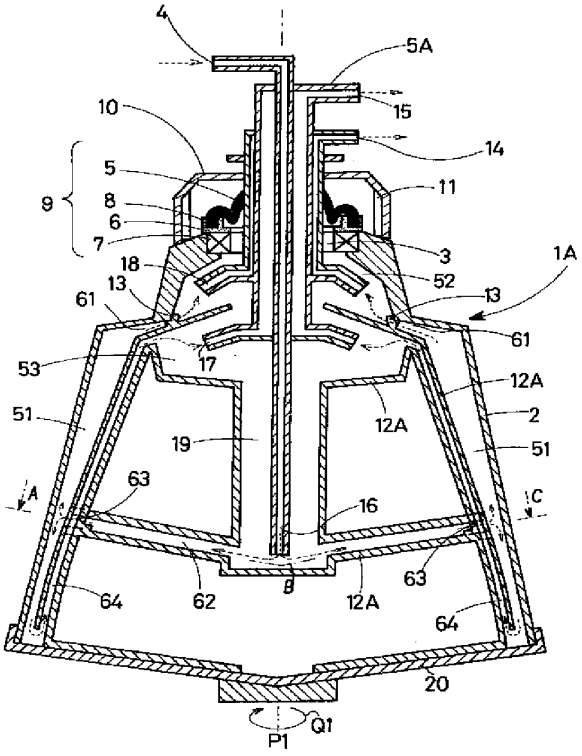


【図１０】

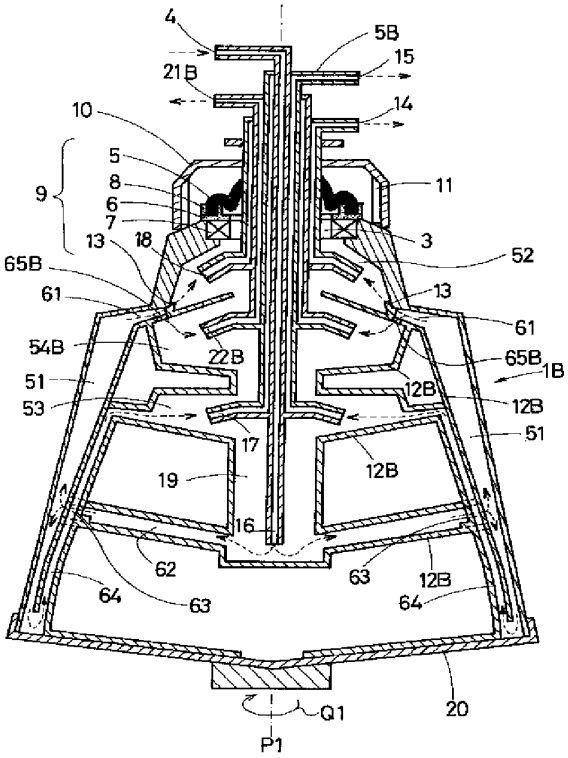


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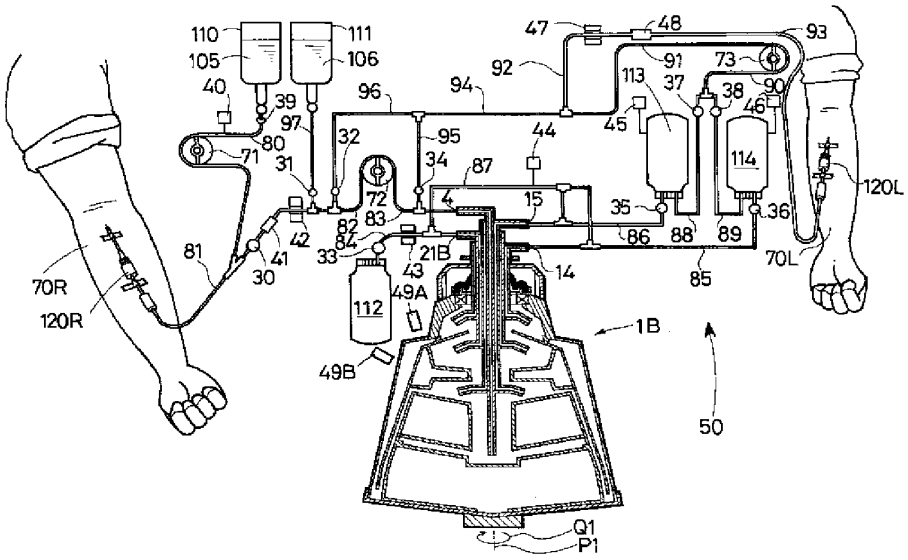
【図１】



【図３】

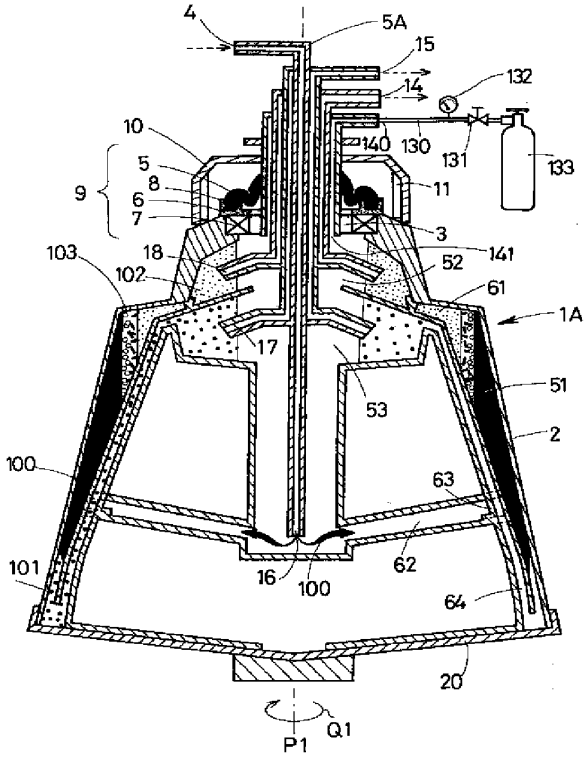


【図５】

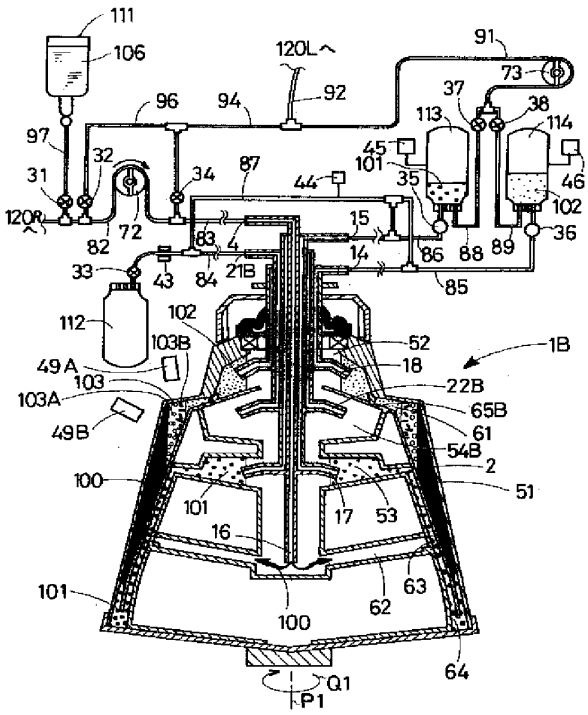


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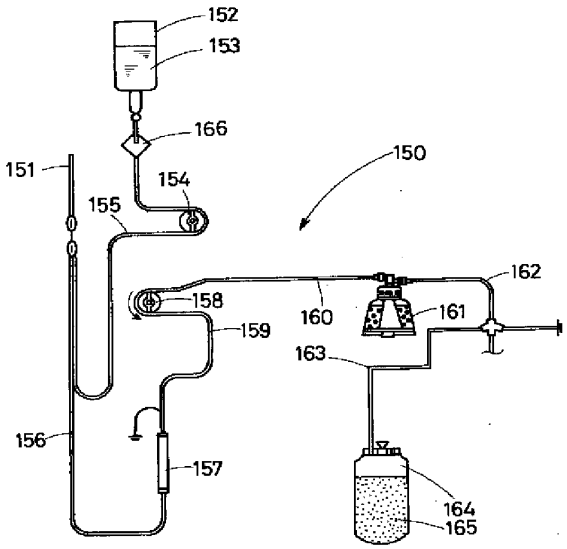
【図４】



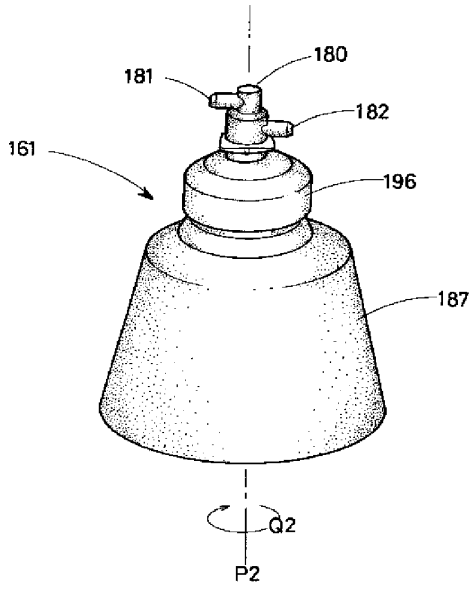
【図６】



【図１１】

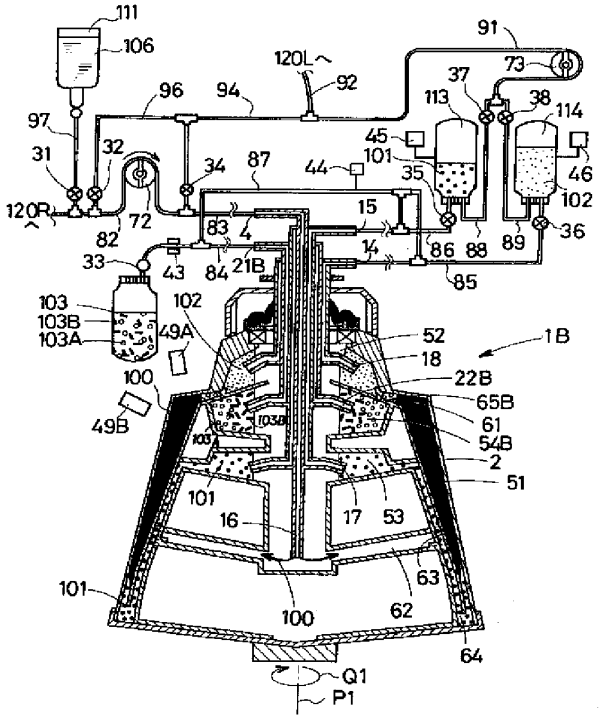


【図１２】

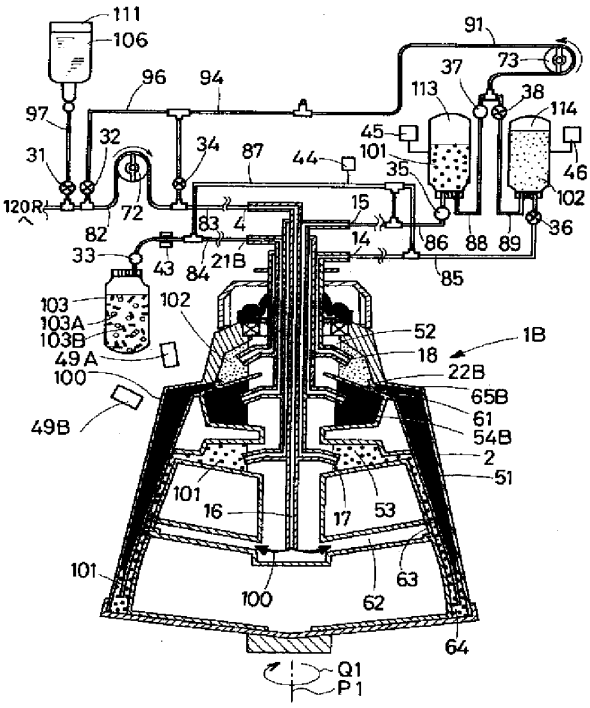


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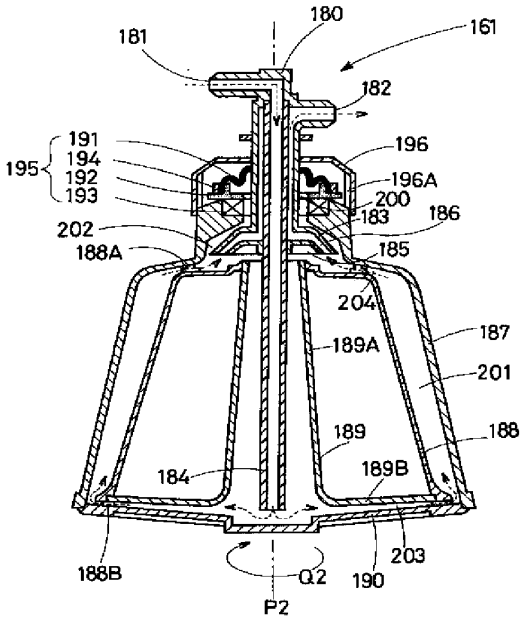
【図７】



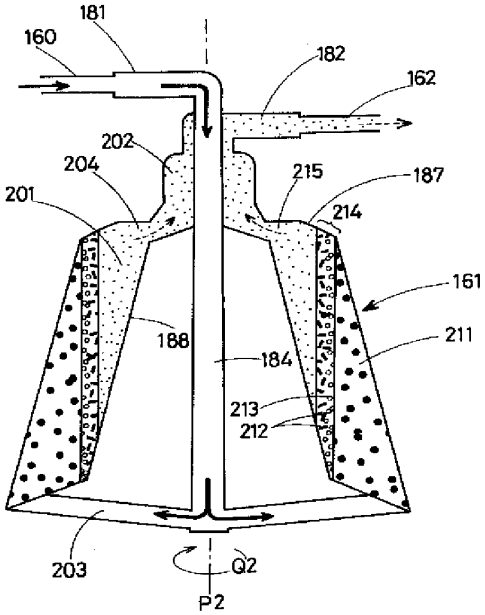
【図８】



【図１３】

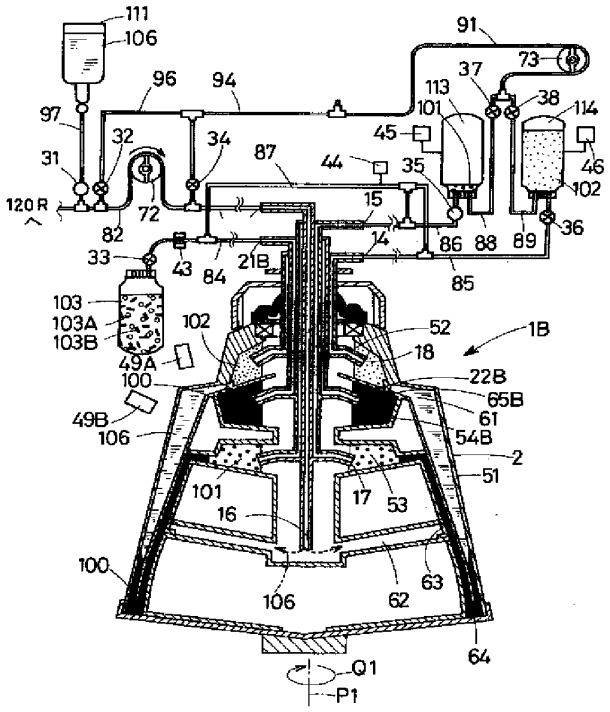


【図１４】



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【図９】


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Espacenet

Bibliographic data: JPS596952 (A) — 1984-01-14

ROTARY SEAL STRUCTURE FOR FLOWING SAMPLE INTO ROTARY CONTAINER AND DISCHARGING THE SAME THEREFROM

Inventor(s): NAKAGAWA TAKASATO ± (NAKAGAWA TAKASATO)

Applicant(s): HITACHI KOKI KK ± (HITACHI KOKI KK)

Classification: **- international:** ***B04B1/02; B04B5/00; G01N33/48;*** (IPC1-7): B04B5/00; G01N33/48
- cooperative: B04B2005/0464

Application number: JP19820115868 19820702

Priority number (s): JP19820115868 19820702

Abstract of JPS596952 (A)

PURPOSE:To prevent the rising in the temp. of blood components, by a method wherein a slide surface interposed between a stationary part and a rotary container is formed into an anti-wear structure holding airtightness during sliding and a passage for centrifugally separated blood components is provided at a position avoiding a slide part. CONSTITUTION:In a centrifugal separator container, an anti-wear seal plate 7 is interposed between a stationary part having an inlet 2 and an outlet 3 for a sample (e.g., blood) from the outside and a rotary container 4 to be slid therewith. Blood introduced from the inlet 2 is freely fallen to a sump part 11 and enters the container 4 through an opening part 5 by centrifugal force to be subjected to centrifugal separation. As the result, a separated layer is formed successively in the order of erythrocyte, leukocyte and serum from the outer peripheral surface. Corresponding to the amount of blood entering from the inlet 2, serum is at first discharged from the outlet 3 through an opening part 6, vertical grooves 13, 14 and a ring groove 12. This passage is provided at a position avoiding the vicinity where friction heat is generated by sliding. By this mechanism, the rising in the temp. of blood components is prevented.

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⑲ 日本国特許庁（JP）　　⑪ 特許出願公開

⑫ 公開特許公報（A）　　昭59—6952

⑤1Int. Cl.³　識別記号　庁内整理番号
B 04 B 5/00　A 7636—4D
G 01 N 33/48　8305—2G

⑬公開　昭和59年(1984)1月14日

発明の数　1
審査請求　未請求

（全 3 頁）

⑤4回転容器にサンプルを流入流出させる回転シール構造

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⑳特　　願　昭57—115868
㉒出　　願　昭57(1982)7月2日

明　細　書

1. 発明の名称　回転容器にサンプルを流入流出させる回転シール構造

2. 特許請求の範囲

遠心分離容器において、外部からのサンプルの入口と出口を有する静止部と回転容器との間に耐摩耗シール板を介在滑動させて、気密を保ちながら静止部と回転部を連絡するサンプル流路を形成させ、耐摩耗シール板の滑動面以外の位置に互いの連絡口を設けたことを特徴とする回転シール構造。

3. 発明の詳細な説明

本発明は、血液成分分離抽出用遠心分離器において、取りだす血液成分の温度上昇が生じないような回転シール部の構造に関するものである。

第1図、第2図は、従来技術の例を示す。流入流出させるサンプルとして血液を例にとる。第1図の連続遠心分離器の回転シール構造は、血液流入口2、流出口3を有する静止部材1と回転容器4に固定された耐摩耗材で作られたシール板7（第2図ではシール円筒）とが面8で互に気密を保つよう密着しながら滑動する。第1図の流入口2は、回転中心に設けてある例である。流出口3は中心からはずれた位置にある場合の例で、静止部材（または回転部材でもよい）の側にリング状溝9を設けて開口部6に連絡する。静止部材1と摺動シール板7の接触圧は、ばね10により加えられる。流入口2より入った血液は回転中心の底部に設けた溜部11に自由落下したのち、遠心力により開口部5にとばされ、回転容器4内に導かれる。つづいて血液は外周側から赤血球、白血球及び血漿の順に分離され、分離層は流入口2より入る血液の量の増加とともに分離境界層は回転中心に移動し、ついには開口部6より摺動シール板7を通過し静止部のリング溝9を経て流出口3より血漿が出ていく。白血球の占める割合は小さいので、精度よく白血球をとりだすには、白血球層の移動速度を小さくして検出を容易ならしめるのが簡単な方策である。白血球層以外は、供血者に

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再び戻す場合もあるので、極めて低い速度で発熱中の摺動部を通過させれば、体温に比べて高温の血液（白血球以外）が戻されるので、害が予想される。また白血球層は人体に戻さず患者用に採取するものであるにしても、必要以上の高温にさらされない注意を欠いてはならない。

本発明の目的は、上記の従来技術の欠点をなくし、連続遠心分離された分離物たとえば血液成分を遅い速度でとり出す場合でも温度上昇が生じないような対策をほどこすことにある。

静止部と回転容器との間を気密を保持しながら互に連絡する通路を有する連続遠心分離器の回転シール構造の改善を行うものである。温度上昇を極力低くする必要のある血液成分分離において、分離境界層付近を精度よく採取できるような低速度でとり出しても、温度上昇させないことが必要である。そのために、静止部と回転容器との間に介在させる摺動面は、摺動中気密を保つことを主目的とした耐摩耗構造とし、血液の通路は直接発熱体となる摺動部を避けた位置に設ける構造にした。

静止部材１に流入口２と流出口３があり、回転容器４に耐摩耗材で作られた摺動シール板７がピン１５で固定されている。静止部材１と摺動シール板７とは面８で適当な接触圧の下で摺動する。またリング状摺動シール板１７の片面で静止部材１と回転容器４にねじこんだナット１８との間にＯリング１６をはさみ密封および接触圧付加作用を行っている。このときリング状摺動シール板１７は、Ｏリング１６の摩擦により回転容器４と一体をなして回転し、静止部材１とは密封摺動が行われる。

かくして流入口２より入った血液は溜部１１に自由落下し、遠心力で開口部５に達し回転容器内に入り遠心分離が行われる結果、外周側より赤血球、白血液及び血漿の順に分離層を形成する。流入口２から入る血液量に応じて、最初に血漿が開口部６よりタテ溝１３、１４、リング溝１２を経て流出口３に出ていく。この通路は、摺動による摩擦熱が発生する付近を避けた位置に設けてある。

白血球採取の場合は、白血球が全血に占める割合が微小なため、流出速度があまり速いと血漿との境界を検出することがおつかしく、また白血球と赤血球の境界検出も困難である。精度よく白血球をとり出そうと思えば、できるだけゆっくりとり出し境界層の検出を容易にするのが有力な方策である。しかし、流出速度を極めて遅速にすれば、流出口が摺動シール板７を通過させる従来構造では流出する血液成分の温度上昇につながりやすい欠点がある。本発明では、流出路は摺動面８を避けているので、血液成分の温度上昇はない。

血液成分連続採取の場合は、健康者から採る血液の中から目的とする白血球成分だけとり出し、残余の血漿や赤血球は再び体内にもどすので、体温とほぼ同温で戻すのがよいと考えられる。また採取した白血球成分は、患者に注射するものでとくに顆粒球数が多いものほど有効とされている。顆粒球の生存時間は極めて短かいといわれているので、体温以上の高温にさらさないにこしたことはない。

4. 図面の簡単な説明

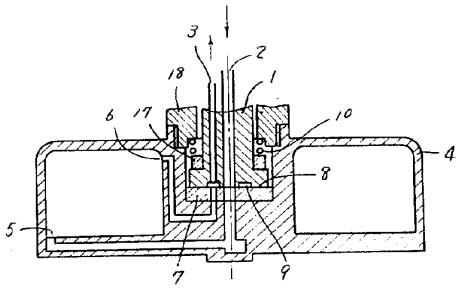
第１図、第２図は夫々従来のシール構造を示す縦断面図である。第３図は本発明の実施例を示す縦断面図であり、第４図は第３図のＡ－Ａ線断面図である。

１は静止部材、２は流入口、３は流出口、４は回転容器、５は開口部、６は開口部、７は摺動シール板、８は摺動面、９はリング溝、１０は凹ね、１１は溜部、１２はリング溝、１３はタテ溝、１４はタテ溝、１５はピン、１６はＯリング、１７はリング状摺動シール板、１８はナットである。

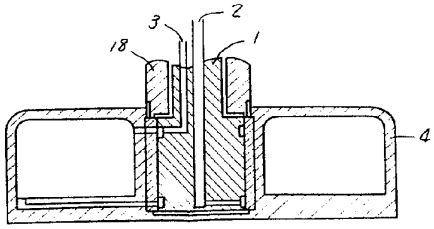
特許出願人の名称　　日立工機株式会社

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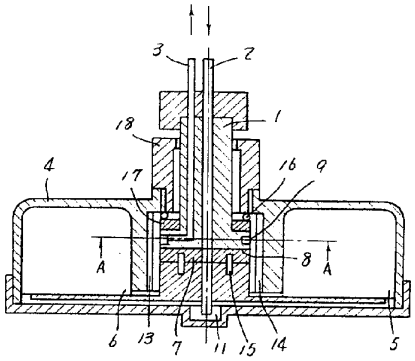
第1図



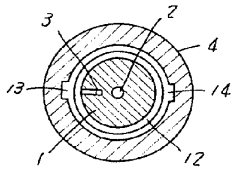
第2図



第3図



第4図



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Espacenet

Bibliographic data: JPS5969166 (A) — 1984-04-19

CENTRIFUGAL SEPARATING BOWL

Inventor(s): TAKEUCHI ATSUSANE; NODA TOSHIAKI; AIZAWA TAKESHI ± (TAKEUCHI ATSUSANE, ; NODA TOSHIAKI, ; AIZAWA TAKESHI)

Applicant(s): NIKKISO CO LTD ± (NITSUKISOU KK, ; NIKKISO CO LTD)

Classification: **- international:** ***A61M1/02; B01D15/00; B04B1/02; B04B11/00; B04B11/02; B04B7/12; B04B7/14; B04B7/18;*** (IPC1-7): B04B11/00; B04B7/12
- cooperative: B04B2005/0464

Application number: JP19820179257 19821013

Priority number (s): JP19820179257 19821013

Also published as: JPS644820 (B2)

Abstract of JPS5969166 (A)

PURPOSE:To obtain a centrifugal separating bowl which is capable of executing continuously and effectively blood plasma separation and blood plasma purification, by providing the second centrifugal separating chamber on the outside of the first centrifugal separating chamber, and separating further blood plasma separated from blood to a polymer substance and purified blood plasma. CONSTITUTION:Blood is led into a centrifugal separating bowl from a leading-in pipe 12 and is led to the first centrifugal separating chamber through a conduit 13. When a rotating vessel 14 rotates, the blood is separated into a blood corpuscle component and blood plasma. The separated blood plasma flows by an overflow into the second centrifugal separating chamber 16, and is separated into a high polymer substance and purified blood plasma.; The separated purified blood plasma passes through a path 17 of the bottom part of the rotating vessel 14 and flows to a leading-out pipe consisting of a double pipe formed concentrically with the leading-in pipe 12, and an outlet port 19. When the quantity of the blood corpuscle component increases in the first centrifugal separating chamber 15, it flows out soon to the leading-out pipe 18 and the outlet port 19 from the second centrifugal separating chamber 16.

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⑲ 日本国特許庁（JP）　　⑪ 特許出願公開

⑫ 公開特許公報（A）　　昭59—69166

⑤1Int. Cl.³	識別記号	庁内整理番号	⑬公開　昭和59年(1984)4月19日
B 04 B 11/00		7636—4D	
7/12		7636—4D	

発明の数　1
審査請求　未請求

（全 4 頁）

⑤4遠心分離ボウル

⑳特　　願　昭57—179257
㉒出　　願　昭57(1982)10月13日
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明　細　書

1. 発明の名称

遠心分離ボウル

2. 特許請求の範囲

(1) 血液導入管および浄化血漿導出管とを有する固定部と該固定部と同心に軸支持された回転容器とを備える遠心分離ボウルであって、中央の血液導入管から血液を導入し、該血液を回転容器の底部から回転容器の第1の遠心分離室へ導びき血球成分と血漿とに分離した後、該血漿を第1の遠心分離室の外側に設けられた第2の遠心分離室へ導びき、血漿を高分子物質と浄化血漿とに分離し、しかる後に浄化血漿を血液導入管と同心に形成される二重管からなる浄化血漿導出管に導びくようにしたことを特徴とする遠心分離ボウル。

(2) 第2の遠心分離室の外壁に特定の高分子物質と特異的に作用する吸着物質をコーティングしたことを特徴とする特許請求の範囲第(1)項記載の遠心分離ボウル。

(3) 第2の遠心分離室内に特定の高分子物質と特異的に作用する吸着物質を内填したことを特徴とする特許請求の範囲第(1)項記載の遠心分離ボウル。

3. 発明の詳細な説明

本発明は血液を血球成分と血漿とに分離した後、該血漿をさらに高分子物質と浄化血漿とに分離する遠心分離ボウルに関する。以下、血液を血球成分と血漿とに分離することを血漿分離、また、血液から分離した血漿から高分子物質を分離することを血漿浄化、また高分子物質を分離した血漿を浄化血漿と言う。

周知のごとく従来から遠心力を利用した遠心分離装置は広く利用されて来た。当初遠心分離装置は成分輸血等を目的に赤血球、白血球、血小板と言った細胞成分の分離に多く利用されていたが、最近免疫疾患等の治療に血漿交換が試みられるようになり血漿分離にも有効に試用されている。

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遠心分離の方法としては、遠心容器中に形成される分離層から必要とする成分を取り出す方法とディスポーザブルな遠心分離ボウルにより必要とする成分のみを取り出す方法とに大別される。本発明は、後者の遠心分離ボウルに関するものである。

これ迄、ディスポーザブルな遠心分離ボウルは臨床的には血漿交換に広く使用されている。即ち血液を血球成分と血漿とに分離し、分離した高分子物質を含む血漿はそのまま捨ててしまい、新しい血漿または代替血漿と交換することで血液の浄化を行う方法である。しかしこの方法では大量の新しい血漿または代替血漿を必要とするため、単に治療費が高くつくだけでなく不足がちである新しい血漿または代替血漿の確保そのこと自体が非常に困難となる。従って、何らかの手段により血液より分離した血漿から有害な高分子物質を分離し、浄化血漿を血球成分と共に生体へ返血することが望ましい。

このことを満足させる方法として遠心分離により血液を血球成分と血漿とに分離し、ろ過膜を通して該血漿から高分子物質を分離し浄化血漿を得る方法がある。また遠心分離により血液を血球成分と血漿とに分離し、該血漿を段階的に遠心分離することによって高分子物質を分離し浄化血漿を得る方法も可能である。

しかしながら、上記2つの方法は装置上あるいは操作上、煩雑でありまた高価なものとなるという欠点を有している。

そこで本発明者らは、前述した従来の欠点を改良・改善するべく鋭意検討を重ねた結果、血液を血液導入管から遠心分離ボウルの第1の遠心分離室に導き、血球成分と血漿とに分離した後、該血漿を第1の遠心分離室の外側に設けられた第2の遠心分離室へ導き、血漿を高分子物質と浄化血漿とに分離し、しかる後に浄化血漿を血液導入管と同心に形成される二重管からなる浄化血漿導出管に導けば、効果的に血漿を分離できることを突き止めた。

従って、本発明の目的は、従来の遠心分離による血漿交換における欠点を解消し、安価で操作性の優れた遠心分離ボウルを提供することにある。

この目的を達成するため、本発明による遠心分離ボウルにおいては、血液導入管および浄化血漿導出管とを有する固定部と、該固定部と同心に軸支持された回転容器とを備え、中央の血液導入管から血液を導入し、該血液を、回転容器の底部から回転容器の第1の遠心分離室へ導いて血球成分と血漿とに分離した後、該血漿を第1の遠心分離室の外側に設けられた第2の遠心分離室へ導び き、血漿を高分子物質と浄化血漿とに分離し、しかる後に浄化血漿を血液導入管と同心に形成される二重管からなる浄化血漿導出管に導びくようにしたことを特徴とする。さらに、第2の遠心分離室の外側に有害な特定の高分子物質と特異的に作用する吸着物質をコーティングすると好適である。さらにまた、第2の遠心分離室内に有害な特定の高分子物質と特異的に作用する吸着物質を内填しておくと好適である。

本発明によれば、1個の遠心分離ボウルにより血漿分離と血漿浄化を連続的、かつ効率的に行うことが出来るようになり同時にコスト、操作性の面での改善も極めて大きい。この点は、本発明を二段ろ過血漿分離と比較すればさらに明瞭である。

即ち、これ迄、主に遠心分離による血漿分離および血漿浄化と言う観点で本発明について述べて来たが、周知のごとく血漿分離ならびに血漿浄化にいずれもろ過膜を使用したいわゆる二段ろ過血漿分離（ＤＦＰＰ）がある。この二段ろ過血漿分離は2個のろ過膜が必要であるのに対して、本発明に係る遠心分離ボウルは1個のみであって、費用の差は大きい。さらに性能上の問題として、二段ろ過血漿分離の二段目の膜即ち血漿浄化膜においては高分子物質の目詰りによる膜性能の劣化が起り、特に分離した血漿を約4℃に冷却する冷却持続法による冷却ゲルの分離においては膜性能の劣化は極めて顕著で

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ある。しかるに本発明に係る遠心分離ボウルでは目詰りはない。また、取扱上の操作性は1個の遠心分離ボウルのみを扱う本発明が優れていることは明白である。

以下、本発明に係る遠心分離ボウルの実施例について添付図面により詳細に説明する。

第1図は従来の遠心分離ボウルの例、第2図は本発明に係る遠心分離ボウルの実施例、また第3図は第2図におけるA－A'矢視図である。

まず、第1図において、従来の遠心分離の手段を説明すると、血液は中央の入口ポート1、血液導入管2から導入され、血液導入管2と同心に軸支持された回転容器3の底部3'から遠心分離室4へ導かれる。血液は遠心分離室4で所定の遠心力を受け血球成分と血漿とに分離される。血液が連続的に遠心分離ボウル内へ送られると、遠心分離室4で血球成分と血漿とは分離されて、血漿が血液導入管2と同心に形成されていて遠心分離室4に開口する二重管からなる血漿導出管5、出口ポート6を経て遠心分離ボウルの外部へ取り出される。8はシールリング、7はシールパッキン材で、8と7は相助けて血漿のためのシール作用と回転体の軸受けの作用をはたしている。遠心分離室4の内部に血球成分が満たされると血漿導出管5へ流れ出す。この時検出器またはタイマ（いずれも図示せず）によって遠心分離ボウルの回転を停止し、血球成分を別の手段により回収することが出来る。遠心分離ボウルの外部へ取り出された血漿は前述のごとく必要に応じた処理を行わねばならない。

次に、本発明に係る遠心分離ボウルについて第2図、第3図に従って説明する。

第2図において遠心分離ボウルは入口ポート11と血液導入管12および浄化血漿導出管18と出口ポート19を有する固定部と該固定部と同心に軸支持される回転容器14とからなる。20は軸受である。血液は入口ポート11、血液導入管12から遠心分離ボウルへ導入され、血液導入管12の最下端の4本の分岐からなる導管13を経て第1遠心分離室15へ導びかれる。回転容器14は所定の回転数で回転され第1遠心分離室15において血液は血球成分と血漿とに分離される。血液が連続的に遠心分離ボウルへ送られると遠心力によって分離された血漿は第1遠心分離室15より第2遠心分離室16へ溢流で流入する。第2遠心分離室において高分子物質と浄化血漿とに分離される。分離された浄化血漿は回転容器14の底部にある通路17を経て血液導入管12と同心に形成されている二重管からなる浄化血漿導出管18、出口ポート19へと流れ外部へ取り出される。外部へ取り出された浄化血漿は先に分離した血球成分と混合して生体へ返血される。第1遠心分離室15の内部に血球成分の量が増大して来るとやがて第2遠心分離室16から浄化血漿導出管18、出口ポート19へ流出するに至る。この状態になった時適宜検出器またはタイマ（いずれも図示せず）によって遠心分離ボウルの回転を停止し、血球成分を別の手段により回収することが出来る。この操作を何回か繰り返し必要量の血液を処理すればよい。

なお、最近血漿を4℃付近迄冷却していわゆる冷却ゲルを分離する方法が試みられているが本発明に係る遠心分離ボウルを使用した場合にも遠心機（図示せず）の内部を冷却することによって冷却ゲルを分離することが可能である。

また、第2の遠心分離室16の内壁に特定の高分子物質と特異的に作用する吸着物質をコーティングするか、あるいは遠心分離室内に内填することにより特定の高分子物質を効果的に除去することが可能であり有効である。

本発明に係る遠心分離ボウルを使用して血液浄化を行ったところ血漿分離ならびに血漿浄化共極めて良好な結果を得ることが出来た。

以上、本発明の好適な実施例について説明したが本発明の応用範囲は極めて広く本発明の精神を逸脱しない範囲において、種々設計変更をなし得ることは言う迄もない。

4. 図面の簡単な説明

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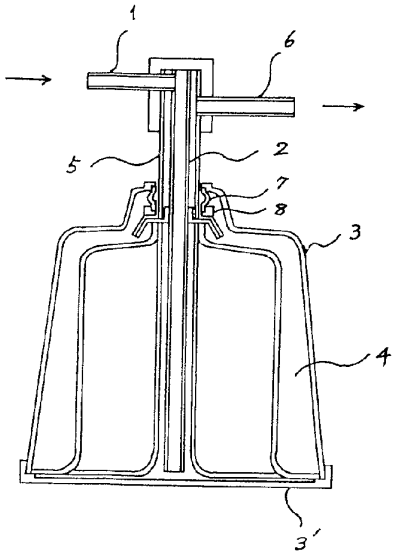
第1図は従来の遠心分離ボウルの例、第2図は本発明に係る遠心分離ボウルの実施例、また第3図は第2図におけるA－A'矢視図である。

11・・・入口ポート　12・・・血液導入管
13・・・導管　14・・・回転容器
15・・・第1遠心分離室　16・・・第2遠心分離室
17・・・通路　18・・・浄化血漿導出管
19・・・出口ポート　20・・・軸受

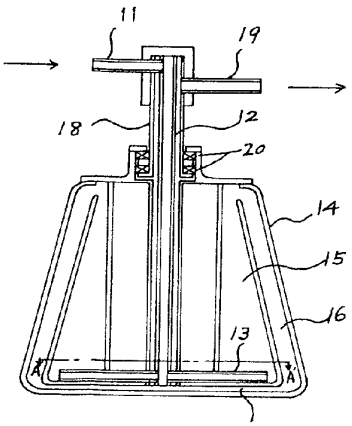
特許出願人　日機装株式会社

代理人　弁理士　前田篤男

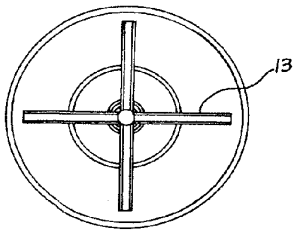
第1図



第2図



第3図



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Espacenet

Bibliographic data: SU1146098 (A1) — 1985-03-23

ROTOR FOR SEPARATING BLOOD AND WASHING HEAVY FRACTIONS

Inventor(s): IGNATOV VIKTOR I [SU]; PERMINOVA ZOYA A [SU]; TYURIN VLADIMIR L [SU]; TSIMARKINA GALINA E [SU]; LOTTS YURIJ A [SU] ± (IGNATOV VIKTOR I,SU, ; PERMINOVA ZOYA A,SU, ; TYURIN VLADIMIR L,SU, ; TSIMARKINA GALINA E,SU, ; LOTTS YURIJ A,SU)

Applicant(s): SP K B BIOFIZ APP [SU] ± (SP K BYURO BIOFIZ APP)

Classification: **- international:** ***B04B5/00; B04B5/04;*** (IPC1-7): B04B5/00
- cooperative: **B04B5/0442**

Application number: SU19833590453 19830511

Priority number(s): SU19833590453 19830511

Abstract not available for SU1146098 (A1)

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СОЮЗ СОВЕТСКИХ СОЦИАЛИСТИЧЕСКИХ РЕСПУБЛИК

(19) SU (11) 1146098 A

4(51) B 04 B 5/00

ГОСУДАРСТВЕННЫЙ КОМИТЕТ СССР ПО ДЕЛАМ ИЗОБРЕТЕНИЙ И ОТКРЫТИЙ

ВСЕСОЮЗНАЯ ПАТЕНТНО-ТЕХНИЧЕСКАЯ БИБЛИОТЕКА 13 13

ОПИСАНИЕ ИЗОБРЕТЕНИЯ

К АВТОРСКОМУ СВИДЕТЕЛЬСТВУ

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(22) 11.05.83
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(72) В.И. Игнатов, З.А. Перминова, В.Л. Тюрин, Г.Е. Цимаркина и Ю.А. Лотц
(71) Специальное конструкторское бюро биофизической аппаратуры
(53) 66.067.57(088.8)
(56) 1. Авторское свидетельство СССР № 762982, кл. B 04 B 5/00, 1978.
2. Авторское свидетельство СССР № 1061333, кл. B 04 B 5/00, 1981 (прототип).

(54)(57) РОТОР ДЛЯ РАЗДЕЛЕНИЯ КРОВИ И ПРОМЫВКИ ТЯЖЕЛОЙ ФРАКЦИИ, содержащий корпус со съемным днищем, размещенную в нем с образованием кольцевой рабочей полости конусообразную вставку, состоящую из колпака, связанного с ним днища со стойкой, расположенной вертикально по оси ротора, устройство для подвода жидкости и отвода разделенных фракций и уплотнительную эластичную втулку, установленную в верхней части корпуса, о т л и ч а ю щ и й с я тем, что, с целью предотвращения деформации деталей ротора при стерилизации и повышения надежности ротора в работе, нижняя часть втулки выполнена конусообразной и размещена внутри стойки, при этом горловина колпака вставки расположена с зазором относительно стойки, причем торцовая поверхность последней и торцовая поверхность втулки образуют кольцевой канал, а в теле втулки выполнены сообщающиеся с последним сквозные каналы для отвода и подвода воздуха из атмосферы во внутреннюю полость вставки.

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Изобретение относится к медицинской технике, в частности к устройствам, предназначенным для разделения крови на легкую и тяжелую фракции и отмывки тяжелой фракции от криофилактиков после ее длительного хранения в замороженном состоянии.

Известен ротор для разделения крови и промывки тяжелой фракции, содержащий корпус с днищем, размещенную между ними конусообразную вставку, трубку для подвода крови, промывной жидкости и отвода легкой фракции и затвора ротора, который может использоваться многократно [1].

Однако большое число деталей усложняет сборку и предстерилизационную обработку ротора, кроме того, наличие затвора, требующего смазки трущихся поверхностей в процессе вращения ротора, неизбежно приводит к попаданию смазки в рабочую зону ротора, что снижает его надежность в работе и качество разделенных компонентов.

Наиболее близким к изобретению по технической сущности и достигаемому результату является ротор для разделения крови и промывки тяжелой фракции, содержащий корпус со съемным днищем, размещенную в нем с образованием кольцевой рабочей полости конусообразную вставку, состоящую из колпака, связанного с ним днища со стойкой, расположенной вертикально по оси ротора, устройство для подвода жидкости и отвода разделенных фракций и уплотнительную эластичную втулку, установленную в верхней части корпуса [2].

Недостатками известного устройства являются недостаточная надежность ротора при максимальном факторе разделения из-за разгерметизации рабочей зоны ротора и попадания жидкости во внутреннюю полость вставки через вертикальный канал стойки, недолговечность при стерилизации автоклавированием в общепринятом режиме, что вызывает деформацию или серебрение (растрескивание) деталей вставки.

Целью изобретения является предотвращение деформации деталей ротора при стерилизации и повышение надежности ротора в работе.

Поставленная цель достигается тем, что в роторе для разделения крови и промывки тяжелой фракции, содержащем корпус со съемным днищем, размещенную в нем с образованием кольцевой рабочей полости конусообразную вставку, состоящую из колпака, связанного с ним днища со стойкой, расположенной вертикально по оси ротора, устройство для подвода жидкости и отвода разделенных фракций и уплотнительную эластичную втулку, установленную в верхней части корпуса, нижняя часть втулки выполнена конусообразной и размещена внутри стойки, при этом горловина колпака вставки расположена с зазором относительно стойки, причем торцовая поверхность последней и торцовая поверхность втулки образуют кольцевой канал, а в теле втулки выполнены сообщающиеся с последним сквозные каналы для отвода и подвода воздуха из атмосферы во внутреннюю полость вставки.

На фиг. 1 дано устройство, общий вид; на фиг. 2 - узел I на фиг. 1; на фиг. 3 - разрез А-А на фиг. 2.

Ротор для разделения крови и промывки тяжелой фракции состоит из корпуса 1, представляющего собой полый усеченный конус, который установлен расширенной частью на съемном днище 2 с прокладкой 3 между ними. Внутри корпуса 1 размещена с образованием кольцевой рабочей полости конусообразная вставка 4, установленная на днище, имеющем на верхней плоскости радиальные выступы 5 и упоры 6.

Вставка 4 состоит из колпака 7 и стойки 8, причем горловина колпака 7 вставки 4 расположена с кольцевым зазором 9 относительно стойки 8, а в нижней части размещена прокладка 10 для герметизации внутреннего объема вставки 4. Стойка 8 размещена вертикально по оси ротора.

В верхней части ротора между корпусом 1 и вставкой 4 размещены устройство для отвода легкой фракции и подвижный элемент затвора ротора, выполненные за одно целое в виде втулки 11 из эластичного материала, центрально установленной над вставкой 4, в центральной части которой расположены радиальные каналы 12 для отвода легкой фракции.

Втулка 11 плотно входит в горловину колпака 7 вставки 4 с образова-

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нием кольцевого зазора 13 между торцовой поверхностью втулки 11 и торцом стойки 8. В теле втулки 11 выполнены сквозные каналы 14, которые проходят через втулку 11 для соединения внутренней полости вставки 4 с внешней средой для отвода и подвода воздуха из атмосферы. Количество отверстий должно быть не менее двух, и расположены они на одном радиусе. Нижняя часть 15 втулки 11 выполнена конусообразной и плотно вставлена в вертикальный канал стойки 8.

Верхняя часть втулки 11 - уплотнительный элемент затвора - выступает над ротором и за счет проточки 16 фиксирована и плотно размещена в горловине корпуса 1 ротора, герметизируя внутреннюю рабочую полость 17 ротора. Внутри втулки 11 выполнена кольцевая камера 18 для сбора легкой фракции, соединенная с радиальными каналами 12 втулки 11.

Затвор 19 ротора, закрепленный неподвижно концентрично вставке 4, своей нижней частью размещен во втулке 11 так, что трубка 20 подвода крови, промывной жидкости и отвода тяжелой фракции расположена по оси вставки до днища 2 ротора. Детали ротора соединены вместе винтами 21, размещенными по периферии нижней части корпуса 1 и днища 2 ротора. Днище 2 снизу имеет кольцевой выступ 22, которым ротор устанавливают и закрепляют на планшайбе приводного устройства (не показано).

Ротор имеет набор колпаков 7 для конусообразной вставки 4, отличающихся углом наклона корпуса, что позволяет при необходимости изменять объем внутренней рабочей полости 17 ротора. При этом максимальный объем ротора на 100 мл превышает объем известного ротора.

Ротор работает следующим образом.

Собранный ротор с ослабленными винтами подвергают стерилизации в паровом стерилизаторе в общепринятом режиме при 120°С (под давлением 1,2 атм). При стерилизации наиболее напряженным узлом ротора является вставка 4. Под воздействием температуры воздух, находящийся внутри вставки 4, расширяется и избыток его удаляется через зазоры 9 и 13 и сквозные каналы 14.

В период охлаждения ротора вместе со стерилизатором (автоклавом) воздух сжимается и недостаток его во вставке 4 пополняется из окружающей среды (воздух из автоклава) через каналы 14 и зазоры 9 и 13.

Таким образом, при стерилизации в периоды нагревания и охлаждения не возникает изменения давления внутри вставки 4, а следовательно, деформации колпака и стойки 8.

После стерилизации винты ротора затягиваются и ротор устанавливается на планшайбе приводного устройства, при этом неподвижный элемент затвора ротора закрепляется при помощи специального фиксатора (не показано). К штуцерам неподвижного элемента затвора 19 подсоединяются трубки: к центральному - от насоса подачи крови (или эритроцитной массы и промывной жидкости) и отбора тяжелой фракции, к боковому - от емкости для сбора легкой фракции.

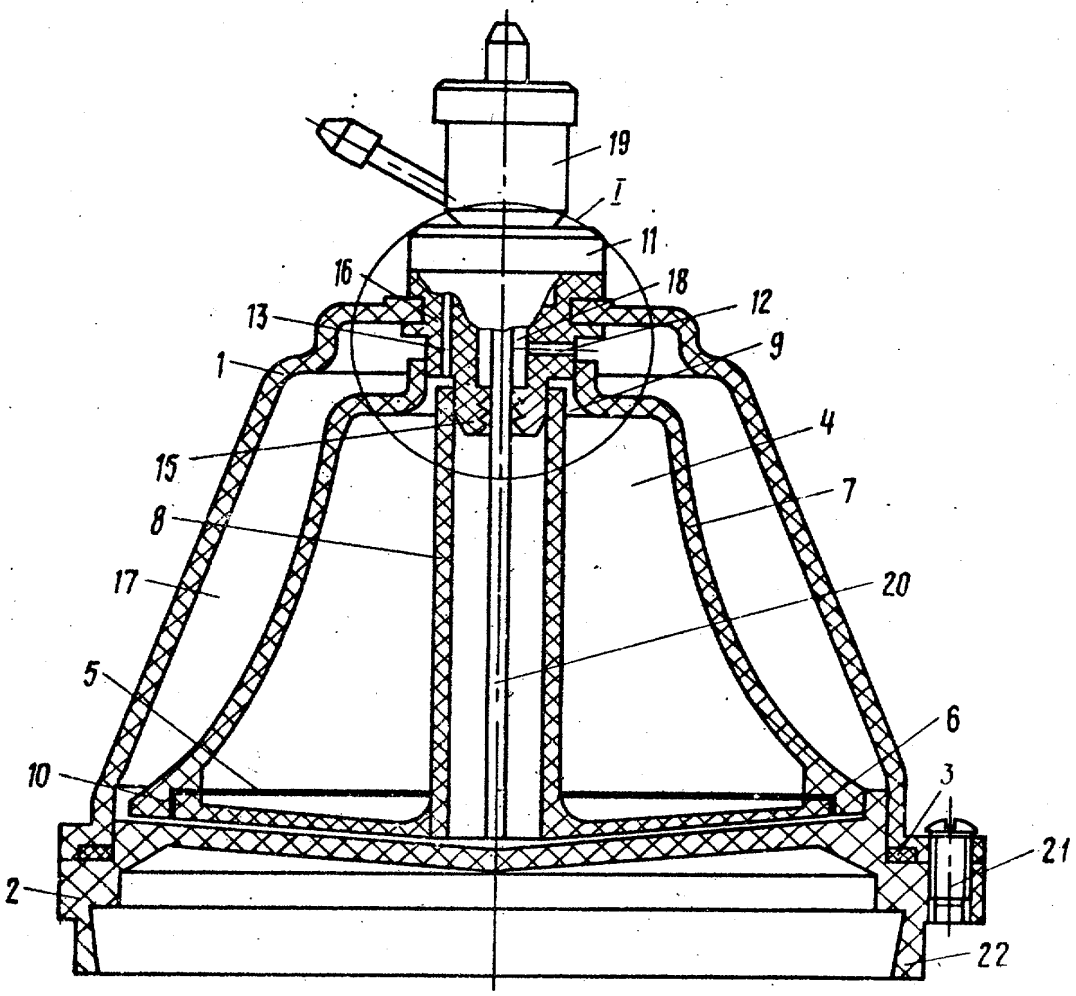
При вращении ротора с заданной частотой насосом в него подается кровь или размороженная эритроцитная масса с промывными растворами. При этом кровь по трубке 20, попадая на днище 2 ротора, центробежной силой отбрасывается к периферии и разделяется на фракции: тяжелую (эритроцитную массу) и легкую (плазму или отливной раствор), располагающуюся ближе к центру ротора. По мере заполнения ротора вновь поступающими порциями крови легкая фракция вытесняется к центру ротора и по каналу 12 втулки 11 поступает в кольцевую камеру 18 втулки 11, откуда отводится в специальную емкость.

После разделения дозы крови или подачи всего необходимого количества промывного раствора ротор останавливают и эритроцитную массу отбирают по трубке 20 в специальную емкость обратным ходом насоса.

Изобретение позволяет предотвратить деформацию деталей ротора при стерилизации в самых жестких условиях автоклавирования за счет наличия зазоров, обеспечивающих соединение внутренней полости вставки с внешней средой, что приводит к постоянному стабильному давлению внутри вставки в периоды нагревания.

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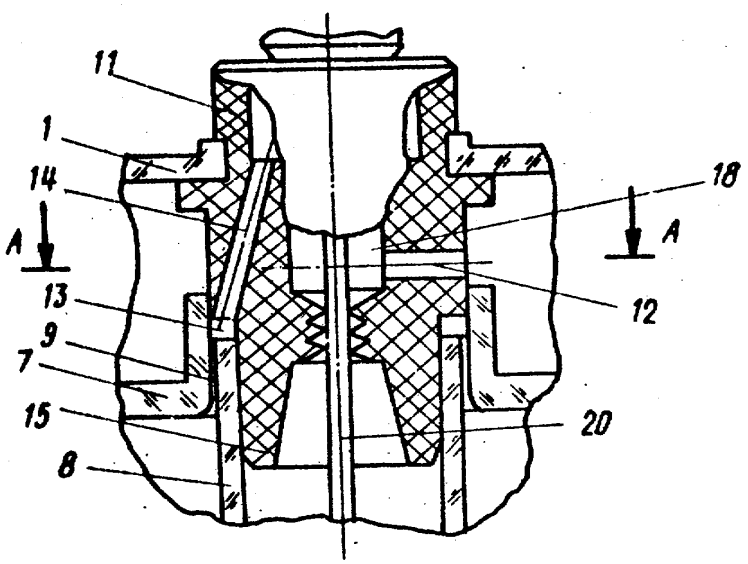
и охлаждения в процессе стерилизации, и повысить надежность ротора в работе при максимальном факторе разделения (1850) за счет надежной герметизации и изоляции всех полостей ротора.



Фиг.1

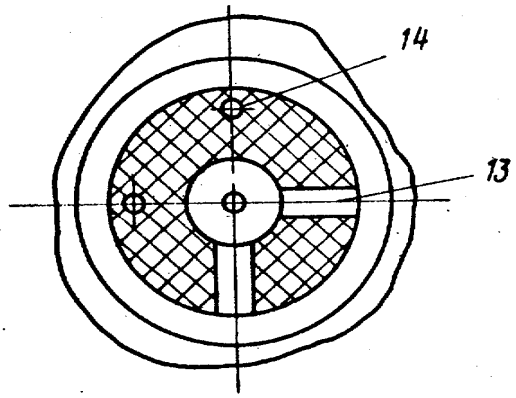
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I



Фиг.2

А – А



Фиг.3

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Petitioner Terumo Exhibit 1021-0594

Espacenet

Bibliographic data: SU660718 (A1) — 1979-05-05

ROBOT FOR SEPARATING BLOOD AND FLUSHING THE HEAVIER FRACTION

Inventor(s): TSIMARKINA GALINA E; TYURIN VLADIMIR L ± (TSIMARKINA GALINA E,SU, ; TYURIN VLADIMIR L,SU)

Applicant(s): SP K B BIOFIZICHESKOJ APPARATU [SU] ± (SP K BYURO BIOFIZICHESKOJ APPARATURY)

Classification: **- international:** ***B04B5/00; B04B5/04;*** (IPC1-7): B04B5/00
- cooperative: **B04B5/0442**; B04B2005/0464

Application number: SU19772478910 19770425

Priority number (s): SU19772478910 19770425

Abstract not available for SU660718 (A1)

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Petitioner Terumo Exhibit 1021-0595

Союз Советских Социалистических Республик

Государственный комитет СССР по делам изобретений и открытий

ОПИСАНИЕ ИЗОБРЕТЕНИЯ

К АВТОРСКОМУ СВИДЕТЕЛЬСТВУ

(11) 660718

(61) Дополнительное к авт. свид-ву —

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(54) РОТОР ДЛЯ РАЗДЕЛЕНИЯ КРОВИ И ПРОМЫВКИ ТЯЖЕЛОЙ ФРАКЦИИ

1

Изобретение относится к области медицинской техники, а именно к роторам, предназначенным для разделения крови на плазму и форменные элементы и промывки тяжелой фракции крови (эритроцитной массы) от криоагентов после ее длительного хранения.

Известен ротор для разделения крови и промывки тяжелой фракции, включающий корпус с днищем, размещенную в нем конусообразную вставку с образованием между ними кольцевой рабочей полости и состоящую из связанных между собой колпака днища и стойки, расположенной вертикально по оси ротора, укрепленную неподвижно, концентрично стойке, трубку для подвода крови, промывной жидкости и отвода отмытой тяжелой фракции, устройство для отвода легкой фракции, смонтированное на последней над вставкой, затвор ротор, содержащий неподвижную втулку с патрубком для отвода легкой фракции.

В известном роторе корпус с днищем и вставка неразъемно скреплены между собой [1].

Недостатком известного ротора является невозможность его многократного использования, что удорожает стоимость отмывной

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дозы крови и ухудшает качество разделяемых фракций.

Целью настоящего изобретения является повышение качества и выхода разделенных фракций крови при сохранении их биологической активности.

Поставленная цель достигается тем, что затвор ротора снабжен имеющим по внутреннему периметру бортик диском, размещенным на корпусе ротора на демпфирующем уплотнении, и кольцом, жестко связанным со втулкой с образованием между ними полости для подвода охлаждающей жидкости и имеющим отверстия для прохода последней на трущиеся поверхности, при этом колпак вставки укреплен на стойке с помощью гаек и втулки с отверстием, связывающим внутренние полости вставки и ротора, причем днище вставки и корпуса выполнены конусообразными и съемными.

На чертеже представлен общий вид ротора в разрезе.

Ротор выполнен разборным и содержит корпус 1 с днищем 2, к которому винтом 3 прикреплена конусообразная вставка 4, состоящая из стойки 5 и колпака 6, герметично соединенных между собой с помощью гаек 7 и 8.

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Для герметичности внутренней полости вставки предусмотрены два уплотнительных кольца 9 и 10. Стойка 5 в нижней своей части имеет ребра жесткости 11 для сохранения геометрической формы конусообразной вставки 4 при увеличении давления воздуха в ней при автоклавировании. В гайке 8 выполнено отверстие 12, связывающее внутреннюю полость вставки 4 и кольцевую рабочую полость ротора, образованную корпусом 1 и колпаком 6. Снаружи корпуса 1 размещена подвижная часть затвора — диск 13 с бортиком 14 по внутреннему периметру на демпфирующем уплотнении 15. Бортик 14 предназначен для предохранения кольцевой рабочей полости от попадания в нее смазочной жидкости после остановки ротора. Для уменьшения коэффициента трения диск 13 выполнен из низкофрикционного материала.

Неподвижная часть затвора, выполненная в виде втулки 16 с патрубком 17, закреплена гайкой 18 на трубке 19 для подвода крови, промывной жидкости и отвода отмытой тяжелой фракции. В нижней части втулки 16 жестко закреплено кольцо 20 так, что между ним и втулкой 16 образована кольцевая полость 21 для подвода охлаждающей жидкости через штуцер 22. В кольце 20 выполнены несколько капиллярных отверстий 23 для прохода охлаждающей жидкости на трущиеся поверхности затвора.

Для отвода легкой фракции крови предусмотрены вставленные друг в друга втулки 24 и 25, смонтированные на трубке 19 над вставкой 4 таким образом, что между ними образовано узкое щелевидное пространство, начинающееся в рабочей полости ротора и заканчивающееся в верхней части втулки 16 патрубком 17. Днище 2 ротора выполнено конусообразным и съемным.

Работа ротора заключается в следующем.

Собранный из чистых деталей ротор с неполностью затянутым винтом 3 и гайкой 18 стерилизуется в автоклаве. После охлаждения ротора винт 3 и гайка 18 затягиваются до упора. Ротор помещается на планшайбу приводного устройства (на чертеже не показано), а к штуцерам 22 подсоединяются трубки от насоса подачи физиологического раствора и емкости для сливной охлаждающей жидкости. К трубке подвода 19 подсоединяются коммуникации от насоса подачи крови, а к патрубку 17 — емкость для сбора плазмы. Перед вращением ротора по штуцеру 22 подается при небольшом давлении стерильный физиологический раствор, после чего включается приводное устройство ротора.

При вращении ротора по трубке подвода 19 подается насосом кровь, которая, поступая в нижнюю часть кольцевой рабочей полости ротора, центробежной силой отбрасывается к периферии его и разделяется на фракции: тяжелую (эритроцитную массу) и легкую (плазму), располагающуюся ближе к центру ротора. При достижении слоем плазмы наружных втулок 24 и 25 плазма поступающих в ротор последующих порций крови будет вытесняться в щелевидное пространство внутри втулки 16 и отводиться патрубком 17 в специальную емкость. После заполнения рабочей полости ротора эритроцитной массой, соответствующей одной дозе крови, подача крови прекращается, ротор останавливается, после чего насос подачи физиологического раствора отключается и эритроцитная масса стекает в нижнюю часть ротора, откуда обратным ходом насоса подачи крови по трубке 19 отбирается в специальную емкость.

Отмывка клеток крови от криоагентов производится аналогичным способом, после подачи в ротор по трубке 19 размороженных эритроцитов насосом непрерывно подаются для отмывки растворы определенного состава. Отмытые клетки крови отбираются после остановки ротора обратным ходом насоса подачи крови.

Благодаря выполнению подвижной части затвора в виде диска с бортиком по внутреннему периметру, установленного на демпфирующем уплотнении, а его неподвижной части — в виде втулки, размещенной на трубке для подвода крови и содержащей кольцевую полость для охлаждающей жидкости, соединенную капиллярными отверстиями для прохода жидкости на трущиеся поверхности затвора, обеспечивается снижение температуры деталей, контактирующих с компонентами крови, что, в свою очередь, повышает качество и выход разделяемых фракцией при сохранении их биологической активности.

Кроме того, выполнение вставки ротора из двух частей — стойки и колпака, герметччично скрепленных между собой гайкой с отверстиями, позволяет снизить давление воздуха при нагреве ротора и тем самым исключает возможность деформации вставки при тепловой стерилизации.

Поэтому, благодаря конструктивным особенностям предлагаемого ротора, появилась возможность многократного его использования, что снижает стоимость отмывки и разделения одной дозы крови по сравнению с известным. Разборность конструкции ротора позволяет проводить тщательную обработку всех поверхностей его, соприкасающихся с кровью, что исключает возможность инфицирования разделенных компонентов и гарантирует полную безопасность для здоровья реципиента.

Формула изобретения

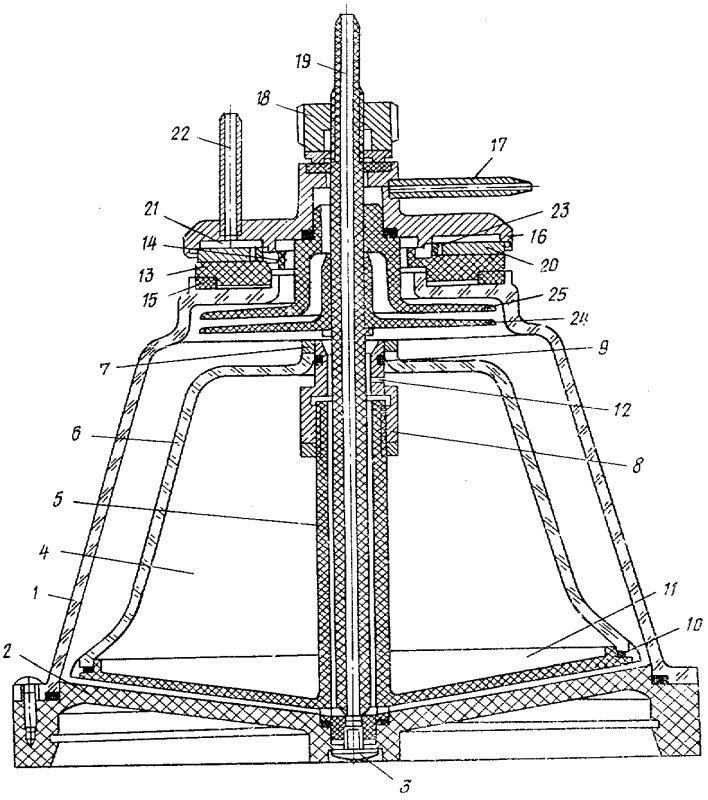
Ротор для разделения крови и промывки тяжелой фракции, включающий корпус с днищем, размещенную в нем конусообраз-

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ную вставку с образованием между ними кольцевой рабочей полости и состоящую из связанных между собой колпака, днища и стойки, расположенной вертикально по оси ротора, укрепленную неподвижно, концентрично стойке, трубку для подвода крови, промывной жидкости и отвода отмытой тяжелой фракции, устройство для отвода легкой фракции, смонтированное на трубке над вставкой, и затвор ротора, содержащий неподвижную втулку с патрубком для отвода легкой фракции, *отличающийся* тем, что, с целью повышения качества разделенных фракций, затвор ротора снабжен имеющим по внутреннему периметру бортик диском, размещенным на корпусе ротора на демпфирующем уплотнении, и кольцом, жестко связанным со втулкой с образованием между ними полости для подвода охлаждающей жидкости и имеющим отверстия для прохода последней на трущиеся поверхности при этом колпак вставки укреплен на стойке с помощью гаек и втулки с отверстием, связывающим внутренние полости вставки и ротора, причем днище вставки и корпуса выполнены конусообразными и съемными.

Источники информации, принятые во внимание при экспертизе

1. Выложенная заявка Франции № 2294757, кл. В 04 В 15/00, 1976.



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Petitioner Terumo Exhibit 1021-0598

Espacenet

Bibliographic data: SU762982 (A1) — 1980-09-15

ROTOR FOR BLOOD SEPARATION AND WASHING HEAVY FRACTION

Inventor(s): TSIMARKINA GALINA E; TYURIN VLADIMIR L; PAVLINOVA NATALYA E; IGNATOV VIKTOR; LOTTS YURIJ A ± (TSIMARKINA GALINA E,SU, ; TYURIN VLADIMIR L,SU, ; PAVLINOVA NATALYA E,SU, ; IGNATOV VIKTOR ,SU, ; LOTTS YURIJ A,SU)

Applicant(s): SP K B BIOFIZICHESKOJ APPARATU [SU] ± (SP K BYURO BIOFIZICHESKOJ APPARATURY)

Classification: **- international:** ***B04B5/04;*** (IPC1-7): B04B5/00
- cooperative: **B04B5/0442;** B04B2005/0464

Application number: SU19782666638 19780922

Priority number(s): SU19782666638 19780922

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Союз Советских Социалистических Республик

Государственный комитет СССР по делам изобретений и открытий

ОПИСАНИЕ ИЗОБРЕТЕНИЯ

К АВТОРСКОМУ СВИДЕТЕЛЬСТВУ

(11) 762982

(61) Дополнительное к авт. свид-ву –

(22) Заявлено 22.09.78 (21) 2666638/23-13

с присоединением заявки № –

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(51) М. Кл.^{3} В 04 В 5/00

(53) УДК 66.067.57(088.8)

(72) Авторы изобретения: Г.Е. Цимаркина, В.Л. Тюрин, Н.Е. Павлинова, В.И. Игнатов и Ю.А. Лотц

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ВПТБ ФОНД ЭКСПЕРТОВ

(54) РОТОР ДЛЯ РАЗДЕЛЕНИЯ КРОВИ И ПРОМЫВКИ ТЯЖЕЛОЙ ФРАКЦИИ

1

Изобретение относится к области медицинской техники, а именно к роторам, предназначенным для разделения крови на плазму и форменные элементы и промывки тяжелой фракции крови (эритроцитной массы) от криоагентов после длительного хранения.

Известны роторы для разделения крови и промывки тяжелой фракции, содержащие корпус с днищем, размещенную между ними конусообразную вставку, трубку для подвода крови, промывной жидкости отвода отмытой тяжелой фракции, устройство для отвода легкой фракции и затвор ротора [1] и [2].

Эти роторы предназначены для разового использования, что значительно удорожает стоимость обработанной дозы крови.

Ближайшим техническим решением к предложенному изобретению является ротор для разделения крови и промывки тяжелой фракции, включающий корпус со съемным днищем, размещенную в нем с образованием кольцевой рабочей полости конусообразную вставку, состоящую из связанных между собой колпака, съемного днища и стойки, расположенной вертикально по оси ротора, укрепленную неподвижно концентрично стойке трубку для подвода крови, промывной жидкости и отвода отмытой тяжелой фракции, устройство для отвода легкой фракции, смонтированное над вставкой, и затвор ротора [3].

2

Недостатком такого ротора является сложность сборки вставки из-за наличия специальных гаек и уплотнительных колец, что значительно затрудняет сборку и разборку ротора и увеличивает время стерилизации вставки. Кроме того, из-за различных коэффициентов теплового расширения металла и пластмассы дно стойки после тепловой стерилизации деформируется, нарушая уплотнение между колпаком и дном стойки, что приводит к попаданию крови во внутреннюю полость вставки.

Необходимо отметить, что большое количество деталей ротора удорожает его стоимость, при этом повышается трудоемкость и снижается качество сборки ротора.

Целью изобретения является упрощение конструкции, повышение надежности работы и снижение стоимости.

Для этого в предложенном роторе в рабочей полости нижняя часть корпуса

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выполнена с симметрично расположенными вертикальными ребрами, имеющими участки, прилегающие к наружной поверхности вставки, а днище корпуса снабжено радиальными ступенчатыми выступами, служащими опорой для вставки и размещенными в одной плоскости с вертикальными ребрами.

На чертеже показан описываемый ротор для разделения крови и промывки тяжелой фракции, разрез.

Ротор выполнен разборным и состоит из днища 1, корпуса 2 и конусообразной вставки 3, скрепленных вместе с помощью винтов 4 так, что между ними образована кольцевая рабочая полость. На внутренней поверхности днища 1 выполнены радиально ступенчатые выступы 5, служащие опорой для вставки 3. Вставка 3 состоит из колпака 6 и стойки 7, вставленных друг в друга, причем в нижней части стойки 7 вставлено уплотнительное резиновое кольцо 8, обеспечивающее герметизацию соединения колпака 6 со стойкой 7 по периметру вставки 3. Внутри нижней части корпуса 2 выполнены вертикальные ребра 9, расположенные симметрично и имеющие участки, прилегающие к наружной поверхности колпака 6 вставки 3 и предназначенные для прижима кромки вставки 3 через резиновое уплотнительное кольцо 8 к дну стойки 7, опирающемуся на ступенчатые выступы 5 днища 1.

Снаружи корпуса 2 размещена подвижная часть затвора - диск 10. Неподвижная часть затвора, выполненная в виде втулки 11 с патрубком 12, закреплена гайкой 13 на трубке 14 для подвода крови, промывной жидкости и отвода отмытой тяжелой фракции.

Снизу втулки 11 жестко закреплено кольцо 15 так, что между ним и втулкой 11 образована кольцевая полость для подвода охлаждающей жидкости через штуцер 16. В кольце 15 выполнены несколько капиллярных отверстий для прохода охлаждающей жидкости на трущиеся поверхности затвора.

Для отвода легкой фракции крови предусмотрены вставленные одна в другую втулки 17 и 18, смонтированные на трубке 14 над вставкой 3 таким образом, что между ними образовано узкое щелевидное пространство, начинающееся в рабочей полости ротора и заканчивающееся в верхней части втулки 11 патрубком 12.

Ротор работает следующим образом.

Собранный из чистых деталей ротор с неполностью затянутыми винтами 4 и гайкой 13 стерилизуется в специальном автоклаве, где перегретый пар поступает по штуцеру во внутреннюю полость ротора, стерилизуя все поверхности его, соприкасающиеся с кровью.

После охлаждения ротора винты 4 и гайка 13 затягиваются до упора, при этом обеспечивается герметичность соединения колпака 6 и стойки 7 по всему периметру вставки 3.

Ротор помещается на планшайбу приводного устройства (на чертеже не показано), а к штуцерам 16 подсоединяются трубки от насоса подачи физиологического раствора и емкости для сливной охлаждающей жидкости.

К трубке 14 ввода подсоединяются коммуникационная трубка от насоса подачи крови (на чертеже не показано), а к патрубку 12 - емкость для сбора плазмы. При небольшой скорости вращения ротора включается подача стерильного физиологического раствора, после чего скорость вращения ротора увеличивается до заданной, и насосом подается по трубке 14 кровь, которая, попадая на днище 1 ротора, центробежной силой откидывается к периферии его и разделяется на фракции: тяжелую (эритроцитную массу) и легкую (плазму) располагающуюся ближе к центру ротора. При достижении слоем плазмы наружных кромок втулок 17 и 18 плазма напором поступающих в ротор последующих порций крови вытесняется в вертикальную полость втулки 11 и отводится патрубком 12 в специальную емкость. После заполнения внутренней полости ротора эритроцитной массой, что соответствует объему эритроцитов в одной дозе крови, ротор останавливается, после чего насос подачи физиологического раствора отключается, эритроцитная масса стекает в нижнюю часть ротора, откуда обратным ходом насоса подачи крови по трубке 14 отбирается в специальную емкость.

Отмывка клеток крови от криоагентов производится аналогичным образом, только после подачи в ротор по трубке 14 размороженных эритроцитов насосом непрерывно подаются отмывные растворы определенного состава. Отмывные клетки крови отбираются после остановки ротора обратным ходом насоса подачи крови.

Благодаря выполнению в корпусе ротора симметрично расположенных вертикальных ребер, прилегающих к боковой поверхности колпака вставки, а на днище ротора - радиальных ступенчатых выступов, являющихся опорой для стойки, обеспечивается герметичность нижней части вставки в месте соединения колпачка и стойки за счет только внешних винтов, скрепляющих корпус и днище ротора.

При этом отпадает необходимость введения дополнительных крепежных деталей для вставки, что позволяет сократить металлоемкость и трудоемкость изготовления и полностью исключить деформацию вставки ротора при автоклавировании, являющуюся результатом различия коэффициентов термического расширения пластмассы и стали.

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Данная конструкция удобна в сборке, работе и стерильной обработке ротора после проведения экспериментов, так как все крепежные детали, сведенные до минимума, вынесены на наружную поверхность ротора. В то же время детали корпуса и днища, кроме основной функции изолирования разделяемого объема крови, выполняют функцию герметичного соединения деталей вставки в рабочем состоянии.

Выполнение на днище ротора ступенчатых выступов позволяет упростить конструкцию стойки днища, что улучшает технологию ее изготовления, а также исключает дополнительное сопротивление потоку крови, что может вызвать частичный гемолиз клеток, проталкиваемых во внутреннюю полость ротора через узкие отверстия.

В связи с тем, что во внутренней полости ротора исключены металлические крепежные детали, появилась возможность использования других способов стерилизации, например химическим дезоксоном, применяемым только для стерильной обработки изделий из пластмассы.

Таким образом, предлагаемая конструкция позволяет улучшить эксплуатационные характеристики ротора за счет легкости сборки и обработки деталей его, расширения видов стерилизации, исключения дополнительного сопротивления потоку крови, снижения гемолиза.

Упрощение конструкции за счет уменьшения количества деталей уменьшает трудоемкость изготовления, сокращает использование металла и снижает стоимость ротора.

Формула изобретения

Ротор для разделения крови и промывки тяжелой фракции, включающий корпус со съемным днищем, размещенную в нем с образованием кольцевой рабочей полости конусообразную вставку, состоящую из связанных между собой колпака, съемного днища и стойки, расположенной вертикально по оси ротора, укрепленную неподвижно концентрично стойке трубку для подвода крови, промывной жидкости и отвода отмытой тяжелой фракции, устройство для отвода легкой фракции, смонтированное над вставкой, и затвор ротора, отличающийся тем, что, с целью упрощения конструкции, повышения надежности работы и снижения стоимости, в рабочей полости нижняя часть корпуса выполнена с симметрично расположенными вертикальными ребрами, имеющими участки, прилегающие к наружной поверхности вставки, а днище корпуса снабжено радиальными ступенчатыми выступами, служащими опорой для вставки и размещенными в одной плоскости с вертикальными ребрами.

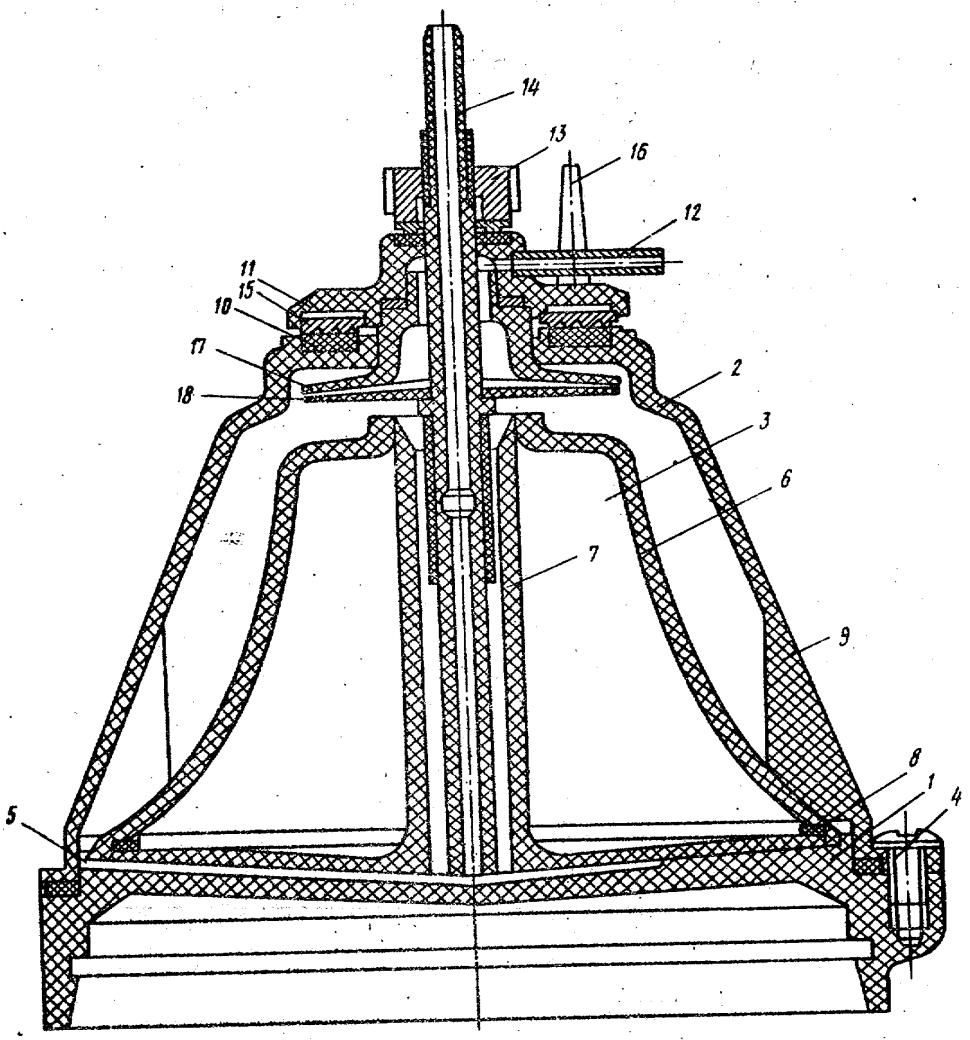
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FLEXIBLE DISPOSABLE CENTRIFUGE SYSTEM

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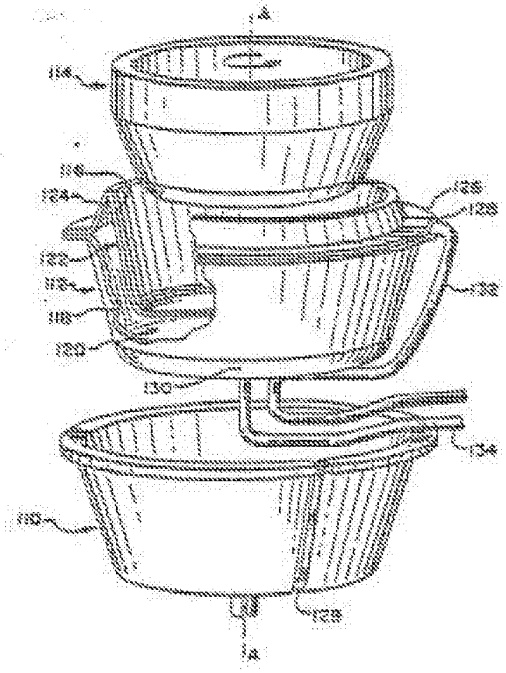
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A bowl-shaped chamber for use in centrifugal apheresis. The chamber is used for receiving whole blood, separating blood into therapeutic components and selectively collecting the therapeutic components. In one embodiment, the chamber (10) includes a bladder-like casing, which is formable into a bowl-like chamber having a bowl-shaped outer wall (32) and a bowl-shaped inner wall (34). The inner and outer walls (32, 34) define a blood processing cavity (37) therebetween and a flexible rim area (40) connects the inner and outer walls. The rim area (40) defines a rim edge (34c) and the bowl is substantially symmetric about a central spin axis. The rim area (40) is adapted to fold against itself so as to form the rim edge (34) which is adapted to advance and retract as the chamber volume changes. In another embodiment, the bowl (112) has inner and outer walls (116 and 118) which define bottom and side walls sections (120 and 122), a blood receiving cavity between said walls, and at least one port (128, 130) for fluid communication with said cavity. The bowl bottom section (120) defines a cylindrically-shaped plasma processing volume (136) and the side wall section defines an annularly-shaped red blood cell processing volume (140). The red blood cell processing volume (140) and the plasma processing volume (136) are approximately equal.

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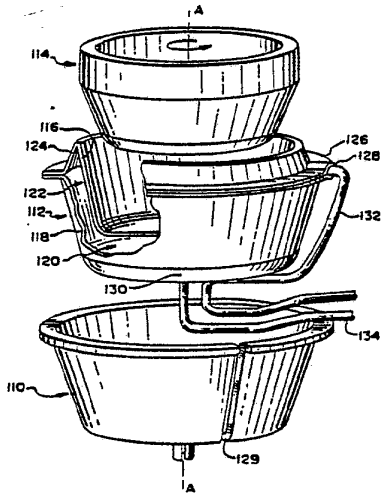
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(57) Abstract

A bowl-shaped chamber for use in centrifugal apheresis. The chamber is used for receiving whole blood, separating blood into therapeutic components and selectively collecting the therapeutic components. In one embodiment, the chamber (10) includes a bladder-like casing, which is formable into a bowl-like chamber having a bowl-shaped outer wall (32) and a bowl-shaped inner wall (34). The inner and outer walls (32, 34) define a blood processing cavity (37) therebetween and a flexible rim area (40) connects the inner and outer walls. The rim area (40) defines a rim edge (34c) and the bowl is substantially symmetric about a central spin axis. The rim area (40) is adapted to fold against itself so as to form the rim edge (34) which is adapted to advance and retract as the chamber volume changes. In another embodiment, the bowl (112) has inner and outer walls (116 and 118) which define bottom and side walls sections (120 and 122), a blood receiving cavity between said walls, and at least one port (128, 130) for fluid communication with said cavity. The bowl bottom section (120) defines a cylindrically-shaped plasma processing volume (136) and the side wall section defines an annularly-shaped red blood cell processing volume (140). The red blood cell processing volume (140) and the plasma processing volume (136) are approximately equal.



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FLEXIBLE DISPOSABLE CENTRIFUGE SYSTEM

BACKGROUND OF THE INVENTION:

This invention relates to a centrifugal liquid processing apparatus, and more particularly, to a novel processing or separation chamber and system for use in centrifugal apheresis (e.g., plasmapheresis or plateletapheresis).

In recent years long-term storage of human blood has been achieved by first obtaining whole blood from a donor at a collection center and, thereafter, separating the blood into therapeutic aomponents, such as plasma, platelets, and red cells at a central processing laboratory. The separated components are then collected and stored for future use.

The separation of the blood into constituent components is typically performed using a centrifuge or centrifugal liquid processing apparatus. Such systems are disclosed in U.S. Patents 3,987,961; 4,132,349; and 4,285,464. In such systems the processing chamber into which the whole blood is delivered for separation has in general been bowl-shaped, rigid and usually disposable. A number of different fluid connection systems are known for connecting the rotating processing chamber to external stationary blood sources or

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component collection containers. Some of these systems use stationary rather than rotating seals. See, for example, U.S. Patent 4,151,844; 4,285,464; and 4,389,207.

In addition to central processing laboratories, newer systems are being developed in which the centrifuge is located at the collection center and the donor is connected to the processing apparatus during the donation, separation and collection operations. A number of advantages are recognized from such systems, such as speed of collection, increased component yield, reduced cost, and the like.

It has been determined that in the newer systems it is particularly desirable that the volume of the separation chamber be variable so as to accommodate those volume changes occurring during the separation and collection procedures. Furthermore, the chamber should be one-piece and removable from the centrifugal processing apparatus for transporting of blood or components within the chamber.

In addition, the chamber should be sterilely sealed to external sites such as component collection bags and catheters. Desirably, the entire system should be integral and disposable.

It is also desirable to provide a processing chamber which is less expensive to manufacture than the existing bowl systems.

It is therefore an object of this invention to provide a one-piece, variable-volume processing chamber which can be economically manufactured and which may be part of a complete collection and separation system.

In the processing of blood, it is generally desirable to first separate red blood cells from the whole blood and thereafter separate and collect platelets from the remaining plasma. It is also desirable to maximize platelet collection in general and, more specifically, to maximize collection of platelets which may be associated with the red blood cells.

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During centrifugal processing the red blood cells separate or sediment against the bowl wall. In existing bowls the plasma forms a layer inwardly of and adjacent the red blood cell layer with an interface of "buffy layer" of platelets forming therebetween. In such a situation three adjacent layers are formed: the red blood cell layer, the platelet or buffy layer, and the plasma layer. However the discreteness of the layers may not be as precise as desired.

Thus when collecting the components, it may be difficult to precisely separate each component without including another component. For example, some platelets may be collected during collection of the red blood cells. Thus separation and collection of the components will not have been maximized.

It is particularly important in collecting platelets to maximize the collection of platelets from whatever quantity of blood is taken from the donor. To this end it is believed to be desirable to minimize the separation of platelets from plasma during the separation of red blood cells.

It is therefore an object of this invention to provide a processing chamber which is shaped to assure maximum separation of red blood cells while also minimizing platelet separation.

These and other objects of this invention will become apparent from the following description and appended claims.

SUMMARY OF THE INVENTION

There is provided herein a flexible, one-piece, variable-volume processing chamber for use in centrifugal apheresis (e.g., plasmapheresis or plateletapheresis) which can be easily and economically manufactured. The chamber is useful in receiving whole blood, separating the blood into therapeutic components, and the selective collection of such components.

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The chamber includes a flexible, bladder-like casing which is formable to a bowl-like shape having an outer wall and an inner wall which when spaced from each other define the blood-receiving and processing cavity. A flexible rim area connects the inner and outer walls and defines a flexible rim edge. The resulting bowl is substantially symmetric about a central spin axis, is flexible, and the rim area is constructed to fold or lay against itself and to roll in an axial direction or advance and retract as the chamber is filled and emptied. At least one port provides fluid communication between the flood-receiving cavity and external sites.

The chamber may be one component of an integral sterile and disposable separation and collection system which also includes fluid-carrying tubing, collection bags, and a catheter.

There is also disclosed herein an enclosed processing bowl for use in centrifugal apheresis which minimizes platelet separation during red blood cell separation and collection and which maximizes platelet collection by maximizing the blood sedimentation surface area and minimizing the buffy layer interface area.

The bowl has inner and outer walls which define bottom and side wall sections, a blood receiving cavity between said walls, and at least one port for fluid communication with said cavity. The bowl bottom section defines a cylindrically-shaped plasma processing volume, and the side wall section defines an annularly-shaped red blood cell processing volume. The red blood cell processing volume and the plasma processing volume are approximately equal.

The plasma processing volume and red blood cell processing volume form a generally cylindrical interface at the transition from the bottom section to the side wall section. The buffy layer forms at this interface.

The outer wall of the side wall section forms a red blood sedimentation surface and the area of the sedimentation surface is greater than the surface area of the blood cell/plasma interface.

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BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a perspective view showing the flexible, variable-volume, bowl-shaped chamber with mating parts of a centrifugal processing apparatus;

FIGURE 2 shows the bowl-shaped chamber distended to show the bladder-like casing shape and show how the bowl-shaped chamber is formed;

FIGURE 3 shows a rim edge and a portion of the rim area rolled back upon itself in advanced and retracted positions;

FIGURE 4 shows another version of the chamber with the rim edge;

FIGURE 5 through FIGURE 12 show the operation of a centrifuge system using the bowl-shaped chamber;

FIGURE 13 shows a integral sterile and disposable separation and collection system.

FIGURE 14 is a perspective view showing a processing apparatus and variable volume bowl;

FIGURE 15 is a sectional and perspective view showing a fully filled bowl and the red blood cell and the plasma volumes;

FIGURE 16 is a sectional and perspective view showing a partially filled bowl and the red blood cell and the plasma volumes;

FIGURE 17 is a perspective view, partially in section, showing a fixed volume and the red blood cell and the plasma volumes.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Referring now to Figure 1, a flexible, variable-volume, bowl-shaped processing chamber 10 generally is shown positioned between a bowl-shaped rotor 12 and a conformingly-shaped and movable mandrel 14.

As previously indicated, centrifugal liquid processing apparatus of the type used in centrifugal apheresis are known in the art. Drive systems for spinning the separation chambers, speed

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control systems, and the like, are also known in the art. Those systems are not shown herein as they are known in the art, and as this invention is directed to the flexible, variable-volume chamber and the system of which it may be a part.

The rotor bowl 12 includes a bottom wall portion 16, upwardly-extending side wall 18, an upper lip or edge 20, a tube-receiving slot 21, and is generally symmetric about a vertical spin axis 22-22. The rotor bowl also includes at least one port or passageway 24, which is located in the bottom wall 16 at the spin axis 22-22.

The flexible chamber 10 is constructed to fit within the rotor bowl 12 for rotation therewith, and the chamber may have a shape which is generally complementary to that of the rotor bowl.

The mandrel 14 is a cup-shaped member, similar in shape to the rotor bowl 12, and is adapted to nest therein. The mandrel 14 includes a bottom wall 26, an upwardly-extending side wall 28, and skirt 30. The mandrel is axially movable toward and away from the chamber 10 so that the chamber's volume may be controlled by the cooperation of the mandrel 14 and rotor bowl 12. The mandrel is mounted to the processing apparatus so as to spin with the rotor bowl 12 and the chamber 10 about axis 22-22.

The flexible chamber 10, as shown herein, includes an outer wall 32 and an inner wall 34 which are joined along a flange or shoulder-like seal 36 to form an enclosed casing. The space between the walls defines a blood-receiving cavity 37.

The inner and outer walls, as shown here, are formed of a flexible, medical-grade, polymeric material, such as polyvinylchloride. In the preferred embodiment, the walls are sealed, flexible and pliable. The outerwall 32 includes a fluid port 38 and integral conduit 39, which provides fluid communication between the cavity 37 and external blood sources or therapeutic component collection sites. The port 38 is shown as aligned with

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the spin axis and forms what is known as the low-gravity or low-G port. The inner wall 34 is shown as depressed inwardly toward the outer wall 32 and forming a rim area 40 generally adjacent the flange 36.

As can be seen in Figure 1, the flexible processing chamber 10 fits within the rotor bowl 12, and since it is flexible, the outerwall 32 will conform to the shape of the rotor wall when the chamber is filled and spinning. The conduit 39 and port 38 are positioned in the cover 12 through the slot 21. The mandrel 14 fits within the depression or space formed in the inner wall 34, and the inner wall 34 will conform to the mandrel. Axial movement of the mandrel 14 cooperates in controlling the volume of the cavity 37 as well as the pressure within the chamber.

The chamber 10 is vacuum formed by separately vacuum forming each of two polyvinyl sheets over a male die, and thereafter, nesting the formed sheets and RF (radio frequency) sealing the sheets along the peripheral edge or flange line. When a high-G port is desired, tubing is sealed in place between the sheets at the flange area and provides fluid communication with the cavity 37 via a high-G port.

When the chamber is distended, as suggested in Figure 2, the casing assumes a bladder-like configuration which may be referred to as a prolate ellipsoid. From the distended position, the top end of the inner wall 34 is depressed inwardly so as to form the depression which receives the mandrel 14.

In some situations, it is important at the end of the separation procedures to fully express all liquid from the processing chamber. This requires that the chamber walls be capable of being flattened against themselves and that the only space provided between the rotor bowl 12 and mandrel 14 will be about the thickness of the chamber's inner and outer walls.

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As shown in Figure 3, the chamber material is sufficiently flexible at the rim area 40 that it can be folded back upon itself. Thus the inner wall 34 is folded back so that wall portions, such as 34a and 34b, contact each other and there is no space therebetween. The folded wall portions form the rim edge 34c.

As the bowl fills and empties, the rim edge 34c advances and retracts, and in a sense rolls, while retaining an edge. In Figure 3, the bowl is shown in an expanded position by the dashed lines with the inner wall 34 flattened against itself as it rolls axially upwardly and downwardly. Thus one of the inherent characteristics of the material selected for the inner wall is that it be capable of being folded flat against itself so as to define a rim area and rim edge and roll upwardly and downwardly without tearing or leaking.

Referring now to Figure 4, there are situations in which it is desirable to begin processing with an initial liquid volume in the chamber and/or to leave some liquid in the chamber at the end of the processing cycle. In such situations, the mandrel and rotor are arranged to permit the inner wall portions 34a and 34b to be spaced from each other in the rim area while still forming the rim edge 34c. The rim edge 34c advances upwardly and downwardly, but with the inner and outer walls spaced from each other. Again, the rim edge will not tear or leak.

In the simplest form, shown in Figure 1, only a single fluid port 38 is provided. Depending upon how the system is used, all fluid flow and separation can be accomplished through the port 38. Since the port is located on the spin axis, the port is referred to as the low-G (low-gravity) port. Alternatively, a single port could be provided at the greatest radial distance from the spin axis and this would be referred to as the high-G (high-gravity) port. In Figure 1, that position would be at the flange line 36. Other single port systems can be envisioned.

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For some applications, multiple port systems are desirable. Referring now to Figure 2, the low-G port is shown as 38 and the high-G port as 42.

The high-G port is formed by bonding tubing between the inner and outer walls at the flange 36. The tubing connects the port to a Y-connector 43 or to a harness which holds the tubing connecting the low-G port 38. The connection between the rotating parts and stationary parts external of the rotor and chamber may be made in the manner disclosed in U.S. Patents Re. 29,738; 3,986,442; and 4,108,353.

A number of different processing techniques can be used for separating the therapeutic components using the rate of the spin, the mandrel and either one or two ports.

In some situations a three-port system may be desirable. In such a system a third port 44 is provided through the outer wall 32 at a position intermediate the low-G port 38 and high-G 42. The third port could be used as a blood inlet, so that blood entering at port 44 would immediately begin to separate with high density components (such as red blood cells) moving toward the high-G port 42 and the low density components (such as plasma) separating toward the low-G port 38.

This is but one technique to be used, and it is important to note that blood inlet port 44 can be provided through the side wall 32. If such a port were added, it could be connected via tubing to the Y-connector 43 adjacent port 38 in the same manner as the tubing from the high-G port 42.

The embodiment previously described is fabricated by the vacuum forming of two sheets and inclusion of molded ports and tubing. Another technique by which such a system can be prepared is by blow-molding in which, for example, the high-G port and return tubing are molded into the side wall.

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One mode for operating the flexible volume reservoir is shown in diagrammatic form in Figures 5-12. Here for ease of consideration the variable-volume chamber is shown without the mandrel and rotor. It is understood that the chamber is held against the rotor wall and has assumed the shape of the rotor wall and mandrel.

In the system shown in Figure 5, the chamber 50 includes a low-G port 52 and line 53, and a high-G port 54 and line 56. The lines 53 and 58 are shown connected to a multiple-lumen umbilicus, which connects the low-G and high-G ports to external points. Various valves, clamps and pumps can be provided external of the chamber for controlling flow through the ports 52 and 54. One such system is described hereinafter.

As shown in Figure 5, the mandrel has compressed the chamber so that the chamber's inner and outer walls are compressed together.

Initially a small amount of anticoagulant is metered into the processing chamber (or is provided at the time of manufactured), and as shown in Figure 6, whole blood is delivered to the chamber and enters via low-G port 52. The blood fills the chamber and mixes with the anticoagulant. As the blood enters the chamber, the rotor rotates slowly and the mandrel retracts so as to fill the chamber with about 525 milliliters of whole blood.

Thereafter, the processing apparatus spins the rotor, chamber and mandrel in a first spin so as to separate the blood into red blood cells (RBC) and platelet-rich plasma (PRP). This spin is sometimes referred to as a soft spin and the specific spin conditions, as is known in the art, depend on factors such as rotational velocity, bowl surface area, time, initial blood hematocrit, and the like.

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Referring now to Figure 7, the red blood cells (RBC) move radially outwardly along the sides of the chamber, and the platelet-rich plasma collects in the center portion of the chamber and is identified as PRP. Red blood cells may be collected by closing the low-G port 52, opening the high-G port 54, and moving the mandrel downwardly so that the volume of the processing chamber is reduced, and red blood cells are forced from the chamber through the high-G port 54 and line 58 for harvesting and collection. This leaves the platelet-rich plasma (PRP) in the flexible bowl as shown in Figure 8.

Referring now to Figure 9, the bowl is than subjected to a second spin which separates the platelets from the platelet-rich plasma by driving the platelets along the outer wall, which leaves the platelet-free plasma at the center. This is sometimes known as a hard spin. Thereafter, the high-G port 54 is closed, the low-G port 52 is opened, the mandrel is moved downwardly, and the platelet-free plasma (PRP) is expressed from the chamber, as shown in Figure 10.

The mandrel is then retracted, which draws a small amount of air into the system from an empty but sterile and closed transfer pack or collection bag. Agitation resuspends the platelets into a small volume of carrier plasma. Under a third spin, or soft spin, as shown in Figure 12, the mandrel expresses the platelet concentrate out of the chamber and into a collection bag for transporting. Alternatively, the platelets can be transported in the processing bowl rather than being collected and transported in a separate bag.

As can be seen from these drawings, the volume of the chamber varies as blood is introduced into the chamber and in accordance with the separation procedure which is being used. In so doing, the rim edge 34c moves upwardly and downwardly, and thus that area must be flexible as previously described.

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In an alternative embodiment, the outer wall of the chamber may be rigid and a predetermined portion of the inner wall may be rigid. But the rim area and the rim edge must remain flexible.

A complete, integral, disposable, sterile and sealed collection and separation system is shown in Figure 13. This entire system is sterilely sealed upon manufacture and, as such, can be used to store and transport whole blood and components for times greater than those permitted by regulation when the system is open or pierced in the field.

In this system the flexible, variable-volume processing chamber 60 includes a high-G port 62 and tubing 64 and a low-G port 66 and tubing 68. The tubing may be threaded through peristaltic roller pumps 70 and 72 and then connected at a Y-junction 74. It will be recalled that the chamber 60 is rotating while the pumps 70 and 72 are fixed in place.

The rotating chamber and stationary pumps are connected via tubing 64 and 68. This connection is made in accordance with the teaching of U.S. Patents Re. 29,738; 3,986,442; and 4,108,353, which permit a sealless connection between rotary and stationary members. This fluid communication is established without rotary seals or the like.

The tubing 76 leading from junction 74 connects to a standard red blood cell collection bag 78, a standard plasma collection bag 80, a special breathable platelet collection bag 82, a saline-containing bag 84, an anticoagulant bag 85, and a catheter 86. Anticoagulant can be provided from a separate bag as shown or may be initially provided in the processing chamber 60 in which case an anticoagulant bag, such as 85, is not included the system.

With this system the saline solution may be drawn from bag 84 and anticoagulant from bag 85, through line 76, and into the chamber 60 for priming. Thereafter, blood is taken from the patient

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via catheter 86 and delivered via line 76 to chamber 60, preferably through low-G port 62. During this phase, the collection bags may be clamped using external clamping means, such as forceps or hemostats.

Various separation procedures have been described above, and as can be seen, red blood cells, for example, may be drawn from the high-G port 62 utilizing roller pump 70 and delivered to the red blood cell collection bag 78. Next, platelet-free plasma may be drawn from the low-G port 66 using pump 72 and delivered to the plasma collection bag 80. Then platelet concentrate may be collected via high-G port 62, pump 70 and delivered to the special platelet collection bag 82.

It will be understood that the entire system is disposable and sterilely sealed at the plant. Thus, it may be removed from the centrifuge, from the roller pumps 70 and 72, from the patient 86 and delivered to the processing site.

A preferred embodiment of the processing chamber is shown in Figures 14 through 17, being therein identified by reference numeral 112. As shown, the chamber 112 includes an inner wall 116 and an outer wall 118. These walls form a bowl-shaped chamber having a generally cylindrical bottom section 120 and a generally annular upstanding side wall section 122.

Referring now to Figure 15, it is seen that the bottom section 120 is formed by the transverse bottom wall portions of the inner wall 116a and of the outer wall 118a. The side wall portions are formed by the upstanding side wall 116b of inner wall and upstanding side wall 118b of the outer wall.

The inner wall 116 and outer wall 118 form a flexible rim area 124 which flexes and appears to roll as the chamber volume increases and decreases, thereby permitting changes without tearing or rupturing. The walls are each formed from a flexible

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polyvinylchloride sheet which is vacuum formed and the sheets are then heat sealed along a peripheral flange 126 so as to form the sealed chamber.

As shown in Figure 14, a high-gravity port 128 is formed in the flange at the radially outermost point and a low-gravity port 130 is formed in the bottom wall at the intersection of the spin axis A-A. Conduits 132 and 134 connect the ports 128 and 130 to external blood sources and collection containers. The chamber 112 is fitted into the bowl cover 110 and tubing from the chamber ports its within slot 129. A chamber engaging mandrel 114 is also provided as heretofore described. Stationary seal connections are made to the external blood sources and collection points as shown in U.S. Patents 4,151,844; 4,285,464; and 4,389,207.

Referring again to Figure 15, when the chamber is filled, it expands and the inner bottom wall portion 116a moves upwardly away from the bottom wall portion 118a, the inner side wall 116b moves inwardly from the outer wall 118a, and the rim area 124 moves axially upwardly.

The space between the bottom walls forms a cylindrical or disc-like plasma processing volume (Vp) 36, which has an outer cylindrical surface 138. The space between the side wall forms an annularly shaped red blood cell processing volume (Vbc) 40.

The interface between the blood volume and plasma volume is along the cylindrical surface 138, which forms at the transition from the bottom to the side wall. The bowl is shaped so that when blood having a hematocrit between 40-60 (ie., volume percent red blood cells) is processed, the red blood cell volume 40 and plasma volume 36 are approximately equal whether the bowl is fully filled as in Figure 15 or partially filled as in Figure 16.

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The bowl is also constructed such that the red blood cell sedimentation surface area (S_1) 118b is greater than the interface surface area (S_2) 132. For example, when the bowl is fully filled, the red blood cell sedimentation surface area 118b may be about four times that of the interface 138.

When the bowl is partially filled, as seen in Figure 16, the red blood cell area (S_1) 118b is clearly greater than the interface surface area (S_2) 138.

In operation, whole blood is introduced into the chamber through the low-G port 130, for example, and the apparatus is spun about the axis A-A in a first or hard spin. During this first spin the heavier red blood cells are driven toward or sediment against the outer wall 118b and red blood cells fill the blood cell volume 40. Platelet-rich plasma in the volume 40 is displaced inwardly toward the plasma volume 36. Eventually the red blood cells, which are experiencing high gravity forces, sediment or "pack out", thus filling the volume 40. Using this procedure, platelet separation from the red blood cells is maximized as is red blood cell purity.

The plasma volume 36 fills with the platelet-rich plasma initially in the volume and with the platelet-rich plasma displaced into the volume. The platelet-rich plasma in the plasma volume 36 experiences low-G forces as compared to the forces experienced by the red blood cells. The plasma at the axis A-A experiences almost no centrifugal forces, and the plasma at the interface 138 experiences some centrifugal forces.

Due to displacement and centrifugal forces some platelets will separate from the plasma and form a buffy layer at the interface 120. However, the amount of platelet separation and buffy layer formation is minimized and is related to the spin rate, plasma viscosity, interface position, and the like. The intent is to minimize platelet separation and buffy layer formation during red blood cell separation.

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In one example, the chamber was fully filled with about 500 milliliters of whole blood which has a hematocrit of about 40 (ie., 40 volume per cent red blood cells).

After the first or hard spin, the red blood cells formed a bed of packed cells in the volume 40, platelet-rich plasma collected in volume 36, and a thin buffy layer formed at interface 138. The packed cell volume was about 250 milliliters and the plasma volume was about 250 milliliters.

It will be appreciated that due to the higher G forces and larger surface area, the red blood cells separated or sedimented faster than the platelets at the interface 138.

After separation, the red blood cells can be collected through the high-G port 128 with minimal platelet contamination. Thereafter, the chamber can be utilized for platelet/plasma separation.

Since the volume relationships remain substantially constant (ie., about equal) and the red blood cell sedimentation area is greater than the buffy layer area, small or large quantities of whole blood can be processed.

Figure 16 shows the variable volume chamber set to process less than 525 milliliters of whole blood. As in Figure 15, the volumes are about equal and the red blood cell surface area is greater than the interface area. Processing is performed in substantially the same manner and the same type of separation is effected.

In Figure 17, an enclosed, rigid, fixed volume processing bowl 150 is shown. The housings, drives and controls for operating a rigid bowl system are known in the art. The bowl 150 may be blow-molded or fabricated from plastic members and includes rigid inner and outer walls 152 and 154 which define a fixed internal volume that includes a red blood cell volume 56 in the side wall and a plasma volume 58 in the bottom wall. The bowl includes a red

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blood cell sedimentation surface 160 and is structured to permit a buffy layer or interface 162 to form and be defined. High-G and low-G ports 164 and 166 and related conduits are also provided. Separation of therapeutic components using this bowl is similar to separation using the variable volume bowl except that no volume variation occurs.

It will be appreciated that numerous changes and modifications can be made to the embodiments disclosed herein without departing from the spirit and scope of this invention.

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CLAIMS:

1. A flexible, variable-volume, bowl-shaped chamber for use in centrifugal apheresis for receiving whole blood, separating blood into therapeutic components, and selectively collecting therapeutic components of blood, said chamber comprising:

an enclosed bladder-like casing which is formable into said bowl-shaped chamber, said chamber having a bowl-shaped outer wall, and a bowl-shaped inner wall positioned within said outer wall which defines a blood processing cavity therebetween and a flexible rim area connecting said inner wall and outer wall, which area defines a rim edge;

said flexible rim area being adapted to fold against itself to form a rim edge which is adapted to advance and retract as said chamber volume changes; and

said outer wall having at least one port extending therethrough for fluid communication with the blood-processing space.

2. A variable-volume chamber as in Claim 1, wherein a pair of ports are provided, with one port passing through the outer wall at the central spin axis to form a low-gravity port and the other port passes through the casing at a radially outermost point so as to form a high-gravity port.

3. A variable-volume chamber as in Claim 2 wherein a third port is provided, which passes through the outer wall at a point intermediate the low-gravity and high-gravity ports.

4. A variable-volume chamber as in Claim 1, wherein said inner and outer walls at said rim area are spaced from each other and are constructed to move in axially opposite directions as said chamber is filled and emptied so that the rim edge appears to roll axially.

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5. A variable-volume chamber as in Claim 1, wherein said inner and outer walls at said rim area contact each other and slide against each other in opposite directions as said chamber is filled and emptied so that the rim edge appears to roll axially.

6. A variable-volume chamber as in Claim 1, wherein said chamber forms a part of a disposable blood collection and component separation system which comprises said chamber, at least one therapeutic component collection container integrally and sterilely connected to at least one port of said bowl-shaped chamber, and catheter means integrally and sterilely connected to said bowl-shaped chamber to at least one port of said bowl-shaped chamber.

7. A system as in Claim 6, wherein there is provided three component collection containers, each adapted and constructed to receive a therapeutic component; one of said containers adapted to receive red blood cells; a second to receive platelets; and a third for receiving platelet-free plasma, each of said collection containers being constructed to be selectively opened and closed to receive a component from said processing chamber.

8. An enclosed processing bowl for use in centrifugal apheresis, said bowl having inner and outer walls which define a bottom section, a side wall section, and a blood-receiving cavity between said walls and at least one port for fluid communication with said cavity, and said bowl having a spin axis extending centrally through said bowl;

the bottom section of the bowl defining a cylindrically-shaped plasma processing volume between the inner and outer walls of said bottom;

the side wall section of the bowl defining an annularly-shaped red blood cell processing volume between the inner and outer walls of said side wall;

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said plasma processing volume and red blood cell processing volume being adjacent each other at the transition from the bottom wall to the side wall to form a generally cylindrical interface;

said outer wall of said annularly-shaped red blood cell processing volume forming a red blood cell sedimentation surface; and

the surface area of the red blood cell sedimentation surface being greater than the area of the cylindrical blood cell plasma interface.

9. A centrifugal processing bowl as in Claim 8, wherein the bowl is substantially symmetric about said spin axis.

10. A centrifugal processing bowl as in Claim 8, wherein the volume of the red cell processing volume and volume of the plasma processing volume are substantially equal.

11. A centrifugal blood processing bowl as in Claim 8, wherein the red cell processing sedimentation surface area is at least twice the surface area of the interface.

12. A centrifugal blood processing bowl as in Claim 11, wherein the red cell processing sedimentation surface area is about four times greater than the surface area of the interface.

13. A centrifugal blood processing bowl as in Claim 8, wherein said bowl is of a fixed volume and the inner and outer walls are fixed and rigid.

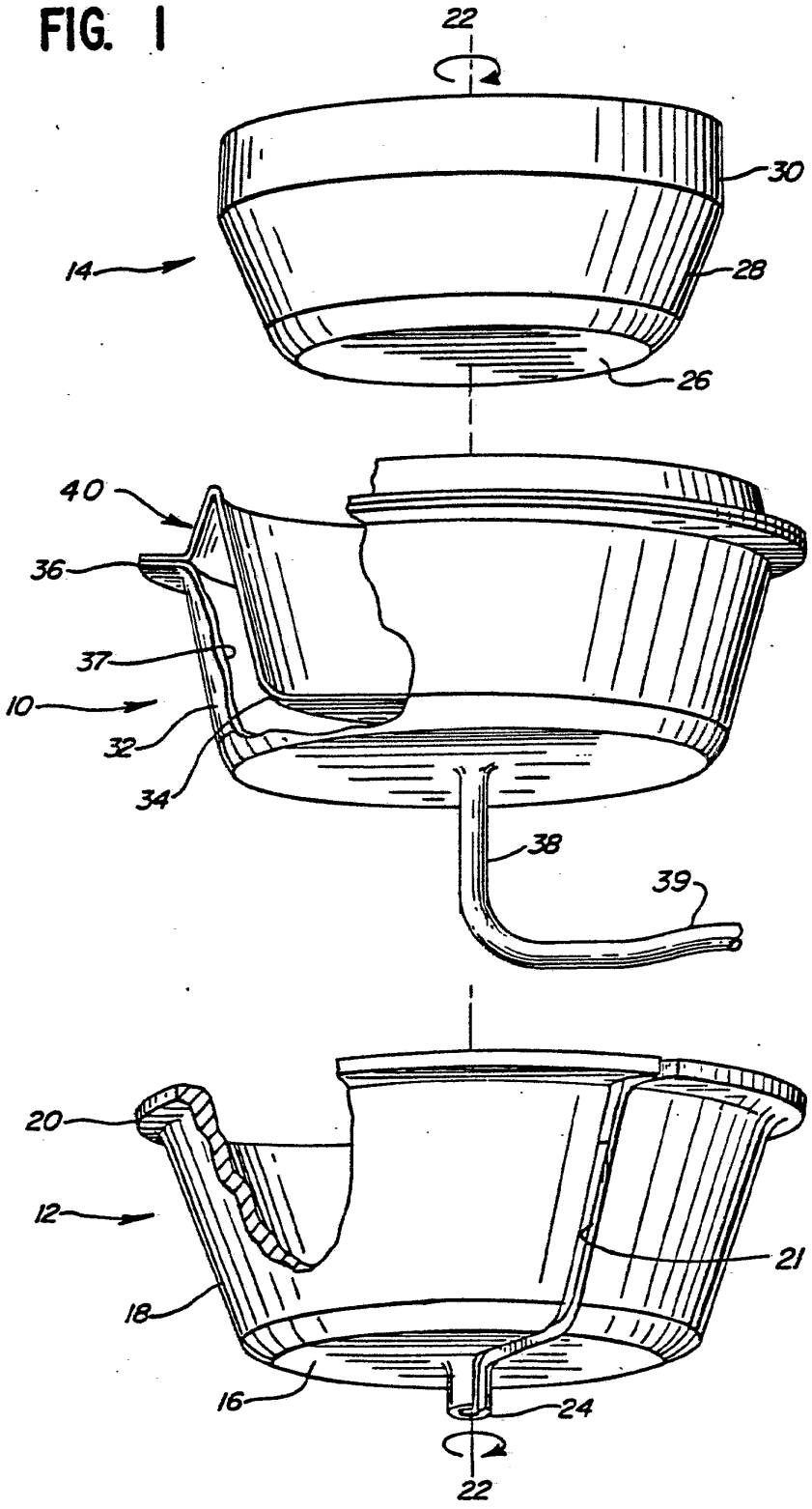
14. A centrifugal blood processing bowl as in Claim 8, wherein said bowl is of a variable volume and the inner and outer walls join at a rim area and at least the rim area of said bowl are flexible so as to accommodate changes in bowl volume.

15. A centrifugal blood processing bowl as in Claim 14, wherein the red cell processing volume and plasma volume are approximately equal and said volumes remain equal to each other throughout the range of chamber column changes from empty to full.

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FIG. 1



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FIG. 2

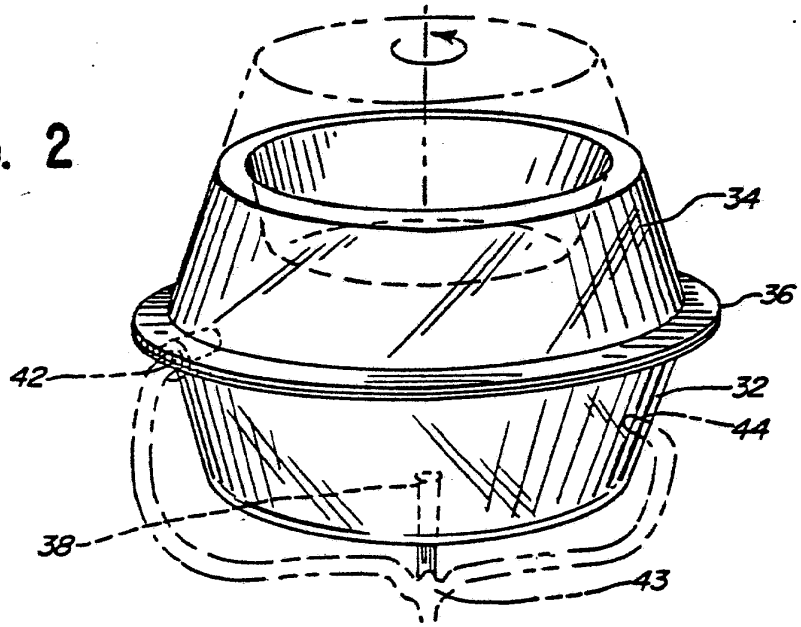


FIG. 3

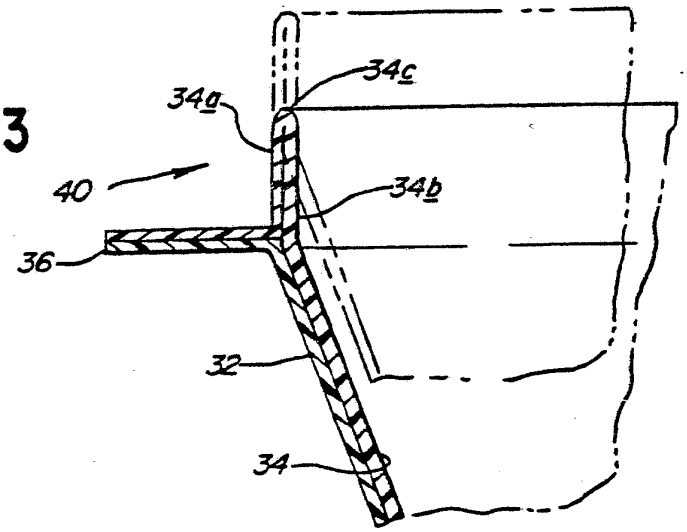
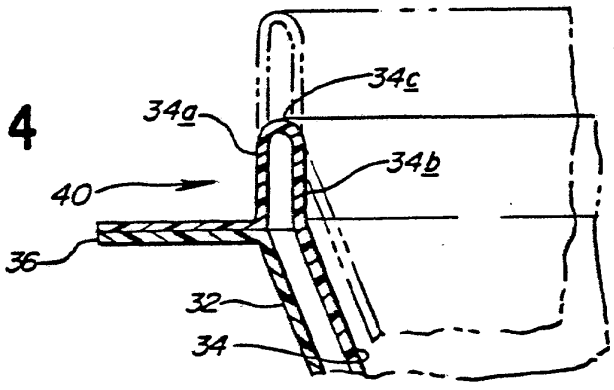


FIG. 4



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FIG. 5

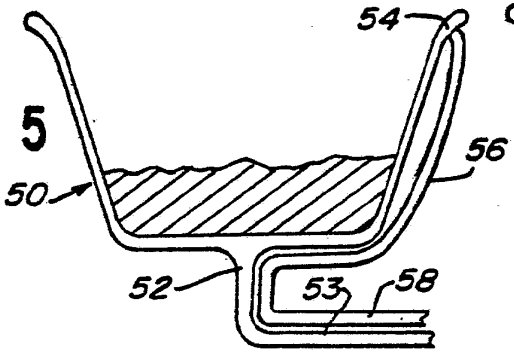


FIG. 9

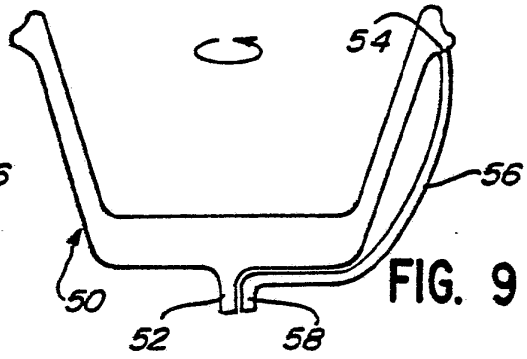


FIG. 6

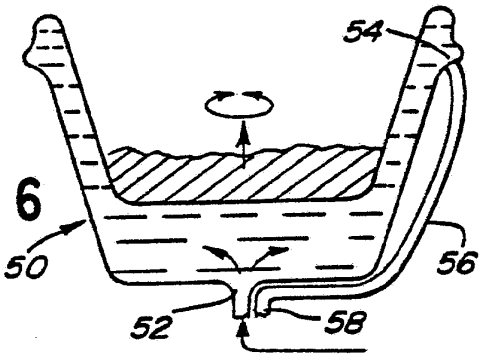


FIG. 10

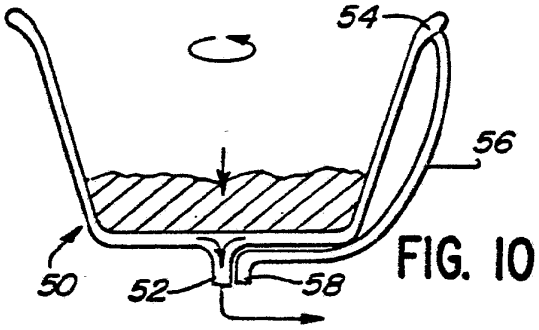


FIG. 7

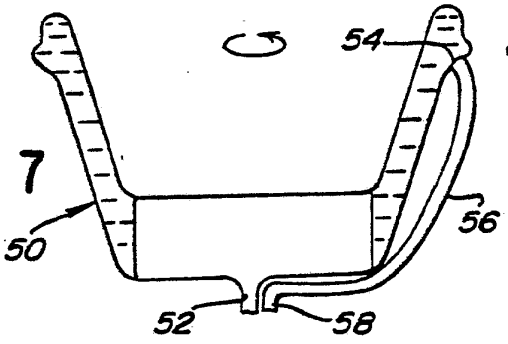


FIG. 11

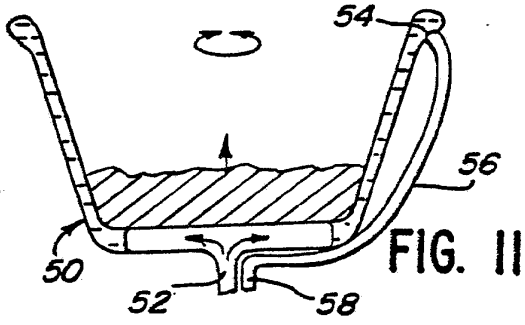


FIG. 8

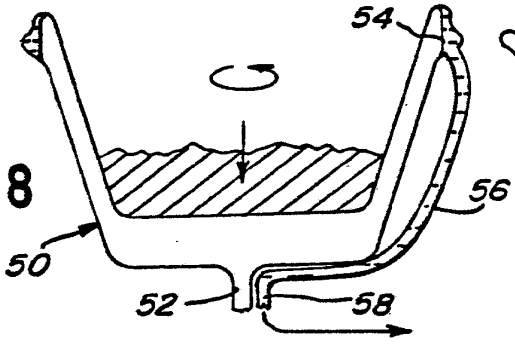
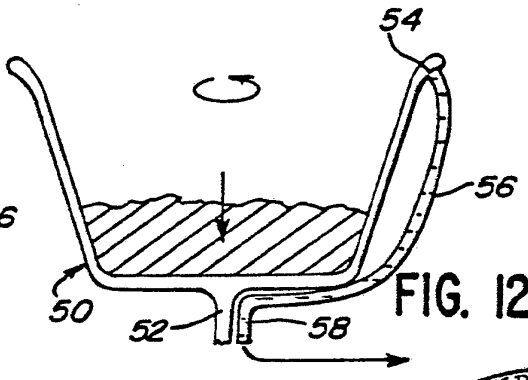


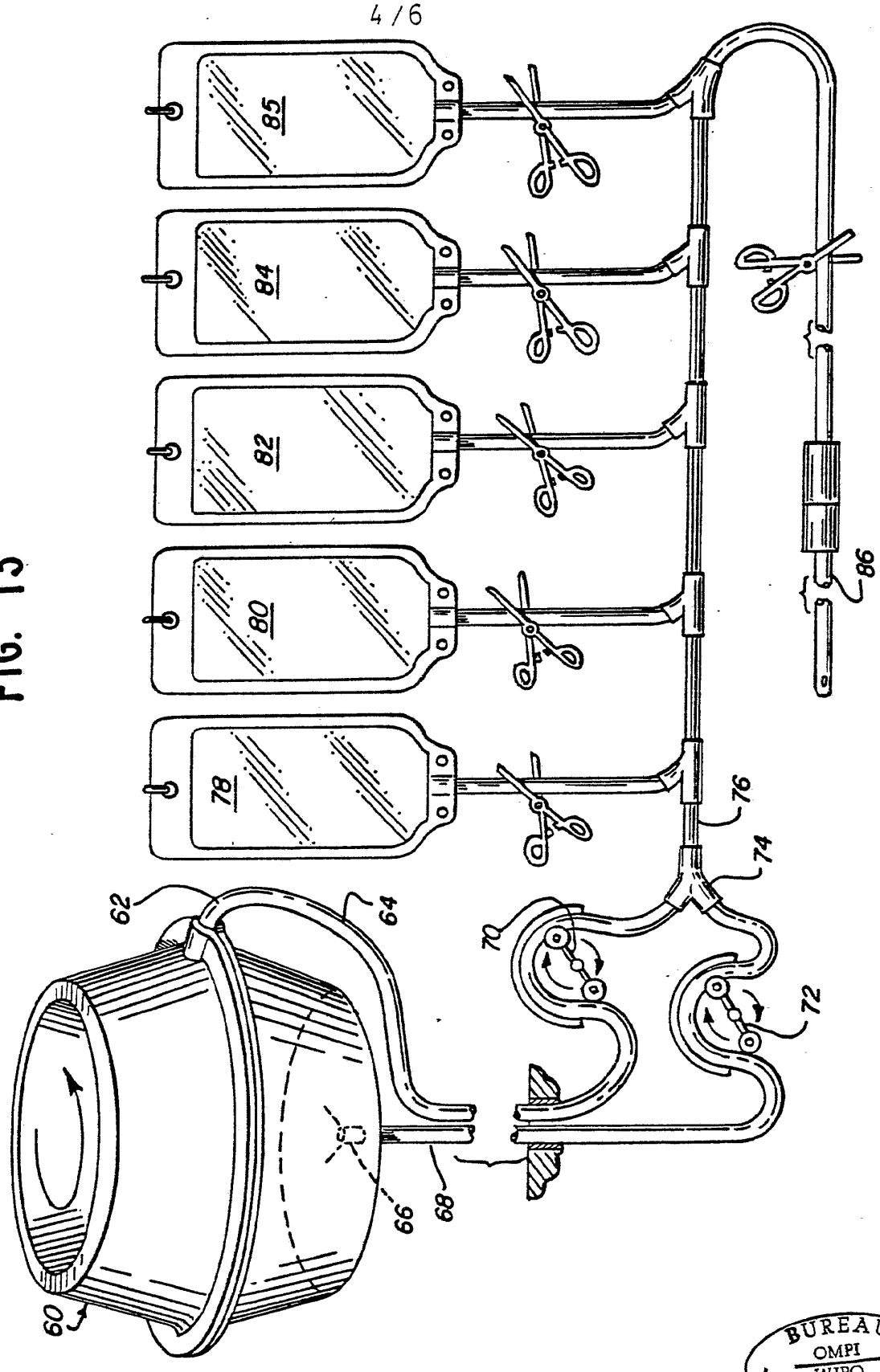
FIG. 12



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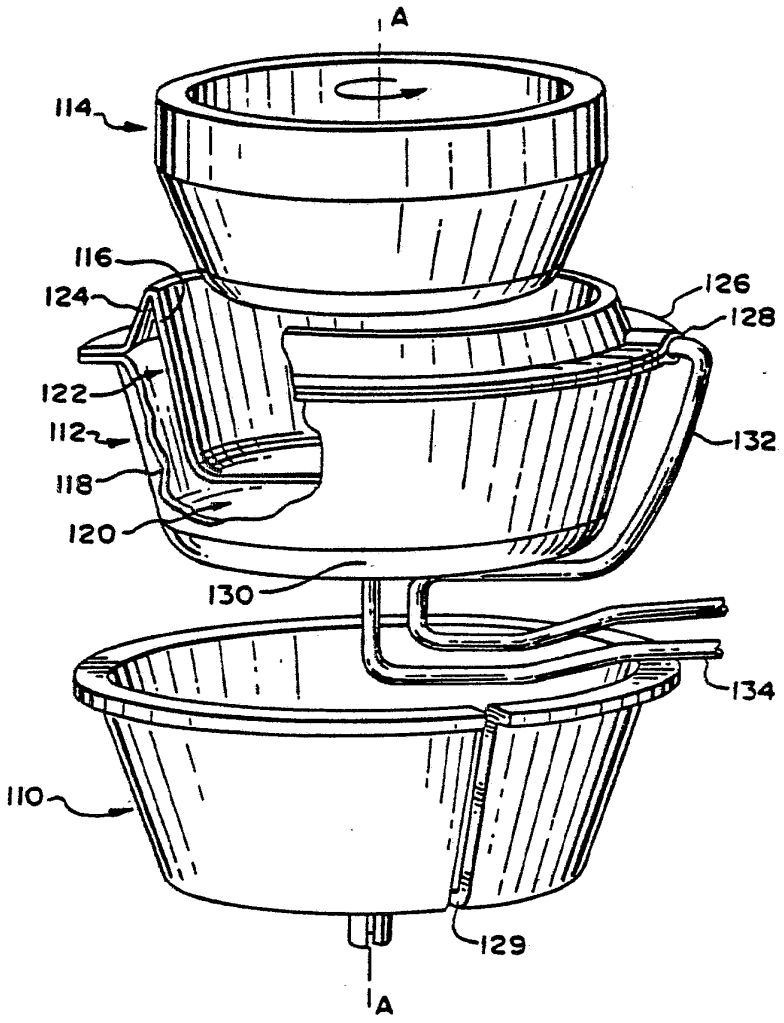
FIG. 13



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FIG. 14



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FIG. 15

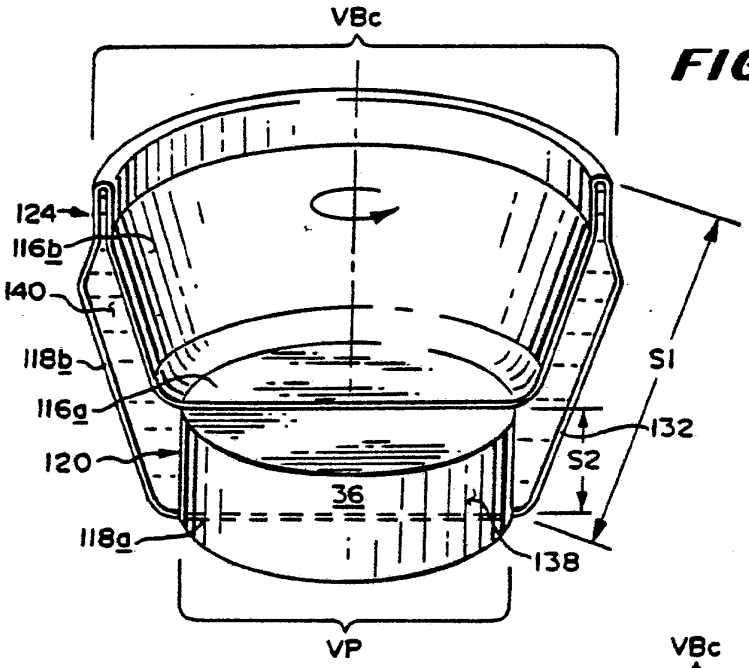


FIG. 16

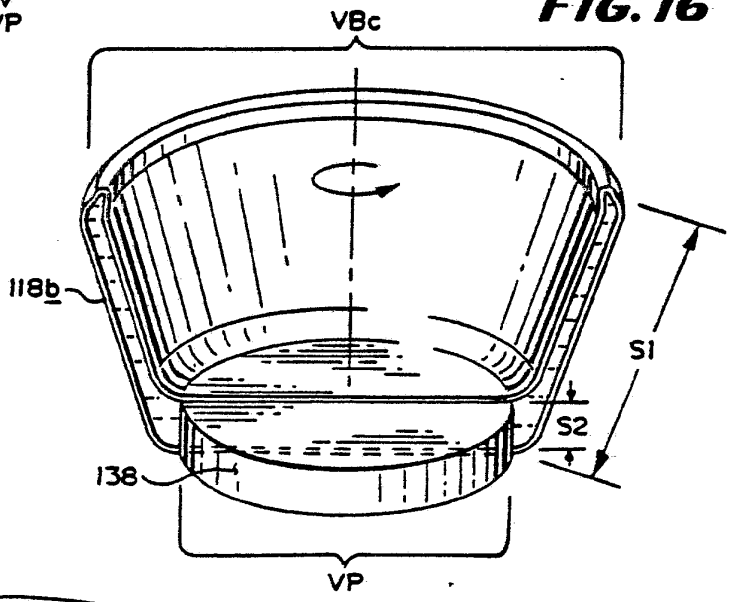
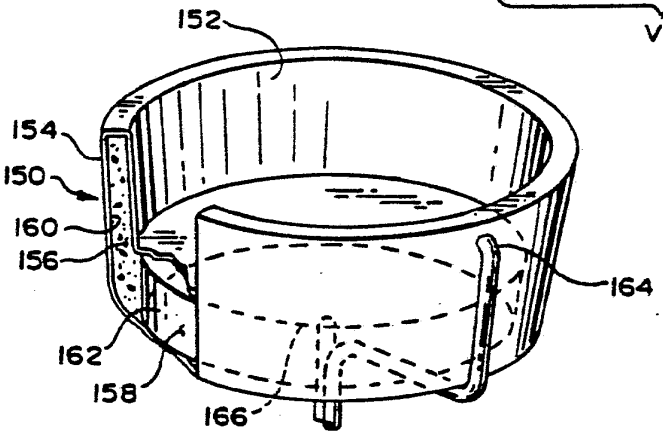


FIG. 17



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INTERNATIONAL SEARCH REPORT

PCT/US84/01796

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

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II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	494/18,20,21,45,65,84 210/512.1,787,927 604/4-6,408

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [6]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	US, A, 4,413,771, PUBLISHED 08 NOVEMBER 1983, ROHDE ET AL.	1-7, 14,15
Y	US, A, 4,413,772, PUBLISHED 08 NOVEMBER 1983, ROHDE ET AL.	1-7, 14,15
Y	US, A, 4,413,773, PUBLISHED 08 NOVEMBER 1983, ROHDE ET AL.	1-7 14,15
Y	US, A, 4,151,844, PUBLISHED 01 MAY 1979, CULLIS ET AL.	1-15
Y	US, A, 3,244,363, PUBLISHED 05 APRIL 1966, HEIN.	1-7, 14,15
A	US, A, 3,145,713, PUBLISHED 25 AUGUST 1964, LATHAM, JR.	1-15
A	US, A, 3,858,796, PUBLISHED 07 JANUARY 1975, UNGER ET AL.	1-15
A	US, A, 3,987,961, PUBLISHED 26 OCTOBER 1976, SINN ET AL.	1-15

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
14 DECEMBER 1984	28 DEC 1984
International Searching Authority [1] ISA/US	Signature of Authorized Officer [20] JOHN DONOFRIO

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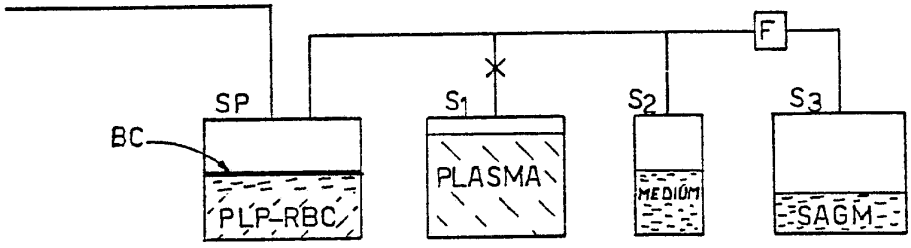
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(54) Title: PROCEDURE AND CONTAINER FOR THE PREPARATION AND STORAGE OF PLATELET CONCENTRATES



(57) Abstract

A procedure for the routine preparation in closed system and storage in a medium made of natural colloid (plasma) and crystalloid solution of PC deprived of leukocytes, which is based on a quadruple blood bag (PB) containing CPD anticoagulant, an empty satellite bag (S1), a satellite bag (S2) containing a synthetic crystalloid solution, a satellite bag with SAGM (or similar) additive solution for red blood cells (RBC), consisting in collecting the blood in the primary bag (PB), in centrifuging the blood bag at high speed, in expressing the supernatant plasma into bag (S1), in collecting 15-20 mL of the buffy-coat (BC) into bag (S2), in adding the SAGM solution of bag (S3) into bag (PB) containing the RBC concentrate, in disconnecting bags (PB) and (S1) from bags (S2) and (S3), in centrifuging bag (S2) at soft spin and in transferring the supernatant platelet concentrate (PLP-PC) formed after this centrifugation into the empty bag (S3), through a cotton wool filter (F) inserted along the tube line so as to remove residual leukocytes which contaminate the PC.

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Procedure and container for the preparation and storage of platelet concentrates.

This invention relates to a procedure for the routine preparation in closed system of platelet concentrates (PC) deprived of leukocytes and stored in a medium consisting of a mixture of natural colloid (plasma) and of crystalloid solution (called thereafter "medium"), and in particular for PC storage.

Standard RBC concentrates and PC, prepared by serial centrifugation from multiple bags and storage in a natural colloid medium (plasma), are contaminated with plasma and leukocytes, which can determine acute and chronic side-effects in transfusion recipients.

The transfusion of platelet concentrates (PC) is necessary for preventing the risk of hemorrhage in patients with low platelet count (thrombocytopenia).

Routine production of blood components (RBC and PC) with higher purity is hampered by technical difficulties concerning particularly the separation and storage of blood cells.

Presently available methods for preparing PC are based on soft spin of whole blood donations, the collection of platelet-rich-plasma, and the concentration of platelets in 50 mL plasma by high speed centrifugation. Such PC can be stored for a maximum of 5 days. A different approach is the collection of buffy-coats (BC) of whole blood donations (the BC is the layer formed at the red blood cell-plasma interface after whole blood high-spedd centrifugation), followed by soft spin of the BC and collection of platelets in the supernatant. The principal untoward effect of PC transfusion is the production of alloantibodies by PC recipients, caused by leukocytes which contaminate the PC. Moreover, allergic reactions to plasma proteins can occur.

To prevent these complications and to improve the quality of platelet transfusion the invention described below was developed.

The aim of this invention is to remove this difficulty by means of a procedure for blood fractionation allowing the routine

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production and storage in closed system of plasma- and leukocyte-poor RBC concentrates (PLP-RBC, ie RBC containing less than 10% of donated plasma and less than 30% of donated leukocytes), and of plasma- and leukocyte-poor platelet concentrates (PLP-PC, ie PC in a medium containing about 15-40% plasma, and free of leukocytes detectable by microscope counting).

In the procedure reported in this invention an additive RBC solution is used (SAGM or similar), in addition to a synthetic crystalloid solution which is added to the platelets so as to improve their quality and prolong storage to about 10 days.

The above crystalloid solution is preferably made (considering, for example, a volume of 40 mL) of 5.26 g sodium chloride; 2.22 g sodium acetate; 5.02 g sodium gluconate; 0.37 g potassium chloride; 0.14 g magnesium chloride; H_2O for IV use qs to 1,000 mL, pH 7.4 $\pm$ 0.1. It must be emphasized that this solution is very similar to one of the crystalloid solutions reported in the patents issued under the names of Gail Ann Rock and George Adams (Canada, Plasma-free medium for platelet storage, application, Nov 1, 1982, 414,583; USA, Plasma-free medium for platelet storage, Pat 4,447,415; Europe, Plasma-free medium for platelet storage, Granted May 16, 1984 - 0108588, Oct 31, 1983, 83306631.9; Canada, Improved plasma-free medium for platelet storage, application, July 20, 1984, 459,369); however, in the invention described here the quality of platelets is improved since the crystalloid solution is fortified with an amount of plasma derived from the BC; this amount is between 10 and 40% of the final medium, preferably 20-30%.

The procedure is carried out with a multiple bag, preferably a quadruple bag consisting of a primary bag and 3 satellite bags.

After high speed centrifugation, the blood contained in the primary bag is separated into a red blood cell button and supernatant plasma; this latter is transferred into one of the

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satellite bags, while the SAGM solution is added to the primary bag for red blood cell storage, after removing an amount of the buffy-coat (BC) layer, which is the layer between red blood cells and plasma, a layer enriched of platelets. The buffy-coat is transferred into a second satellite bag containing the crystalloid solution and, after a soft spin, the supernatant platelet concentrate is transferred in the third, empty satellite bag, through a cotton wool filter inserted along the tubing, which is capable of removing residual leukocytes which contaminate the platelet concentrate. A platelet concentrate prepared according to this method can be stored for about 10 days in this bag, which is made of plastic material with gas exchange characteristics similar to those of polyolefin.

The above procedure and bag system for the preparation of platelet concentrates from buffy-coats (BC) and their storage in a crystalloid colloid medium can be used also with BC prepared with standard blood bag systems, by mixing 6-8 BC in a transfer bag containing an appropriate amount of the above crystalloid solution. After a soft spin, the supernatant, containing the platelets, is transferred through a cotton wool filter into a new transfer bag where it is stored.

The procedure derived from this invention is now described, just for the sake of example, and with no limitation to its implementation, with the aid of enclosed fig. 2 through 5, which describe the procedure steps, as performed with a quadruple blood bag, for the preparation and storage of PLP-PC and PLP-RBC from a blood donation.

The multiple blood bag consists of a primary bag PB and of 3 satellite bags S1, S2, S3, integrally connected to each other with flexible plastic tubes.

The primary bag PB contains CPD (citrate-phosphate-dextrose) anticoagulant, the satellite bag S1 is empty, the satellite bag

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S2, which is cylinder-shaped and has a volume of 40-60 mL, contains 40 mL of crystalloid solution, the satellite bag S3 contains the SAGM red blood cell additive solution, and is made of plastice material with gas permeability characteristics similar to polyolefin. Along the tube connecting bags S2 and S3 a small (2-3 g) cotton wool filter is inserted.

The procedure regarding this invention is carried out as described below.

The blood donation is collected in the primary bag PB through a collection line I, at one end of which the blood collection needle is attached, and mixed with the CPD anticoagulant (fig. 1). The blood collected in the primary bag PB is centrifuged at high speed, e.g. 3,800 rpm for 4 min in a Sorvall RC-3B centrifuge. After this centrifugation, plasma- and leukocyte-poor red blood cells are concentrated in the lower part of the primary bag PB, the supernatant plasma is contained in the higher part of the bag, and in the layer between plasma and red blood cells the vast majority of platelets are concentrated. This small layer, enriched of platelets, which separated red blood cells from supernatant plasma is defined "buffy-coat" (BC)(fig. 2).

The supernatant plasma (except for about 30 mL) is expressed into and stored in satellite bag S2, which is diconnected from the other bags (fig.2).

A total of 25-50 mL of BC are then collected, which contain about 5 g hemoglobin, 80% of donated platelets, 50% of donated leukocytes and 20-40 mL plasma, and expressed into satellite bag S2, which contain the crystalloid medium (fig. 3).

Preferably, the crystalloid solution contained in satellite bag S3 has the following composition (reference to a volume of 40 mL): 5.26 g sodium chloride; 2.22 g sodium acetate; 5.02 g sodium gluconate; 0.37 g potassium chloride; 0.14 g magnesium chloride; H_2O for IV use qs to 1,000 mL, pH 7.4 $\pm$ 0.1.

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The SAGM solution contained in satellite bag S3 is added to the red blood cell concentrate PLP-RBC in the primary bag PB for its storage. The primary bag, containing the PLP-RBC and the satellite bag S1 containing the plasma are disconnected from satellite bags S2 and S3, which are stored, integrally connected to each other, in a platelet tumbler (a rotating machine for platelet resuspension during storage) (fig.4).

The buffy-coat (containing the platelets) contained in satellite bag S2 can be stored at room temperature for a maximum of 48 h. If platelet concentrates are needed the buffy-coat is centrifuged at low speed, so as to concentrate the red blood cells and the leukocytes in the lower part of the bag S2, and to collect the leukocyte-poor platelet concentrate in the higher part of satellite bag S2. The cylinder shape of satellite bag S2 favors a good separation between the 2 layers above after the soft spin.

The supernatant PLP-PC is transferred from satellite bag S2 to satellite bag S3 (which had been previously emptied of the SAGM solution), through filter F, which removes residual leukocytes present in the platelet concentrate (fig. 5).

Filter F can be much smaller than traditional cotton wool filters for leukocyte removal (2-3 g instead of 17 g) because leukocyte contamination of platelet concentrates prepared from buffy-coats is much lower than that of platelet concentrates prepared with traditional methods, in which centrifugation is carried out on platelet-rich-plasma instead of platelet-rich-buffy-coat.

Experimental data indicate that the platelet concentrate PLP-PC prepared with the above method can be stored in the crystalloid/colloid medium for at least 10 days in a bag made of polyolefin, or of a plastic material capable of providing a gas permeability similar to that of polyolefin, with a final pH of about 7.0, hypotonic shock response of 50% and morphology score according to Kunicki of 220. Moreover, PC prepared with this

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method and invention have the following parameters after 7 days of storage: glucose consumption 1.5 mmol/L/10^9 platelets (compared to 2.8 of PC prepared in the medium of G. Rock), and lactate production of 3.56 mmol/L/10^9 platelets (compared to 6.09 of PC prepared in the medium of Rock). Both parameters suggest better platelet quality in our medium. In addition, platelet aggregation is better in our medium compared to that in the medium of Rock.

These excellent results are mainly due to the crystalloid/colloid medium, of which a preferential composition has been given above, in which a crystalloid solution is mixed with a small amount of plasma (natural colloid) present in the buffy-coat, from which the platelet concentrate is prepared.

The above procedure for the preparation of platelet concentrates from buffy-coats (BC) and their storage in crystalloid/colloid medium can be also used with buffy-coats prepared from traditional blood collection bags, e.g. by using a triple bag made of a primary bag and 2 satellite bags, in which the red blood cell concentrate, the plasma and the buffy-coat are collected, respectively.

In this case 6-8 buffy-coats prepared with the methods above or similar are collected in a transfer bag of about 600 mL volume, containing about 350 mL of the previously described crystalloid solution. After soft spin, the platelet-rich supernatant is transferred through a small (2-3 g) cotton wool filter F into a transfer bag of about 1000 mL volume, with the same characteristics of previously described bag S3, where it is then stored.

The procedure described in this invention offers the following advantages, in addition to those already reported, in comparison to traditional procedures:

- leukocyte contamination of platelet concentrates is below detectable limits in all platelet concentrates, which implies a

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series of outstanding advantages for the patients;

- platelet metabolism can be conditioned by modifying the storage medium with the addition of possible additives;

- there is no need to follow ABO compatibility between donor plasma and recipient red cells, due to the small amount of plasma present in the platelet concentrates;

- more plasma can be recovered from standard blood donations;

- it is possible to prepare platelet concentrates only upon request, so reducing the workload;

- the procedure favors the routine production of buffy-coat deprived red blood cell concentrates (which are of better quality than standard red blood cell concentrates), since it is based on the avalability of buffy-coats.

Moreover, the crystalloid solution does not contain glucose, thus reducing the potential risk of bacterial contamination of PLP-PC.

The above advantages are supported by a series of in-vitro and in-vivo evaluations of platelet concentrates prepared from buffy-coats and stored in medium. A set of these evaluations is reported below.

We compared platelet concentrates prepared from pools of buffy-coats removed from standard blood donations and stored in the crystalloid solution described above (BCS-PC), with standard platelet concentrates, prepared from platelet-rich-plasma (PRP-PC). Total cell counts (median and range, n=43) in BCS-PC units were: platelets 3.6×10^{11} (2.2-5.5), leukocytes 21×10^{6} (4-79); values of PRP-PC units (n=23) were: platelets 0.64×10^{11} (0.47-0.83); leukocytes 148×10^{6} (3-611). Since one BCS-PC unit was prepared from 7 blood donations, a meaningful comparison of PRP-PC and BCS-PC data can be made by multiplying PRP-PC data by 7. Both platelet and leukocyte counts of BCS-PC were significantly lower than those of 7 PRP-PC. Platelet yield in BCS-PC and PRP-PC was 59 and 75 percent of donated platelets, respectively. Median number

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of total leukocytes in 1 BCS-PC unit, prepared from a pool of 7 buffy-coats, was 50 times lower than that of 7 PRP-PC. In vitro parameters of adequate platelet quality were maintained for 10 days in BCS-PC stored in 1000 mL polyolefin bags. Prolonged bleeding times were reduced or corrected in 3 of 3 thrombocytopenic leukemic patients evaluated before and after transfusion of stored BCS-PC. Pretransfusion, 1-h and 24-h posttransfusion median platelet counts of 57 leukemic recipients during 4 months of routine transfusion of BCS-PC (n=93) were 14, 35, and 27 x 10^9/L, compared with 13, 37 and 31 x 10^9/L of PRP-PC (n=246), respectively (p=ns). No reactions to BCS-PC were reported, compared with a reaction rate of 1.3 percent for PRP-PC transfusions. The median (and range) titer of ABO agglutinins in BCS-PC and PRP-PC was 8 (2-8) and 64 (32-128), respectively. A detailed description of the results is reported in tables 1-3.

In vitro evaluation of BCS-PC and PRP-PC during storage is reported in table 1.

It can be seen (section A) that in vitro parameters of adequate platelet quality (pH above 6.0, morphology score above 200) were maintained in BCS-PC for at least 10 days of storage in 1000 mL polyolefin bags; at this time the platelet response to hypotonic shock (HSR), a parameter related to platelet recovery and survival in normal volunteers, was still above 80 percent of values at day 1. This was not so for BCS-PC stored in 1000 mL PVC bags (section B), in which the median pH value was below 6.0 at day 3. This was associated with a complete loss of HSR and a marked deterioration of platelet morphology. Similarly to other reports, PRP-PC stored in PVC satellite bags of 400 mL volume showed adequate quality preservation for at least 5 days (section C). On day 1, PO_2 values of BCS-PC in 1000 mL bags were about 2 times higher than those of PRP-PC in 400 mL bags, as expected on the basis of both a larger bag and a smaller platelet concentration in the former. Platelet

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quality during storage in PVC deteriorated more rapidly in BCS-PC than in PRP-PC. A contributory cause could have been the smaller ratio between bag surface area and PC volume in the former, determining a less efficient gas transport during storage. Oxygen consumption for aerobic metabolism, which is more favorable than anaerobic for PC preservation during storage, was maintained longest in BCS-PC stored in polyolefin, as indicated by the slowest PO_2 rise.

Results of in-vivo study are reported in Table 2 and 3.

Pilot phase. Pretransfusion, 1-h and 24-h posttransfusion platelet counts and percent recovery values obtained in "stable" leukemic recipients are reported in table 2. It can be seen that values of BCS-PC stored for 1-8 days were similar to those of PRP-PC stored for 1-3 days. Bleeding time (reference values 2-7 min) was reduced after BCS-PC transfusion in 3 of 3 patients evaluated, dropping from more than 30 to 9 min (6-day old BCS-PC containing 3.0×10^{11} platelets), from 25 to 5 min (4-day old BCS-PC containing 2.8×10^{11} platelets), and from 22 to 6 min (8 day old BCS-PC containing 3.1×10^{11} platelets). On these 3 occasions pre- and 1-h posttransfusion platelet counts were 17-43, 16-56 and 16-39 $\times 10^9$/L, respectively.

Routine phase. A total of 448 and 129 platelet transfusions were issued as 1-3 day-old PRP-PC and 1 day-old BCS-PC, respectively, to 57 leukemic patients. This group included all hematological patients transfused with platelet concentrates in the study period. Pretransfusion, 1-h and 24-h posttransfusion platelet count and percent recovery, available on 55 percent (PRP-PC) and 72 percent (BCS-PC) of occasions, are reported in table 3. Increments of BCS-PC were not significantly different from those of PRP-PC. No reactions were reported for BCS-PC, compared with 6 for PRP-PC; of these, 2 were febrile and 4 allergic.

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Table 1 storage.

Day	pH	PO_2 (mm Hg)	PCO_2 (mm Hg)	HSR (%)	Morphology score	Platelet count (% of day 1)
A) BCS-PC units stored in 1000 mL polyolefin bags (n=8)						
1	6.9 (6.7-6.9)	87 (70-109)	23 (20-31)	62 (39-68)	311 (250-333)	100
3	6.9 (6.4-6.9)	73 (61-115)	26 (19-36)	64 (46-67)	273 (230-306)	95 (75-100)
5	6.8 (6.4-6.9)	93 (40-123)	28 (19-39)	62 (42-70)	266 (215-297)	88 (73- 96)
10	6.7 (6.3-7.0)	101 (76-145)	25 (20-36)	51 (33-69)	203 (185-260)	81 (71- 93)
15	6.9 (5.8-7.2)	122 (65-175)	17 (9-27)	31 (0-60)	180 (105-280)	76 (68- 81)
B) BCS-PC units stored in 1000 mL PVC bags (n=8)						
1	6.8 (6.7-6.9)	90 (82-124)	27 (18-31)	50 (42-67)	312 (270-329)	100
3	5.9 (5.8-6.5)	148 (71-161)	37 (24-69)	0 (0-69)	160 (142-231)	92 (88- 97)
C) PRP-PC units stored in 400 mL PVC bags (n=10)						
1	7.0 (6.7-7.1)	40 (28-149)	56 (19-90)	55 (30-69)	260 (210-331)	100
3	7.0 (6.2-7.2)	47 (16-81)	46 (34-77)	51 (36-56)	226 (122-331)	100 (100-100)
5	7.0 (5.6-7.1)	58 (13-154)	42 (16-48)	47 (0-60)	208 (92-263)	100 (81-100)
10	6.6 (5.5-7.0)	86 (50-199)	35 (13-42)	21 (0-40)	167 (71-195)	94 (88- 97)
15	6.1 (5.7-6.8)	181 (123-201)	14 (6-28)	0 (0-9)	107 (73-154)	72 (60- 94)

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Table 2. In vivo study: pilot phase. Median (and range) platelet counts and percent recovery in 11 "stable" leukemic patients receiving both BCS-PC and PRP-PC.

Type of PC	Storage Days	Storage Bag	Platelet count ($\times 10^9$/L) Pre-	Posttransfusion 1-h	Posttransfusion 24-h	Platelet in vivo recovery (% of expected) 1-h	24-h
BCS-PC n=8	1	1000 mL PVC	13 (9-20)	42 (23-56)	34 (28-46)	59 (19-81)	44 (28-62)
BCS-PC n=8	4- 8	1000 mL polyolefin	17 (9-21)	43 (16-56)	33 (12-40)	50 (0-102)	36 (0-54)
BCS-PC n=5	9-12	1000 mL polyolefin	10 (5-21)	43 (13-91)	21 (12-28)	73 (17-161)	11 (7-40)
PRP-PC n=15	1- 3	400 mL PVC	16 (4-29)	50 (10-92)	37 (14-79)	49 (0-102)	30 (0-92)

Table 3. In vivo study: routine phase. Median (and range) platelet counts and percent recovery in 57 hematologic patients receiving platelet transfusion during 4 months of routine use of both BCS-PC and PRP-PC.

Type of PC	Storage Days	Storage Bag	Platelet count ($\times 10^9$/L) Pre-	Posttransfusion 1-h	Posttransfusion 24-h	Platelet in vivo recovery (% of expected) 1-h	24-h
BCS-PC n=93	1	1000 mL PVC	14 (2-40)	35 (7-83)	27 (3-64)	40 (0-103)	22 (0-98)
PRP-PC n=246	1- 3	400 mL PVC	13 (1-69)	37 (4-114)	31 (1-137)	31 (0-110)	20 (0-124)

It is emphasized that the invention is not limited to the particular description reported above and in the enclosed figures, but it can me modified in several minor parts within the scope of the invention.

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CLAIMS

1. A method for the preparation and storage of plasma- and leukocyte-poor platelet concentrates from buffy-coats, which comprises the transfer of at least 1 buffy-coat into a bag (S2) containing a synthetic crystalloid solution (which is diluted with the plasma contained in the buffy-coat so as to constitute a colloid/crystalloid medium for platelet storage), the soft spin of the bag (S2) and the transfer of the supernatant PLP-PC formed after centrifugation into a (S3) bag made of polyolefin or of plastic material with gas permeability similar to polyolefin, through a cotton wool filter (F) of 2-3 g, so as to remove residual leukocytes contained in the platelet concentrate.

2. A method as claimed in claim 1, wherein the above bag S2 has an elongated, cylinder shape.

3. A process according to claim 1, wherein 1000 ml. of said synthetic crystalloid solution contain 5.26 gr sodium chloride, 2.22 gr sodium acetate, 5.02 gr sodium gluconate, 0.37 gr potassium chloride, 0.14 gr magnesium chloride, H_2O for I.V. use qs to 1000 ml and wherein said crystalloid solution has a pH of 7.4 ± 0.1.

4. A process according to claim 1, wherein 6-8 BC obtained from as many donations are transferred into the bag (S2).

5. A process according to claim 1, wherein the PLP-PC are stored in a synthetic crystalloid / natural colloid solution, comprising the crystalloid medium of bag (S2) and the plasma of each BC (about 20-40 ml of plasma in a BC volume of 25-50 ml).

6. A process according to claim 1, wherein the BC are separated in a multiple bag for the preparation and storage of PLP-PC and PLP-RBC (plasma- and leukocyte- poor RBC concentrates), e.g. in a quadruple blood bag comprising a primary bag (PB) and three satellite bags (S1), (S2), (S3).

7. A process according to claim 6, comprising:

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collecting the blood in a primary bag (PB) containing CPD anticoagulant, centrifuging at high speed said primary (PB) bag, tranferring the supernatant plasma into the bag (S2) containing tha crystalloid solution, and tranferring the SAGM solution of bag S3 into the (PB) bag containing PLP-RBC.

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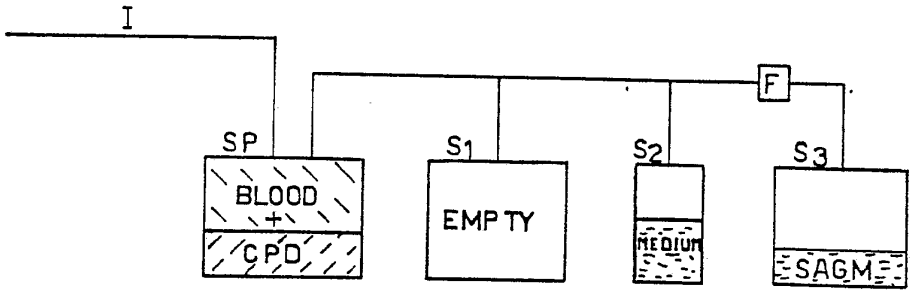


FIG_1

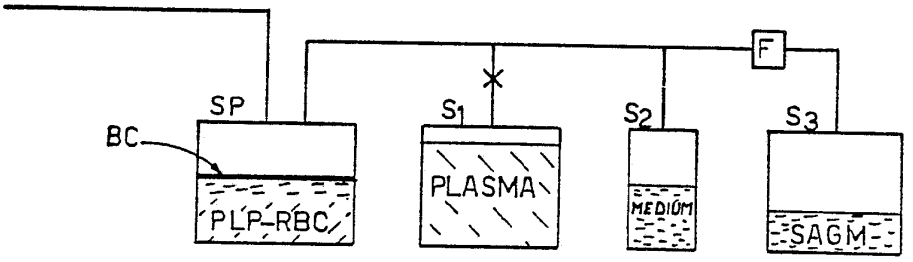


FIG_2

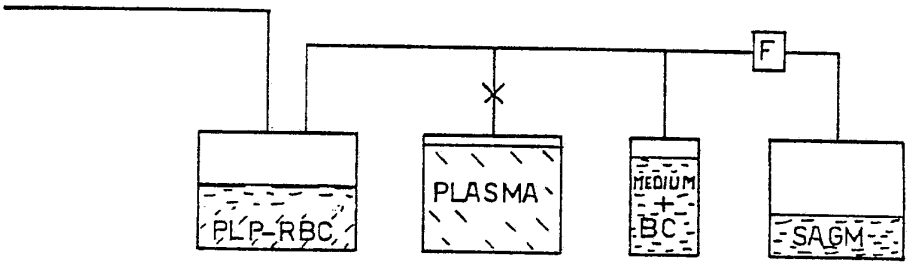


FIG_3

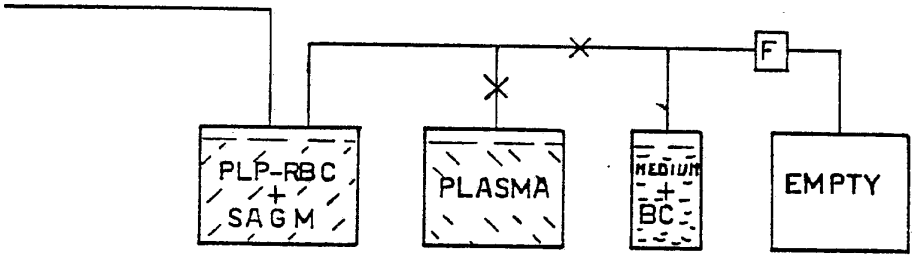


FIG_4

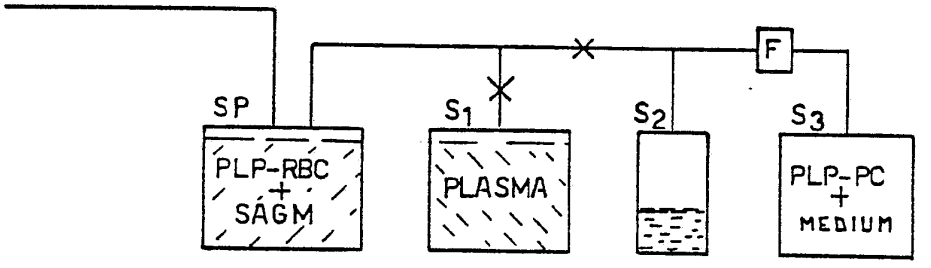


FIG_5

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INTERNATIONAL SEARCH REPORT

International Application No PCT/IT 89/00048

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC [5]: A 61 K 35/14, A 61 M 1/36

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC [5]	A 61 K, A 61 M

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0233112 (TERUMO K.K.) 19 August 1987 see page 4, lines 32-36; page 11, lines 31-36; page 12, lines 22-29; page 20, lines 28-34 --	1
A	US, A, 4639373 (B.M. BABIOR) 27 January 1987 see column 2, lines 18-19 --	1
A	US, A, 4447415 (G.A. ROCK) 8 May 1984 see claims 1,8 cited in the application --	1
A	WO, A, 86/03122 (CURATECH INC.) 5 June 1986 see claim 1 --	1
A	US, A, 4344936 (G. SOSLAU) 17 August 1982 see claim 1 --------	1

* Special categories of cited documents: [10]

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13th September 1989	09. 10. 89
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	T.K. WILLIS

Form PCT/ISA/210 (second sheet) (January 1985)

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. IT 8900048 SA 29644

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 29/09/89
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0233112	19-08-87	AU-A-	1885688	06-10-88
		AU-B-	578554	27-10-88
		AU-A-	6794387	06-08-87
		JP-A-	62258322	10-11-87
US-A- 4639373	27-01-87	None		
US-A- 4447415	08-05-84	CA-A-	1216518	13-01-87
		EP-A,B	0108588	16-05-84
		US-E-	RE32874	21-02-89
WO-A- 8603122	05-06-86	AU-A-	5094985	18-06-86
		DE-T-	3590594	29-01-87
		EP-A-	0202298	26-11-86
		JP-T-	62501628	02-07-87
		NL-T-	8520384	29-11-84
		SE-A-	8603228	25-07-86
US-A- 4344936	17-08-82	None		

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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(30) Priority data:
294,056 5 January 1989 (05.01.89) US

(71) Applicant: HAEMONETICS CORPORATION [US/US]; 400 Wood Road, Braintree, MA 02184 (US).

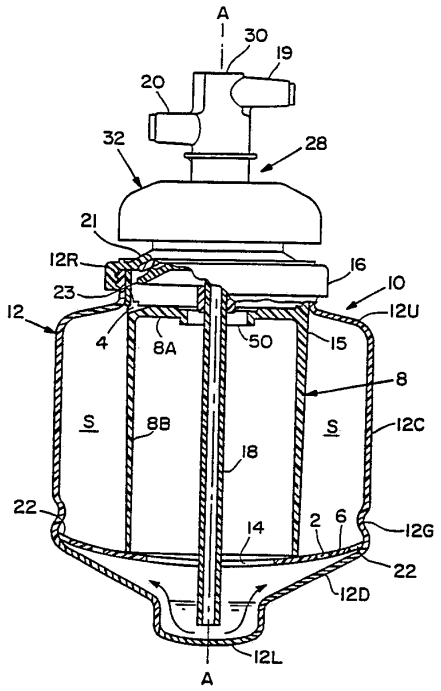
(72) Inventor: PAGES, Etienne ; Le Longchamps B, Arbère, F-01220 Divonne (FR).

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(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), ES (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: DISPOSABLE CENTRIFUGE BOWL FOR BLOOD PROCESSING



(57) Abstract

An improved disposable blood processing centrifuge bowl is described comprising a rotary seal (28) enclosing an aperture in a bowl body (12) through which a two-piece core assembly (8, 6) is inserted.

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DISPOSABLE CENTRIFUGE BOWL FOR BLOOD PROCESSING

Description

Related Applications

This application is a continuation-in-part of U.S. Patent Application Serial No. 07/232,544 filed 8/15/88 entitled "Plasmapheresis Centrifuge Bowl" to Thomas D. Headley, which is a continuation of U.S. Patent Application Serial No. 06/888,764 filed 7/22/86 entitled "Plasmapheresis Centrifuge Bowl" to Thomas D. Headley.

Technical Field

This invention relates to blood processing and, more specifically, centrifuge bowls for blood processing.

Background of the Invention

Disposable centrifuge bowls have been developed for processing anticoagulated whole blood in pheresis and cell washing procedures. Prior to about 1986, commercially available disposable blood processing centrifuge bowls were of the type generally shown in Figs. 1 or 6 of U.S. Patent No. 4,300,717 (hereinafter "Latham bowl"), or U.S. Patent No. 4,086,924 (hereinafter "Grenade bowl"). The overall bowl construction in each case was similar and consisted of three essential units. The first was a multi-piece feed tube and seal assembly, which enable anticoagulated whole blood and/or wash

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solution to be introduced to the interior of a rotating bowl body from a fixed location, and processed blood component to be removed from the bowl body and returned to a patient or donor, or stored. The second unit comprised a two-piece bowl body welded together at a peripheral seam.

The third unit was a core body usually of fairly solid construction. The core body served a number of functions. In the Latham bowl, it provides a narrow bottom fluid channel between the base of the core and the bottom of the bowl, through which fluid admitted through a central feed tube was passed to the outer periphery of the bowl body interior. In passing through this narrow channel, "impeller" vanes, formed on the bottom of the bowl, impart rotational velocity to the incoming feed fluid. With the core design shown in the Latham bowl, fluid feed is forced to pass to the outer separation region between the inner peripheral bowl body wall and the outer peripheral wall of the core. Without this core design, it would be possible for fluid admitted at the bottom of the bowl to by-pass the separation region and pass directly from the feed tube upwardly through the space between the inner core wall and the feed tube out the effluent port formed between the skirts of the seal assembly. The rigid core body was considered essential to avoid or dampen fluid wave vibrations which might occur between the rotating sterile air in the central region between the core and the feed tube

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and the fluid processed in the outer separation region.

The Grenade bowl construction is similar, except that the middle bowl body side walls are not tapered and the bottom of the core is not flared.

In addition to the above designs, a pheresis bowl, which was never commercialized, is described in U.S. Patent No. 4,059,108. This bowl was of two-piece construction, formed of a lower red cell reservoir and a plasma with a core baffle system (shown in Fig. 18) for the red cell reservoir.

Sometime during 1986/87, a new centrifuge bowl became commercially available. The construction of this bowl is shown in the Fig. 4-6 embodiment of co-pending U.S. Patent Application Serial No. 07/232,544 filed 8/15/88, which is a continuation of Serial No. 888,764 filed 7/22/86. This new bowl differed from the prior art bowl by the use of a one-piece integral blow molded bowl body. Among other things, this construction (hereinafter "integral bowl") eliminated the need for a weld about the periphery of the bowl; a possible source of bowl failure at high centrifugal speeds.

The Fig. 4-6 embodiment of the integral bowl utilized a one-piece core body with an outer diameter is equal to or smaller than the opening into the bowl. The small core size is insufficient to enable the core to force feed fluid, entering the bottom of the bowl through the feed tube, to be diverted to the extreme outer periphery of the separation region between the core body and the bowl

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wall. This diversion is extremely important for cell washing procedures.

In cell washing systems, shed blood from a patient is filtered, collected and washed with saline in a disposable centrifuge bowl. Anticoagulated, filtered shed whole blood enters at the bottom center of the bowl and is separated by centrifugal forces into more dense red cells and less dense other components. The red cells fill the outermost portion of the rotating centrifuge bowl. As more shed blood enters the bowl, the red cells remain in the bowl displacing the supernatant (saline, plasma, contaminants, etc.) out of the mid-central region of the bowl. This concentrates the red blood cells in the bowl. Next, saline is directed into the bottom of the bowl, instead of shed blood. Saline, entering the Latham bowl, is directed by the lower extended skirt portion of the core to the outermost radius of the bowl and through the bed of packed red blood cells. In this way, the supernatant is diluted and displaced by the saline until a satisfactory "washout" efficiency is obtained.

The term "washout" efficiency, sometimes referred to as merely "washout", denotes the percentage of non-red blood cell fluid, i.e., plasma and saline and contaminants, originally entering the bowl and which are removed by the wash process. A 90% or greater efficiency is typically the goal of the wash process. At the end of the "wash" cycle,

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the contents of the bowl are red cells suspended in saline. The centrifugal washing procedure in conjunction with filtration concentrates the red blood cells and removes contaminants, such as blood clots, bone chips, fatty tissue and activates clotting factors. The patient can then be reinfused with his or her own washed red blood cells.

The Fig. 4-6 embodiment of the integral bowl body bowl of the parent application does not disclose a diverter structure, as in the Latham type bowl. Therefore, some of the saline wash solution may not be forced to travel through the packed red cells before exiting the bowl through the effluent skirts on the rotary seal. This substantially decreases the washout efficiency and, hence, the time it takes to complete a cell washing procedure. As might be expected, time is an extremely critical factor in cell washing procedures, both from the point of view of cost and patient comfort and safety.

Disclosure of the Invention

In alternate embodiments of the integral bowl patent application, two core structures are disclosed which permit use of an integral bowl body, yet enable the core diameter to exceed the diameter of the bowl body opening. In one embodiment, the core is formed of one-piece construction using semi-rigid plastic material with a flared core and a wall body which can be deflected to allow the flared core to be inserted through the smaller diameter opening. This one-piece core construction, shown in

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cross-section in Fig. 7 of the parent application, is complex and would be difficult and expensive to fabricate. Also, since it is unsecured along its length, it is susceptible to lateral movement in the event of vibrations which could occur as fluid in the bowl is rotated. Such lateral movement may result in blockage of the channel between the bottom flange of the core and the angled bottom wall of the bowl.

In the Fig. 9-10 embodiment of the parent application, the core is of two-piece construction. One piece is comprised of a generally cylindrical hollow walled core. The other piece is a disc-like member with a flared wall portion adapted to be located adjacent the diagonal wall of the bowl body.

The disc-like member is made of semi-rigid plastic and can be compressed to allow it to pass through the top opening in the bowl body. Circular grooves are formed around protrusions on the member to permit the bottom of the cylindrical core wall to made with the member after the walled core is inserted into the bowl body. The circular grooves form a press-fit, holding the two pieces together during rotation of the bowl. A central aperture in the disc-like member permits whole blood from a feed tube stem to enter the bottom of the bowl body.

This two-piece embodiment is difficult to assemble in the bowl body, relies on a press fit with very little penetration between the mating

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members, and is also subject to vibrational displacement since the length of the core is essentially suspended from the top without lateral support.

The above summary of the development of centrifuge bowls over a long period of time reveals a need for a core body for blood processing centrifuge bowls which can be used in integral bowl bodies or non-integral bowl bodies, yet retain the features of the Latham style bowl, especially in connection with cell washing protocol. It would also be desirable to have a core body which could be constructed such that the same core body could be utilized for bowls of various volumetric sizes.

The method and apparatus of the present invention comprises, in general, a disposable centrifuge rotor or bowl formed of a combination of three basic items. The first is a rotary seal and header assembly; the second, a bowl body, preferably of seamless, integral, one-piece construction and the third is a two-piece core assembly capable of being rigidly retained against a bowl wall and used in standard bowl bodies of different internal volumetric capacity. The seal and header assembly is as described in the above-referenced parent application. The bowl body is preferably adapted to be manufactured by blow molding or injection blow molding, as also described in the parent application.

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The core assembly consists of two plastic pieces made by injection molding or similar processes. The first piece is a generally cylindrical rigid hollow-walled core, similar to the walled core in the parent application. The second piece is a diverter in the form of a semi-rigid donut-like member, scalloped at its peripheral edges and having an outer diameter greater than the bowl opening and about equal to the inner diameter of the mid-section of the bowl.

An inner hole is provided on the donut-like member. This hole has a diameter slightly smaller than the diameter of the effluent header.

The core assembly is assembled inside the bowl by first bending the diverter to permit it to fit inside the bowl and then bending it back to its original flat aspect to fit laterally and horizontally across the bowl body. The walled core is then inserted through the bowl opening. The longitudinal length of the core is sized to be just long enough so that when the core is pushed downwardly in the bowl, it pushes the diverter downwardly into the bowl, also, until the diverter is laying in a generally horizontal, slightly bowed, rigid, compressed position opposite that portion of the bowl body which begins to incline radially inwardly and downwardly and become conical.

Optionally, a ring of holes are provided on the diverter with the ring concentric to the inner hole in the diverter and the diameter of the ring and hole size such that the holes in the ring are

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located slightly radially outwardly from the core wall. These holes enable subsequent feed fluid to be introduced to the separation region at a radially inward bottom location after the initial introduction of fluid has occurred and separated component begins to block the peripheral scalloped openings.

The vertical location of the diverter can be adjusted for different volumetric bowl capacities simply by changing the length of the core wall. The semi-rigid diverter is held in compression against the inner circumferential side wall of the bowl body and is, therefore, less susceptible to movement caused by vibration or turbulence when the bowl is rotated at high speeds.

The above and other features and advantages will now be described in detail in connection with the drawings.

Brief Description of the Drawings

Fig. 1 is a cutaway side view showing a centrifuge bowl of the present invention with the core construction shown in cross-section.

Fig. 2 is a top view of the diverter 10 of Fig. 1 in accordance with the invention.

Fig. 3 is a view as in Fig. 1 except that a smaller volume bowl body and shorter length core is employed.

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Best Mode of Carrying Out the Invention

Referring now to Figs. 1-2, the apparatus of the invention will now be described in detail in connection with an integral bowl body cell washing process. It is emphasized that the method and apparatus of the invention is capable of general applicability to other blood processing methods, such as pheresis, and to other bowl body structures.

As shown therein, the centrifuge rotor or bowl 10 of the invention, comprises a seal and header assembly, shown generally at 28; a one-piece integral bowl body, shown generally at 12; and a core assembly comprising core body 8 and diverter 6.

The seal and header assembly 28 is substantially identical to the seal and header assembly utilized in the parent application referenced above. Therefore, it need not be described in detail herein. Briefly, the assembly 28 is comprised of a non-rotatable header 30, an effluent tube (not shown), a feed tube assembly (not shown) and a rotary seal formed beneath secondary shield 32 comprising a seal ring, a flexible member (also not shown) and an outside seal member or crown 16.

The header 30 has a transverse inlet bore 19 extending transverse the longitudinal axis "A" of the bowl and then into a longitudinal passageway coupled to the inner bore of the feed tube assembly. The passageway leads to stem 18 forming an inlet fluid communication path for feed fluid, i.e., whole blood or saline, to enter the interior of centrifuge

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bowl body 12 at the lower longitudinally axial portion 12L of the bowl body 12.

Header 30 is also provided with a transverse outlet bore 20, which extends transversely into a peripheral channel extending in parallel relationship with the feed tube assembly and into an outlet coaxial passageway (not shown). A secondary shield 32 is formed on header 30 and extends over the rotary seal. A pair of complementary skirts 21 and 23 provide an effluent passageway, therebetween, connecting the outlet passageway to the outlet bore 20.

Internal screw threads, on seal crown 16, secure the seal and header assembly to complementary threads on the bowl body.

The bowl body 12 is preferably an integral body adapted to be manufactured by blow molding or injection blow molding and may be formed of a suitable plastic, such as transparent styrene or equivalent.

The bowl body is formed of an upper ring portion 12R, an upper diagonal portion 12U extending radially outwardly and inclined downwardly, a straight middle central portion 12C extending vertically downward, a lower diagonal portion 12D extending radially inwardly and downward, and a lower cross portion 12L. Screw threads are formed on the outer surface of ring portion 12R and an opening extends longitudinally from the inner surface of the ring portion 12R into the main

portion of the bowl body 12. An optional groove is formed about the periphery of the bowl at 12G to form a holding surface for a centrifuge rotor chuck (not shown).

Prior to inserting the header and seal assembly 28 into the bowl body, a core assembly consisting of core body 8 and diverter 6 is inserted into the interior of the bowl.

The core body is adapted to be inserted into the bowl body 12 through the opening in ring portion 12R. Core body 8 is an integral member formed of a suitable rigid, or semi-rigid, blood compatible transparent plastic and has a cylindrical outer wall 8B extending longitudinally downward and coaxial to the axis A of bowl body 12. An upper transverse ring portion 8A of core body 8 is adapted to abut the inner wall of the ring portion 12R of the bowl body 12 when the core body is inserted into the upper opening of the bowl body 12.

Four L-shaped reinforcing tabs (not shown) are formed on the top wall of core body 8 to reinforce the ring portion 8A. Four peripheral slots (one of which is shown at 4) extend along the periphery of the core body at the juncture between the ring portion 8A and the cylindrical outer wall 8B. These slots provide a passageway for the exit of effluent, such as supernatant or plasma, which has been separated from the packed red blood cells by the operation of the centrifuge cell washing or pheresis process within the bowl body 12.

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A coaxial opening 50 is provided in the transverse ring 8A of core body 8B to enable feed tube stem 18 to pass unimpeded into the lower portion 12L of the bowl body.

Diverter 6 is a donut-like member formed of blood-compatible semi-rigid transparent plastic material. The diverter has an outside diameter greater than the diameter of the opening in the top of the bowl body 12 and is provided with scalloped openings 22 at the peripheral edge thereof. The outer diameter of the diverter is about equal to the inner diameter of the bowl body at the mid-section 12C, so that when the diverter is folded and inserted into the bowl body through the top opening and unfolded into its flat aspect horizontal position, it extends across the entire cross-section of the bowl at the mid-section 12C. The core body is then inserted through the opening. The length of the cylindrical longitudinal wall 8B is just sufficient so that when the core body 8 is fully inserted and cover 16 is screwed in place, the diverter 6 is pushed into a horizontal position vertically aligned with the start of the lower radially inwardly diagonal or inclined portion 12D of the bowl.

In this manner, the diverter 6 is retained in a slightly bowed compressed rigid position at the precise vertical location preferred for introduction of fluid to the separation region "S" between the mid-section bowl wall 12C and the core body wall 8B.

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Optionally, a ring of openings 2 are provided intermediate central opening 14 and the peripheral scalloped openings 22 at the periphery of the diverter 4. As fluid, such as anticoagulated shed blood, is first introduced to the bowl, it enters at the bottom region adjacent wall 12L and under the influence of centrifugal force, flows outwardly and upwardly in the direction of the arrows and enters the separation region S at the periphery thereof through scalloped openings 22.

Eventually, a layer of more dense packed red blood cells accumulates at the outermost radius of the separation region, covering the peripheral openings 22.

As wash fluid is next introduced, it is easier for this fluid to enter the separation region S at the radially inward openings 2 than at the peripheral openings 22. In this way, a desirable cell washing cross-flow is established with cell washing fluid flowing generally upwardly from openings 2 while whole blood particulate is in suspension sediment travelling in a radially outward direction.

Fig. 3 shows an alternate embodiment of the disposable centrifuge bowl 10' of the invention in which a smaller volumetric size bowl 12' is utilized in conjunction with a shorter length core body 8'. The bowl body is substantially as described in co-pending design patent application, Serial No. 07/102,646 filed September 30, 1987 to Thomas D. Headley entitled "Bowl Body".

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In this bowl body, the outer diameter of the mid-section of the bowl 12' is stepped from a relatively large diameter equal to the diameter of the mid-section in Fig. 1 to a lesser diameter at a point about halfway along the length thereof. The length of the core 8' is similarly foreshortened, so that when the core is inserted against diverter 6', the diverter is compressed at the beginning of the first diagonal inwardly inclined region 12I of the bowl body.

The diverter 6' may be identical in size and shape to the above previously described diverter 6, in all respects, yet function in a similar manner in the smaller size bowl.

Equivalents

Those skilled in the art will recognize that there are many equivalents to the specific embodiments shown herein. Accordingly, the invention is not to be limited except as may be required by the scope of the claims herein.

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CLAIMS

1. A disposable blood processing centrifuge rotor comprising:

a) a rotatable bowl body having at least one straight section and upper and lower inclined diagonal sections connected to one of said straight sections; said body being rotatable about an axis and having a single aperture therein concentric with said axis through an outer wall of the bowl body; and

b) a rotary seal assembly affixed to said bowl body and covering said aperture and having input and output ports for fluid communication with the interior of said bowl body;

c) a core assembly comprising:

(i) a walled core body having a transverse ring portion which mates with the bowl body at the aperture thereof and a cylindrical portion longitudinally extending from said ring portion; and

(ii) a diverter member having a donut-like shape with an inner opening coaxial to said axis and a diameter smaller than the outer diameter of said cylindrical portion and an outer apertured periphery with a diameter

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about equal to the inner diameter of said straight section and larger than the diameter of the bowl aperture and sufficiently non-rigid as to be capable of being inserted through said bowl aperture and be rigidly retained in a horizontal position against an inner wall of the bowl body by compression as the bottom of the cylindrical portion of said core body abuts the diverter.

2. A disposable blood processing centrifuge rotor comprising:

a) a bowl body rotatable about its longitudinal axis and having a single closeable bowl body aperture concentric with said axis at one end thereof;

b) a core assembly concentric with said axis and having an open center extending within said bowl from said aperture about said axis formed of a longitudinally extending cylindrical wall member and an apertured disc-like diverter held in compression across said bowl body at a location corresponding to the length of said wall member when fully inserted in the bowl body; and

c) a rotary seal assembly having a cover for sealing said seal assembly to the outer body wall about the periphery of said single aperture.

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3. The rotor of Claim 2 wherein the diverter is at least partly flexible at portions having an outer diameter greater than the bowl body aperture.

4. A disposable centrifuge blood processing rotor comprising:

a) a bowl body adapted for rotation about its longitudinal axis and having a bowl body aperture, through an outer wall, to the interior of said bowl body and concentric with said axis at one end of the outer wall of the bowl body;

b) a core assembly comprising a core body and a disc-like diverter with a central opening, and peripheral apertures, said assembly being insertable in said bowl body aperture and said diverter being retained by said bowl body in compression horizontally across the interior of said bowl body; and

c) a rotary seal assembly affixed to the outer wall about the periphery of said aperture and having an effluent port and an input port in fluid communication with the interior of said bowl body.

5. The rotor of Claim 1 wherein the aperture is on the top of the bowl body and the upper section of the bowl body inclines radially outwardly from top to bottom while the lower section of the bowl body inclines radially inwardly from

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top to bottom and the diverter member is retained against the bowl body at a region where the bowl body begins to incline radially inwardly.

6. The rotor of Claim 5 wherein the bowl body has upper and lower straight sections and the diverter is retained between the upper and lower straight sections.

7. The rotor of Claim 1 wherein the outer apertures at the periphery of the diverter member are in the form of scalloped edges.

8. The rotor of Claim 1 wherein a plurality of openings are formed in said diverter member radially intermediate said apertured periphery and said inner opening to permit fluid from below said core body to enter the interior of said bowl body between said cylindrical portion and said straight section.

9. The rotor of Claim 4 wherein the diverter has an outer diameter when flat which exceeds the diameter of the bowl body aperture and is sufficiently flexible as to be capable of insertion through said aperture, yet sufficiently rigid as to be retained, by longitudinal force of said core body, across the interior of said bowl body at a region where said bowl body inclines radially inwardly from top to bottom.

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10. The rotor of Claim 9 wherein the diverter has a ring of openings intermediate the central opening and peripheral apertures.

11. A method of forming an integral continuous flow blood processing centrifuge rotor comprising the steps of:

a) providing a one-piece bowl body having at least one straight section and upper and lower inclined diagonal sections connected to one of said straight sections; said body being rotatable about an axis and having a bowl aperture therein concentric with said axis through an outer wall of the bowl body; and

b) inserting through said bowl aperture a semi-rigid diverter member having a donut-like shape with an inner opening coaxial to said axis and an outer apertured periphery with a diameter about equal to the inner diameter of said straight section and larger than the diameter of the bowl aperture;

c) inserting a walled core body through said bowl aperture having a transverse ring portion which mates with the bowl body at the bowl aperture and a cylindrical portion longitudinally extending from said

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ring portion and pushing said diverter member with said cylindrical portion until said diverter member is rigidly retained by compression against an inner wall of said bowl body; and

d) covering said aperture with a rotary seal assembly affixed to said bowl body and having input and output ports for fluid communication with the interior of said bowl body.

12. A method of forming a disposable blood processing centrifuge rotor comprising:

a) providing a seamless bowl body having a closeable aperture at one end thereof;

b) inserting a semi-rigid diverter into said bowl body through said aperture;

c) inserting a cylindrical wall member into said aperture to compress said diverter across said bowl body at a location corresponding to the length of said wall member when fully inserted in the bowl body; and

d) covering said aperture with a rotary seal assembly.

13. The method of Claim 12 wherein the diverter is at least partly flexible at portions having an outer diameter greater than the bowl body aperture.

14. The method of forming a disposable centrifuge blood processing rotor comprising:

a) providing a bowl body adapted for rotation about its longitudinal axis and having a bowl body aperture concentric with said axis at one end of an outer wall of the bowl body;

b) inserting a core assembly into said bowl body through said aperture by first inserting a disc-like diverter with a central opening, and peripheral apertures, and next inserting a core body into said aperture to retain said diverter in compression horizontally across the interior of said bowl body; and

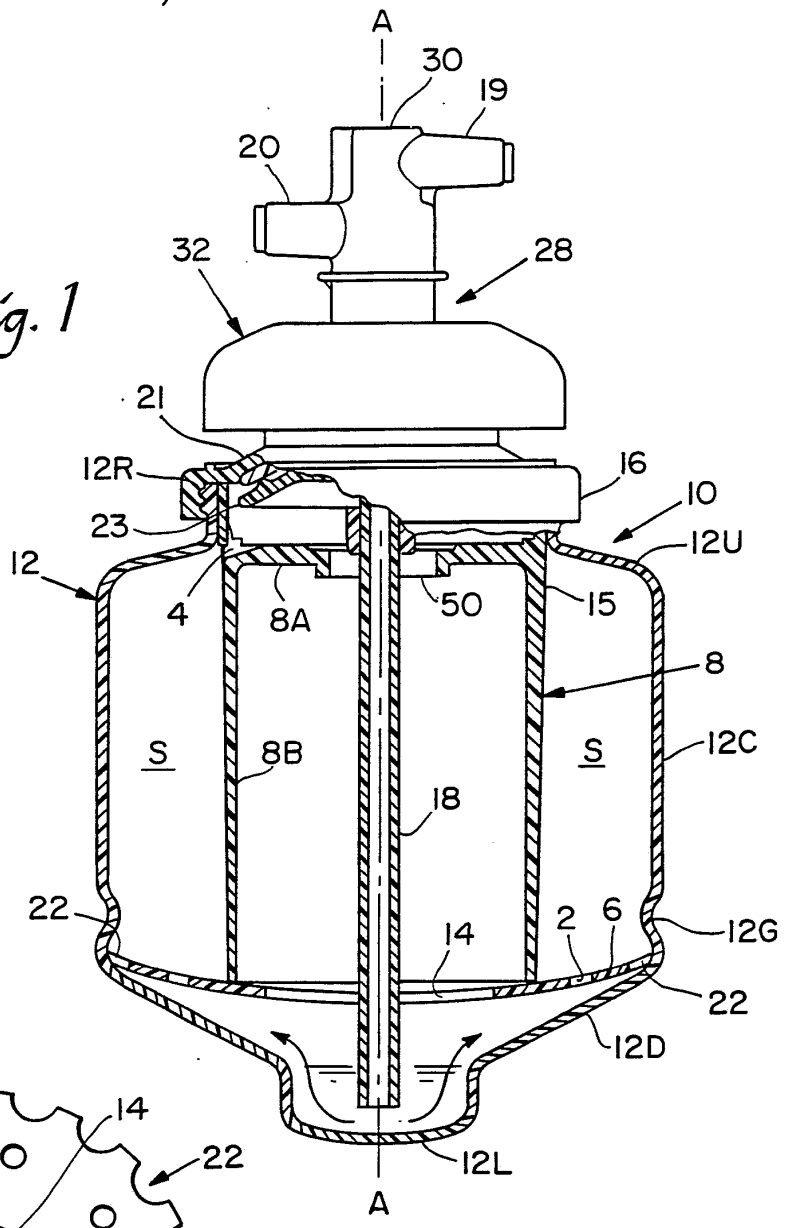
c) covering said aperture with a rotary seal assembly affixed to the outer wall about the periphery of said aperture and having an effluent port and an input port in fluid communication with the interior of said bowl body.

15. The method of Claim 14 including forming a plurality of openings in said diverter radially intermediate said apertured periphery and said central opening to permit fluid from below said core body to enter the interior of said bowl body between said core body and said bowl body.

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1/2

Fig. 1


A
30
19
20
32
28
21
12R
16
10
23
12U
12
4
8A
50
15
8
S
8B
S
12C
18
22
14
2
6
12G
22
12D
12L
A

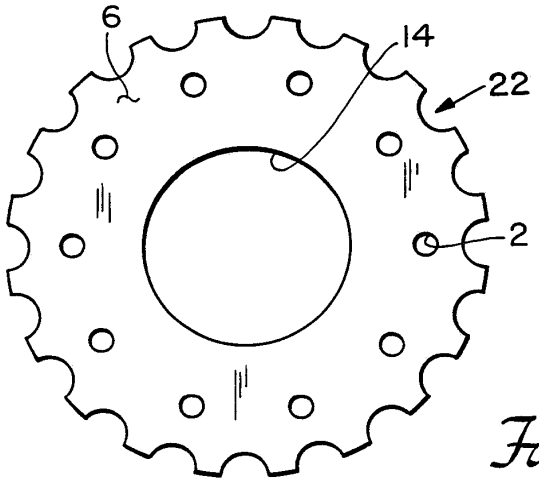

6
14
22
2

Fig. 2

2/2

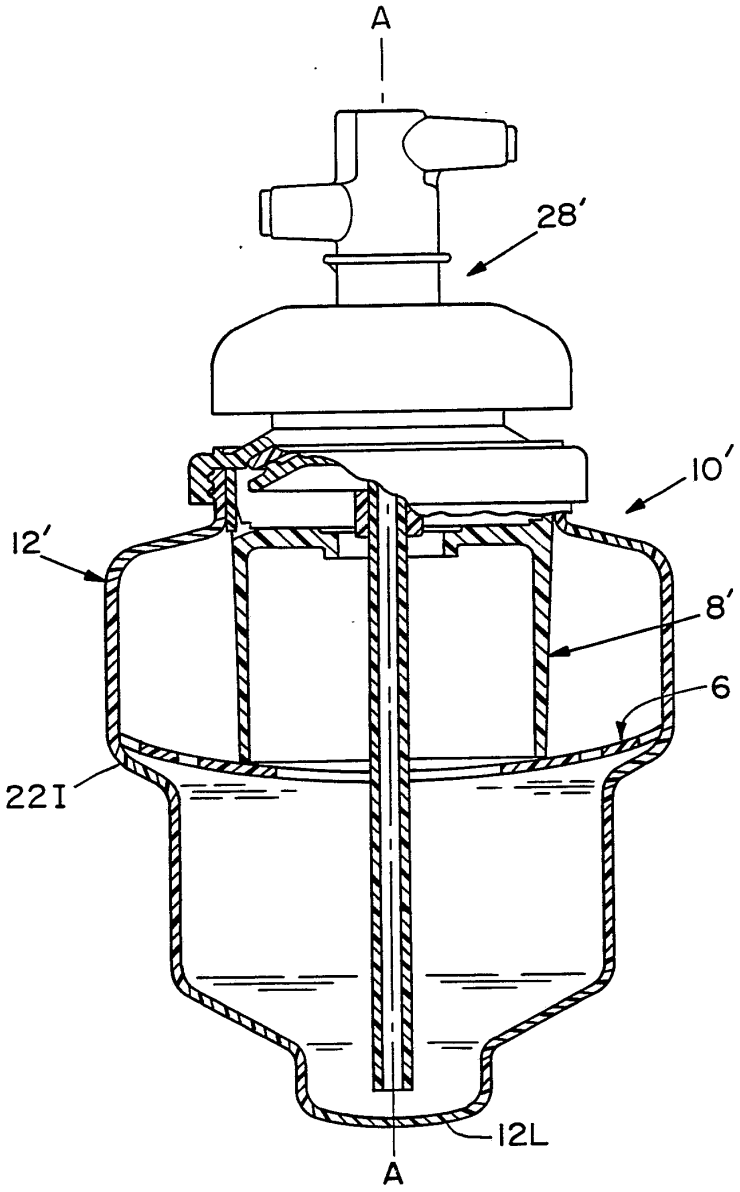


Fig. 3

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 89/05730

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: B 04 B 7/08

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	B 04 B

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0257755 (HAEMONETICS CORP.) 2 March 1988, see abstract	1,2,4,5, 11,12,14

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[10] Special categories of cited documents:

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27th March 1990	23 APR 1990
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme N. KUIPER

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8905730 SA 33409

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/04/90
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0257755	02-03-88	JP-A- 63065873	24-03-88

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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Espacenet

Bibliographic data: WO9406535 (A1) — 1994-03-31

APPARATUS AND METHOD FOR FRACTIONATING A LIQUID MIXTURE

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Classification: **- international:** ***A61M1/36; B01D63/16; B04B5/04;*** *A61M1/26;* (IPC1-7): B01D33/00; B01D61/00
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Application number: WO1993US08523 19930909 Global Dossier

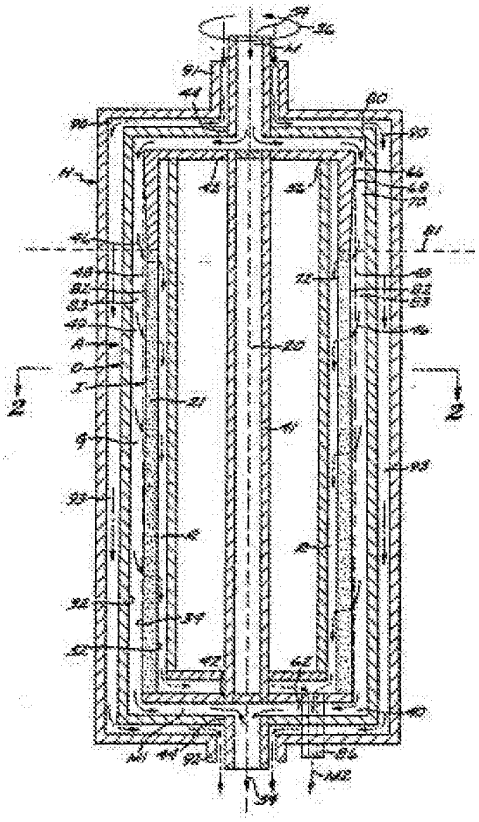
Priority number (s): US19920943731 19920911

Also published as: AU5126693 (A)

Abstract of WO9406535 (A1)

Apparatus and method for fractionating a liquid mixture into a plurality of liquid fractions whose components have different velocities. A rotating cylindrical assembly (A) has inner and outer shells (I, O) defining therebetween a tubular gap (G). One shell includes a porous structure (21) for permeation therethrough of one or more of the liquid fractions and to resist radial inward flow of the remainder. The cylindrical assembly (A) is rotated at a speed effective to impart sufficient centrifugal force to the liquid fractions to maintain one such fraction within the gap (G) while compelling flow of the other liquid fraction radially inwardly through the porous structure. The invention includes a porous structure (21) in both the inner and outer shells (I, O) to allow for levitation of one fraction of the mixture between such structures while a wash of solution bearing beneficial components is flowed radially inwardly therethrough.

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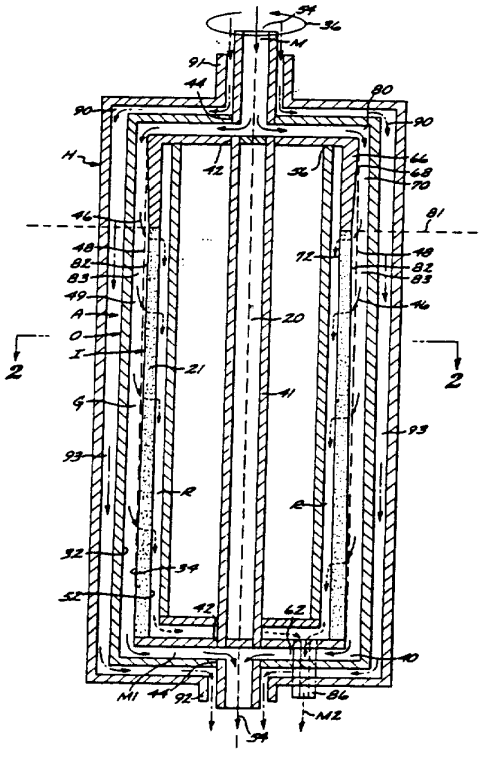
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(54) Title: APPARATUS AND METHOD FOR FRACTIONATING A LIQUID MIXTURE

(57) Abstract

Apparatus and method for fractionating a liquid mixture into a plurality of liquid fractions whose components have different velocities. A rotating cylindrical assembly (A) has inner and outer shells (I, O) defining therebetween a tubular gap (G). One shell includes a porous structure (21) for permeation therethrough of one or more of the liquid fractions and to resist radial inward flow of the remainder. The cylindrical assembly (A) is rotated at a speed effective to impart sufficient centrifugal force to the liquid fractions to maintain one such fraction within the gap (G) while compelling flow of the other liquid fraction radially inwardly through the porous structure. The invention includes a porous structure (21) in both the inner and outer shells (I, O) to allow for levitation of one fraction of the mixture between such structures while a wash of solution bearing beneficial components is flowed radially inwardly therethrough.



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APPARATUS AND METHOD FOR FRACTIONATING A LIQUID MIXTURE

FIELD OF THE INVENTION

The present invention relates to centrifugation apparatus and methods for separating liquid mixture components, as for example, blood, having different sedimentation rates.

BACKGROUND OF THE INVENTION

Prior centrifugal separation systems, either continuous or batch, generally form layers of substantial thickness. The spin axis defines the rotation that produces the centrifugal force, which force causes the eventual separation of components according to differing densities. Greater densities occupy comparatively greater depths when sufficient time is allowed to permit the effective completion of the sedimentation process. The depth of a layer refers to its distance from the spin axis. As some components have a distribution of densities which overlap the density distribution of other components, separation of such components by this means is necessarily incomplete. Even with no overlap of component density distributions, separation may not be complete or as perfect as desired due to instabilities in the suspending media under rotation making it particularly difficult to extract material from thin intermediate layers. Such instabilities tend to increase as total liquid thickness increases, especially when the material is caused to flow for the purpose of decanting various components.

Parameters, such as the time required to produce useful separation by density layering, rotation rates, layer thickness, decanting geometry, volume processing capacity, and component purity have, heretofore,

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required undesirable trade-offs in which one was compelled to compromise purity as against separation time or volume processing capacity. In most cases, limitations are imposed by the decanting geometry, method and rate which may introduce disturbances in the formed layers especially when the latter are very thin as in the case of "white" cells of blood, i.e., the "buffy coat".

Regardless of the many and diverse techniques utilized by prior art centrifugal separators for dealing with the various problems just described, they all require the separated material to form layers which closely approximate the end point of the sedimentation process. The loci of separation as between the several layers can be used to define a surface normal vector that would be substantially perpendicular to the spin axis at all points of the layer. Generally, the decantation of any particular layer requires at least some component of flow transverse to the layer's "surface normal" vector. See, for example, U.S. Patent No. 4,086,924. It is easily seen that one layer is required, at least in part, to "flow" in a shearing fashion over other layers in order to be decanted. This necessarily introduces stress on the interface between layers, which can contribute to contamination between layers. Viscous shear flow between fluid layers is anathema to centrifugal separation by density selective layering due to the instabilities it introduces under a rotational force field. Nevertheless, at least one component of shear flow along separation interfaces has always been involved at some stage of separation in prior centrifugal separators.

Other prior art techniques deliberately utilize shearing of suspensions flowing over membranes to separate components by what is understood to be cross-

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flow filtration (see A.L. Zydney and C.K. Colton, Continuous Flow Membrane Plasmapheresis: Theoretical Models for Flux and Hemolysis Prediction,. Trans ASAIO, Vol 28 (1982), p. 408.). However, membranes become clogged over time.

Efforts to prevent clogging of the membrane have included increasing the membrane area (see B.A. Solomon, et al, U.S. Patent No. 4,212,742), the shear rate of the flowing blood so as to delay the clogging effect (see R.J. Fischel, et al, U.S. Patent No. 4,755,300), or the pressure differential across the membrane (see F. Castino, et al, The Filtration of Plasma from whole Blood: A Novel Approach to Clinical Detoxification, In: Chang, T.M., et al., Artificial Kidney, Artificial Liver, and Artificial Cells, New York: Plenum Press, 1978, pp. 259-266).

Another technique that has long been used for cell separation is usually referred to as centrifugal elutriation or CE (see M.L. Meistrich. Experimental Factors Involved in Separation by Centrifugal Elutriation. Cell Separation Methods and Selected Applications, Ed: Pretlow, T.G., Academic Press, New York, V.2, PP: 33-61 (1983)). The basic principle involved in various embodiments of this technique is separation by differences in particle settling rates. In some instances, a counter-flowing fluid is introduced against the centrifugal force field (see R.L. Berkow et al Purification and Functional Evaluation of Human Polymorphonuclear Leukocytes. Cell Separation: Methods and Selected Applications, Ed: Pretlow, T.G., Academic Press, New York, V.4, PP: 147-170 (1987)), and is referred to as counterflow CE or CCE. These methods are intended as experimental sample batch processes. They are not suitable for rapid processing of large volumes on a continuous basis.

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The blood cell washing procedure of the present invention uses much less costly sterile washing solution than required by prior apparatus employed for this purpose. The speed and thoroughness of blood component separation without the unacceptable blood priming volumes or harsh treatment of the fragile blood elements, not otherwise achieved heretofore, is now possible with particular embodiments of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic central vertical section of a apparatus embodying the present invention showing the basic method of operation thereof;

FIG. 1A is broken, fragmentary, schematic and enlarged view of the right-hand portion of FIG. 1 demonstrating the behavior of fluid components relative to the porous element;FIG. 2 is a horizontal sectional view taken along line 2-2 of FIG 1;

FIG. 3 is a broken foreshortened central, vertical sectional view showing the major components of the form of apparatus of FIG. 1 embodying the present invention;

FIGS. 4 and 5, are horizontal sectional views taken along lines 4-4, and 5-5, of FIG.3;

FIG. 6 is a foreshortened central vertical sectional view showing major components of a second form of apparatus embodying the present invention;

FIG 6A is a fragmentary central vertical sectional view of the apparatus of FIG. 6 showing the parts thereof arranged for a washing function;

FIG. 7 is a horizontal sectional view taken along line 7-7 of FIG. 6.

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FIG. 8 is a central vertical sectional view showing major components of a third form of apparatus embodying the present invention.

FIG. 9 is a horizontal sectional view taken along line 9-9 of FIG. 8.

FIG. 10 is a graph demonstrating one principle of the invention relating to the separation of the components into separate fractions;

FIGS. 11 and 12 are schematic views demonstrating the relationship between rotational speed of the centrifugation unit and movement of the liquid components during operation of the apparatus embodying the present invention;

FIGS. 13, 14 and 15 are plots of diameter, density and settling rate, respectively, of various blood components in terms of population distribution, with FIG. 15 referring to Stokes settling velocity per unit of centrifugal force;

FIG. 16 is a schematic illustration showing how two devices embodying the present invention can be operated as two simultaneous stages for collection of platelet concentrate;

FIGS. 17-20 are schematic illustrations showing various functions which may be obtained employing the method and apparatus of the present invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

There are several important principles applicable to the design and operation of the method and apparatus of the present invention. Critical to the preservation of stability of centrifugal settling is the concept of spinning a "thin", as opposed to a "thick", film. The parameters which distinguish the two will be computed for blood and presented hereinafter. Initially, it is important to understand

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that continuous operation of the method and apparatus requires that blood, or other liquid mixture, enter the spinning "film" at one end, preferably the top, and move axially, downwardly in laminar stream flow, i.e., viscous boundary layer flow, approximately parallel to the spin axis toward an exit from the "film". This flow would not be stable, in the sense that various types of secondary flows would be triggered, thus upsetting the preferred radial convective flow and particle settling geometry, if the film were not sufficiently thin. Thicknesses available to blood under this restriction lead to practical and useful designs.

Referring now to FIGS. 1 and 2, a preferred method and apparatus for separating a liquid mixture, e.g., blood plasma, and a blood component or components in that liquid with the liquid and blood component or components forming a flowable mixture is schematically illustrated. The apparatus includes a cylindrical assembly A adapted for rotation about a central vertical axis 20 and having inner and outer generally cylindrical shells I and O, respectively, defining therebetween an axially extending tubular gap G. The inner shell includes a porous cylindrical structure 21 for at least a part of its axial extension for a purpose to be described hereinafter. The cylindrical assembly A is shown disposed within a fixed housing H, for rotation relative to the housing about axis 20. The flowable liquid mixture which is to be fractionated into first and second liquid fractions, containing components having settling velocities which are higher and lower respectively than a selected value, enters the upper end of the gap G between the inner and outer shells. Fractionation is effected within this gap between spaced apart generally axially concentric and rotationally

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symmetric surfaces 32 and 34 of the inner and outer shells, such surfaces forming boundaries as defined by walls of the inner and outer shells. The boundaries 32 and 34 are shown as concentric tubular boundaries extending about the axis of rotation 20 of the cylindrical assembly A, and may either be cylindrical or variously, somewhat differently tapered, i.e., inclined to the rotational axis of the assembly at particular axial locations, as described hereinafter. The direction of rotation of the cylindrical assembly is indicated by arrow 36, and the liquid mixture, or fractions, in various states of localized concentration of particular components flow generally downwardly, i.e., axially from the top of gap G to the bottom of gap G between the vertically orientated boundary surfaces 32 and 34.

A vertical support tube 41 rigidly interconnects and carries the inner and outer shells I and O at 42 and 44. Power operated means (not shown in FIGS. 1 and 2) are interposed between housing H and the cylindrical assembly A to spin the inner and outer shells and their confronting surfaces 32 and 34 about the common axis of rotation 20 at the same angular velocity. The liquid mixture to be fractionated M may be fed into the axial portion of gap G above an imaginary reference horizontal plane 81 and also pressurized by means not shown in FIGS. 1 and 2, as via a feed stream indicated by flow path 46. Liquid mixture components in the gap more dense than the liquid mixture continuous phase migrate radially outwardly during rotation of the cylindrical assembly due to centrifugal force which is exerted on all elements of the liquid mixture whereby concentration of the said more dense components in the liquid flowing axially (shown) downwardly in FIG. 1 in the gap G becomes greater and less near surfaces 32 and

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34, respectively. If the process of liquid component migration were allowed to proceed to completion in the gap, a boundary marking the separation of the liquid continuous phase from the settled discontinuous liquid components could, in some cases, become visibly well defined and is depicted by an imaginary reference boundary 48 which need not actually form as shown in the drawings. Boundary 48 is an imaginary cylindrical surface essentially parallel to the vertical axis of rotation 20 having a radius which can be controlled by mass balance of the liquid mixture and fraction flows into and out of the apparatus as described more fully hereinafter.

Controlled radially inward flow from gap zone 49, i.e., the axial portion of gap G below horizontal plane 81 of the second liquid fraction consisting of at least the continuous liquid phase of mixture M or a continuous phase including one or more discontinuous components in that zone is enabled in a pressure-drop direction operating to compel flow out of the gap zone 49 and through the porous surface 34 and the porous element 21 of the inner shell I into an inner region R defined between the inner surface of inner shell I and a cylindrical barrel element 50 coaxial with tube 41. Such enablement is effected as a function of the static pressure difference between gap G and interior region R, the effect of angular velocity of rotation ω of the zones defining boundaries, subjecting the liquid to centrifugation pressure opposing inward radial flow, and the porosity of porous structure 21 which resists flow. The thickness of the gap G will vary depending upon the nature of the liquid mixture being fractionated. In the case of blood, the preferred gap thickness is between about 5 to 150 mm.

As noted, the fluid mixture progresses axially and downwardly as it encounters the porous structure 21 of

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the inner shell, the primary purpose of which is to act as a flow distributor. In order to serve this function, the porous structure must have certain properties. First, of course, the pores must be large enough to freely pass without sensible restriction, the discontinuous or formed constituents to be decanted. The pores may offer no restriction to constituents or particles that are intended to remain behind in the gap with the original medium because "filtration", understood as a sieving effect, plays no part in the operation of the method and apparatus of the present invention.

On the other hand, the porous structure must offer flow resistance to that portion of the suspending medium carrying the decanted constituent in the sense of creating a "pressure gradient". The preferred operative requirement is that the Trans Porous Pressure (TPP) drop substantially exceed the pressure loss required to move fluid from its entrance to the spinning film (mixture M) to its exit from the film (first liquid fraction M_1). Consequently, the porous structure means can act as a largely "uniform" flow distributor in accordance with the invention. In practice, this is not a serious restriction in, for example, generally useful blood flow rates, given that the thin film flow cross-sections possible in accordance with the invention, do not lead to significant axial blood flow pressure losses. Furthermore, as discussed in more detail within, there are very effective ways to increase the flow resistance of the porous means so that TPP is always sufficiently greater than the axial pressure gradient to cause substantial uniformity of decanting, i.e., uniform convective radial velocity over the entire porous surface.

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The uniform decanting velocity referred to here is defined by dividing the volumetric decanting rate, of second liquid fraction, M_2 (ml/sec) by the porous area (cm^2). The uniform decanting rate is adjusted by controlling input and output volumetric pumping rates of incompressible fluids.

Centrifugation of the axially (here downwardly) flowing liquid mixtures in gap G tends to move discontinuous components throughout the mixture and separating fractions, which are more dense than the suspending continuous medium, in an outward radial direction generally opposite the inward radial flux through porous surface 34 and away from axis 20. Components which are less dense than the suspending continuous medium (i.e., buoyant particles) move in an inward radial direction under the influence of centrifugal force and are carried with the inward radial flux in all cases. Absent inward radial flux, the velocity of movement of discontinuous components in the radial direction due to centrifugation characterizes their effective settling rate.

Velocities vary among the individual specie of components and tend to retard as concentration of all components taken together increases. In dilute concentration the settling velocity, V_s, of a particular species of component, tends to be narrowly distributed and predicted by the Stokes equation. It is effectively proportional to centrifugal force, density difference, $\Delta\rho$ over that of the suspending medium and the square of particle diameter, D, (or dimension characterizing particle size) and inversely proportional to suspending medium viscosity, μ. Centrifugal force is proportional to the distance from the rotation axis 20 and the second power of the angular velocity, ω.

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Consequently, centrifugation may be controlled, as for example by control of angular velocity, given radial dimensions of boundaries 32 and 34, to allow permeation of any component or components having radially outward characteristic settling velocities below a selected value, in the inward radial direction, along with the liquid, i.e., controlled permeation through the porous boundary 34 and porous cylindrical structure 21, the porosity of the latter in general allowing such components in the mix to pass through unobstructed. In one example, the porosity may be such as to allow all components (of different sizes and settling rates) to pass, i.e., including those of a relatively greater settling rate, but which are not allowed to permeate, due to the angular rate ω of centrifugation tending to retain them in the gap zone 49.

Flow path 54 in FIG. 1 indicates removal from gap G of modified mixture M_1, in the form of, or consisting of, the initial liquid mixture M less any liquid which has flowed radially inwardly through porous structure 21, and less any particle component or components carried with the liquid permeating porous structure 21. In particular, the difference between the rate or amount of feed of mixture M into the gap along path 54 at the top and the rate or amount of removal of M_1 from the gap along path 54 at the bottom is necessarily the net rate or amount of permeation, i.e., decantation for an incompressible liquid such as blood along flow path 46. In practice, static pressure is actually controlled by controlling the feed flow and removal flow rates using positive displacement pumps (not shown in FIGS. 1 and 2). FIGS. 11 and 12 illustrate vectorally the forces on the particles due to centrifugation and decantation.

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With continued reference to FIG. 1, it is important to note, that the upper portion of the inner shell is formed with a impervious inverted cup-shaped entrance member 66, the sides 68 of which are tapered downwardly and inwardly away from boundary 48 towards the center of the cylindrical assembly A. The lower end of entrance member 66 abuts the top of porous element 21 at horizontal plane 81.

Outer surface, 34 of porous element 21 forming the interior surface of the gap G is either parallel to or preferably tapered outward from axis 20 relative to boundary 48. The outer cylinder O also preferably tapers outward from axis 20 at an angle usually similar to that of surface 34, for reasons more fully explained below. Surface 68 is seen to resemble an inverted frusto-conical surface while surfaces 32 and 34 are seen to resemble upright frusto-conical surfaces, respectively. The angle of taper and special shaping, if any, of surfaces 68, 32 and 34 may best be understood by treating boundary 48 as a downward axially moving surface which matches the velocities at boundary 48 associated with the axial flow of liquid in gap regions 82 and 83, respectively. Gap regions 82 and 83 are radially inward and outward of cylindrical boundary 48, respectively. The purpose is to minimize shear, i.e., axial velocity gradient, as between regions 82 and 83 at boundary 48. By limiting shear between fluids of substantially different viscosities in a rotational field subject to strong Coriolis forces, laminar stream viscous boundary flow can be preserved as more fully explained within.

As less highly concentrated fluid (i.e., much of the suspending medium of the original mixture M) is drawn away from that part of region 82 below horizontal plane 81, the axial flow cross-section of

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that region must be reduced in order to maintain matching axial velocity between fluids in regions 82 and 83, respectively at boundary 48. As more concentrated fluid forms in regions 83 below horizontal plane 81, the opposite must obtain. Consequently, solid surface 32, and porous surface 34 have the appearance of frusto-conical sections tapering (downward) away and toward cylindrical boundary 48, respectively. The outward taper of surface 32 further assists the downward (outward) axial flow of concentrated material by providing a resolved component of centrifugal force tangent to surface 32 in an axial direction toward the exit region 40 for the first fraction. The portion of total centrifugal force assignable to the outward axial component is the sine of the angle surface 32 makes with rotational axis 20. Even at one part in one hundred the axial component of force which must be added to one gravity in vertically oriented apparatus can be considerable and always advantageous to the movement of thickened viscous material.

The radial position of boundary 48, to the extent it actually forms, is best understood in relation to the lower extremity of surface 34. If most of the continuous phase contained in the original mixture M is decanted as suspending medium for the second fraction M2 or is itself M2 then boundary 48 will closely approach the lowest extremity of interior surface 34 because very little axial flow cross-section is required for the remainder of M2 to enter zone 62 where it re-mixes with the concentrated material leaving the lower end of gap G to become the final formulation of M1. In the limit where all available M2 is decanted and concentrated material is well formed, that is, boundary 48 is well defined, the latter will just intersect the extreme lower corner of

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surface 34. Even more aggressive decantation of M2 will cause some of the concentrated material to enter M2 and boundary 48 intersects surface 34 at some axial position above the latter's extreme lower corner. Thus, the radial position of a well formed boundary 48 is very sensitive to the fraction of $_{M2}$ decanted through porous surface 34. Boundary 48 is merely a convenient reference for purposes of illustrating the process, however, the permeation of what is, at first, a very minuscule amount of concentrated material into M2 can be used as an observable indicator of conditions within the apparatus in most cases. Nephelometry or hemoglobin detection means placed at the output 86 of M2 will detect the very first permeation of cells or RBC, respectively, in the case of blood, whereby decantation flows may be adjusted at will. Similar techniques are available for most mixtures having concentrated separable components.

The above described liquid fractionating phenomena can be more fully understood by reference to FIG. 1A, when taken in conjunction with FIG. 1.

Referring now to FIG. 1A, there is shown a broken, fragmentary schematic enlarged view of the right-hand portion of the cylindrical assembly A as it is rotated, depicting the flow pattern of the first and second liquid components M1 and M2, respectively, relative to the porous cylindrical structure 21. For purposes of illustration, the space within gap G has been divided into zones RA, RB, RC, and RD. Zone RA is the space radially inward of boundary 48 radially outwardly of the cup-shaped entrance member 66. Zone RB is the space radially outwardly of boundary 48 adjacent zone RA toward which all of the mixture components (more dense than the suspending liquid medium and thus subject to centrifugal force) move. Zone RC is disposed below the imaginary horizontal

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plane 81 adjacent the outer surface 34 of porous element 21 within boundary 48. Zone RD is disposed adjacent zone RC, but radially outwardly thereof and the porous element surface 34. Within zones RA and RB, all of the said more dense components that are subject to centrifugal force move radially outwardly, and there is no opportunity for radially inward flow. The purpose of including these zones is to provide an opportunity for the concentration of otherwise concentrated particles nearest the spinning outer surface of the cup-shaped element 66 to be lowered so as to create dilution of such particles radially inwardly of boundary 48. Within zone RB, increasing concentration of particles is taking place which tends to make boundary 48 more visible. Such boundary could, in fact, become readily visible when the liquid mixture is blood, since the red blood cells, as they start collecting within zone RB become quite dense. As plasma thins out, it begins to appear yellow and clear, even though plasma may be full of platelet particles. Zone RC is the zone which is most proximate to the outer surface 34 of the porous element wherein the separation of component M2 is occurring.

Within zone RC, a predictable or characteristic radially outward settling of particles takes place, since zone RC now contains a diluted mixture of particles. Because a known radially inward flow of liquid, possibly including certain particles and a known outward radial settling velocity of all particles is established in dilute concentration, it is possible to decide whether or not particular particles will be carried with the liquid leaving zone RC through the porous element 21. In zone RD, the particles are becoming more heavily concentrated due to centrifugal force, and accordingly, will not flow

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radially inwardly through the porous cylindrical element 21. The fact that the liquid within zone RA is becoming more dilute means that it is becoming less viscous. The amount of dilute liquid is increasing in volume as the mixture flows axially downward so that the liquid in zone RA is increasing in volume.

Within zone RB, the liquid is becoming more concentrated, and accordingly, becomes more viscous. In zone RC, the liquid is less viscous, as in zone RA, but is also being removed radially inwardly through the porous element, and is accordingly, losing volume as the volume increases in zone RA. In zone RD, the liquid is becoming thicker and is substantially increased in viscosity so as to require more space within which to flow. The aforedescribed tapering of the outer and inner facing surfaces of the outer and inner cylinders is designed to take into account the fundamental physical fact that the division between the liquid portion and the concentrated portion follows a surface that is essentially parallel to the axis of rotation 20, and it should be understood that such cylinder is indicated by boundary 48. Boundary 48 is located radially within the gap depending upon the volumes that are flowing in and out of the cylindrical assembly. Because of the axial downwardly flow of the liquid, in combination with the radially inward flow of liquid component M2, the axial flow and the radial flow are vectorially independent as noted hereinabove. The aforedescribed tapered surfaces insures approximately the same axial velocity for the concentrated and non-concentrated liquid components at boundary 48. If such approximately matched axial velocity is not obtained, there would be a tendency for one or the other liquid component to have a shearing effect that would tend to create vortices in

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the high energy rotational field generated by rotation of the cylindrical assembly A.

One of the most important criteria for a device dedicated to the collection of blood components is the ability to isolate all surfaces and environments that could be exposed or accessible to the blood or its separated products. These must be sterilizable by means approved in the industry (e.g., Gamma, ETO, etc.) and must be capable of retaining sterility under ordinary conditions of use. This is extremely difficult and expensive to achieve when attempting to seal a moving part from the external environment. The solution of the problem in connection with the present invention as disclosed herein is not, in principal, restricted to the present invention, rather it is believed it constitutes a significant contribution to the practical embodiment of devices incorporating, moving, sterile parts.

The basic concept provided by the present invention is to immerse the entire rotating cylindrical assembly A in a bath of sterile solution, compatible with blood, e.g., saline, or anticoagulant, indicated by flow arrows 90, which is contained within the stationary housing H. Access to the interior of the housing H is made through upper and lower conduits 91 and 92, to be described fully hereinafter, which lead into and out of the housing from or to sterile containers respectively. The entire sterile path, including the rotating cylindrical assembly, and the several sterile containers which may be permanently attached to the assembly housing prior to sterilization comprise a closed sterile system. Conventional peristaltic pumps, not shown in FIG. 1, engaging conduits in communication with the interior of the assembly can be used to move fluids to and from the containers and the assembly without invading the

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sterile environment which includes, in part, the extracorporeal blood path and the vessels in which the separated concentrated blood components are stored. See FIG. 18. As indicated by flow path 90 which begins at the upper portion of the rotating assembly and its stationary housing H, a sterile or wash solution is urged downwardly between the space 93 separating the exterior surface of the outer cylinder O and the inner surface of the stationary housing H. Such sterile or wash solution is discharged at the bottom of the rotating assembly and housing combination. Fluid seals (not shown in FIGS. 1 and 2) are interposed between the upper and lower elements of the rotating assembly and its stationary housing H. A portion of the sterile solution flows through these seals.

It is important that the sterile bath is maintained at a higher static pressure than the fluid flowing through paths within the rotating assembly. With this arrangement, the entire rotating assembly is surrounded by the sterile bath and the seals which need not function as bearings, are provided to operate between that bath and the fluid flow paths of the rotating assembly. The criteria governing the design of the seals (preferably rotating seals) are less critical than the criteria normally required for sterility barriers. For example, although these rotating seals (as between the sterile bath and the blood) can be impervious to fluids without detracting from the operation of the apparatus and method of the present invention, because the sterile bath is maintained at a higher static pressure than the blood, or, in the alternative view, caused to flow at a pre-determined rate across the seal by means of positive displacement into the blood, as long as the leakage rate is small, the dissolution effect is harmless, and

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the direction of flow operates to protect the fragile components of the mixture by preventing them from entering the seals. As described hereinafter, however, as in cell washing, the sterile bath may also be the wash solution and a high leakage rate is intended.

The advantages of such a rotating seal concept are significant in connection with high spin rates. First, high sealing and bearing pressure is not required, which mitigates the heating effect. Second, the sterile fluid crossing the sealing surfaces at their interface forms a fluid film that reduces friction, further mitigating the heating effect while absorbing and carrying away what heat is generated. The same concept may be employed in separate load bearing bearings between the housing H and cylindrical assembly A, except that flow through the bearings is much higher and does not represent a "leak" from one fluid into another. The cooling effect of the sterile bath can be enhanced by maintaining a circulation of this bath around the rotating mechanism and through the rotating bearings and seals exposed to the circulating bath. The same sterile bath can be continuously recirculated by providing fluid entrance and exit routes on the stationary containment vessel, as shown in FIG. 1 for that purpose.

It should be noted that not maintaining a positive flow across the rotating seal from sterile bath into the blood path does not result in a critical difficulty. There is no loss of sterility and, contamination of the sterile bath with blood or blood components is not crucial since this material is disposed of, following the procedure. Nevertheless, it is not desirable because blood components, particularly RBC, will inevitably be damaged in transit across the nominal seal. The damaged

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components carried into the sterile bath are of no particular importance, but the material they generate (e.g., free hemoglobin) can and usually does leak back into the primary blood path. This is to be avoided in the manner previously described in keeping with the highest quality blood separation. Heretofore, systems using rotating seals against blood without a protective leakage component, as described herein, have invariably caused measurable contamination with hemoglobin released by RBC damaged within the seals.

Referring now to FIGS. 3, 4, and 5, there is shown the major components of a first form of apparatus embodying the present invention constructed in accordance with the principles of the invention described hereinabove and shown in FIGS. 1, 1A, and 2. Like parts bear the same reference numerals. The power-operated means for rotating the cylindrical assembly A within housing H may take the form of a conventional electro-magnetic armature drive utilizing a stator 100 affixed to the upper part of housing H which cooperates with an armature assembly 102 which is keyed to an upper coaxial drive tube 104 that extends downwardly with its lower end affixed to the upper portion of the support tube 41. An upper bearing member 115 is interposed between the upper portion of drive tube 104 and a drive support member 105 that extends upwardly from a neck 107 formed on housing H. The upper end of drive support member 106 is provided with an inlet fitting 110 which is connected with the upper end of drive tube 104 to conduct the liquid M downwardly therethrough. An upper combination bearing and O-ring assembly 112 is interposed between the upper portion of drive tube 104 and the drive support member 106. A sterile solution conduit 91 is affixed to the neck 107 of the stationary housing H to conduct sterile solution

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upwardly through a first sleeve 113 formed on the neck along the inner surface thereof, radially inwardly and downwardly through vertical passages 114 of upper bearing 115, then radially outwardly below bearing 115 and downwardly along the inner surface of a second sleeve 116 below drive support member 105 and exterior of armature assembly 102. From the space below the armature assembly 102, the sterile solution flows downwardly through a main bearing assembly 118 through vertical passages 119 formed through the intermediate bearing assembly. Main bearing 118 is carried by neck 107.

Thereafter, the sterile solution flows downwardly into space 93 between the interior of the housing H and the exterior of the outer shell O. Next, the sterile solution flows downwardly through the lower confines of the space 93 underneath the outer shell O to flow downwardly out of a discharge conduit 92. It should be noted that additional sterile solution is introduced into the base portion 120 of the housing H through a conduit 130, such sterile solution being indicated by flow arrows 132. The sterile solution entering through conduit 130 flows upwardly through vertical passages 133 formed in a lower bearing assembly 142 to mix with the sterile solution entering through the upper conduit 91, and then flows outwardly through discharge conduit 92. This second flow of sterile solution also moves downwardly through a lower top combination bearing and O-ring seal assembly 140 and upwardly through a lower combination bearing and O-ring seal assembly 142. The sterile solution may serve as a coolant for the bearings and seal assemblies.

Referring to the upper portion of FIG. 3, the liquid component M designated by flow arrows 54 is moved downwardly through drive tube 104 and radially

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oriented in passages 141 formed in the common top wall of the inner and outer cylinder, then into the upper portion of gap G to flow downwardly therethrough to be separated as described herebefore into the first liquid component M1. As indicated by flow arrows 144 liquid M1 flows radially inwardly through passages 145 formed in the common bottom wall of the inner and outer shells, and then downwardly through lower tube 150 to be finally discharged through discharge conduit 86 which is coaxial with the tubes and the cylindrical assembly. It will be seen that the lower tube 150 extends through bearing O-ring seal assemblies 140 and 142 and a bottom combination bearing O-ring assembly 154. The sterile solution entering through lower conduit 130 cools the lower bearing and combination bearing and O-ring seal assemblies.

With continued reference to FIG. 3, liquid component M2 which flows through the porous cylinder 21, as indicated by flow arrows 46, moves radially inwardly from the bottom of inner region R through passages 160 formed in the lower portion of the inner and outer cylinders I and O to be collected in chamber 164 formed between the lower portion of the vertical support tube 41 and the lower drive tube 150 for ultimate discharge through fitting 87.

Shock absorbing pads 156 may be interposed between the horizontally facing surfaces of housing H and outer cylinder O.

It should be understood that the sterile solution entering through the respective upper and lower conduits 91 and 130 follows a sterile path which includes the exterior of the rotating cylindrical assembly A and is maintained at a higher static pressure than the fluids M, M1, and M2 so as to protect the fragile components of these fluids by preventing them from entering the seals as described

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in detail hereinbefore. It should also be understood that it is possible to force a saline solution into the gap G, as hereinbefore described, should it be necessary to re-liquify or otherwise render fluid any packed cells of the liquid component M1 within the lower portion of gap G.

The principles of operation of the separator apparatus shown in FIG. 3 may be seen by reference to the schematic illustration of FIG. 18. Referring thereto, the housing A4 of the separator apparatus receives blood from a donor at its upper end. Upon rotation of the cylindrical assembly, the concentrated blood cells of the donor are returned to the donor, as indicated by the directional arrows. Plasma is transferred to a suitable receptacle from the lower right side of the housing as shown by the directional arrows. The volumetric pumping rate of the blood-handling upper pump P11 is greater than that of the lower pump P12 so as to provide the pressure differential required to effect permeation of the plasma through the walls of the porous cylinder element 21. Saline sterile solution forced by pump P13, enters the upper and lower left-hand portions of the housing A4 and such saline solution is metered out of the lower portion of the housing by pump P14 as shown by the directional arrows. Saline pumps P13 and P14 maintain the saline solution at a higher pressure than the pressure maintained in the separator apparatus and the conduits leading to and from such separator for the reasons set forth hereinbefore.

Referring now to FIGS. 6, 6A, and 7, there is shown the major components of a second form of apparatus embodying the present invention. This form of the invention is similar to the form of the invention shown in FIGS. 3, 4, and 5, with the exception that the inner shell I' is formed at its

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lower portion with a second porous structure in the form of a porous ring 170 disposed below the main porous cylinder 21'. It should be understood that the upper part of the apparatus of this second form of the invention is also provided with a electro-magnetic armature drive (not shown) disposed within a drive support member 106' of the type utilized in the apparatus of FIG. 3 for rotating the cylindrical assembly A as a liquid M to be fractionated is caused to flow downwardly within drive tube 104'. During such rotation, component migration, particularly described in conjunction with the description of FIG. 1 and 1A hereinbefore takes place whereby an imaginary boundary 48' is formed in general alignment with the upper and lower peripheries of the inner shell I' as the liquid fraction M2 flows radially inwardly through the main porous element 21'.

In this form of the apparatus, however, a third liquid fraction M3 is harvested from the lower portion of the fluid within the radially inner lower zone E portion of the boundary 48'. Such liquid component fraction M3 is forced through the lower porous ring 170 by the excess of fluid pressure within the gap G over that maintained in an inner region RR interior of porous ring 170. Such liquid, after passing through the lower porous ring 170 continues to move radially inwardly through the lower region RR which is defined by passages 174 formed in the lower walls of the inner and outer shells. This M3 liquid fraction is collected within a space 176 disposed outwardly of lower tube 150' to be ultimately discharged through an outlet conduit 178 formed in the lower right-hand portion of the stationary housing base 120'.

With continued reference to FIG. 6, 6A, and 7, the lower portion of the outer shell O', generally radially outwardly of the porous ring 170, is formed

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with a cylindrical opening 180 over which is disposed a vertically movable cylindrical valve ring 182. Such valve ring 182 is seated on a pair of O-ring seals 183 mounted in the outer portion of opening 180. The lower portion of the valve ring is formed with a plurality of circumferentially spaced holes 186. A porous diffusion ring 184 is disposed within the reduced diameter opening 185 inwardly of and aligned with opening 180. Valve ring is normally arranged in its lowered position of FIG. 6, however, such valve ring may be moved upwardly into its raised position of FIG. 6A by suitable electro-magnetic means (not shown) in a conventional manner. Steps 188 limit movement of the valve ring. In the raised positions of the valve ring 182, the holes 186 of the valve ring are disposed radially outwardly of the openings 180 and porous diffusion ring 184. With the valve ring is arranged in its normal lowermost position, saline solution entering through upper and lower conduits 91' and 130' flows outwardly through an outlet conduit 190 attached to the left-hand lower portion of housing H' from the space between the outer surface of the outer shell O' and the inner surface of stationary housing H'. The saline wash solution entering lower conduit 130', additionally, flows through the lower bearing and bearing O-ring seal members, just as in the apparatus of FIG. 3 and for the same purposes. When the valve ring 182 is moved to its raised position of FIG. 6A, however, saline wash solution is introduced radially inwardly through valve ring holes 186, as indicated by flow arrows 194, whereby such saline solution will flow radially inwardly from space 93' through the porous rings 184 and then ring 170 at a rate of flow effective to enable an inward radial velocity of controllable and uniform value within the gap G'. Diffusion ring 184 may be somewhat displaced axially

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upward (i.e., toward the entrance zone of the gap) relative to porous ring 170 in order to accommodate downward axial displacement of wash solution in the time required for the latter to cross the gap. After the saline wash solution enters and crosses porous outer ring 184 and gap G', it enters and crosses porous ring 170, and enters inner region R', as noted above. The inward radial convective velocity associated with wash solution flow should be higher than that of prior flow across surface 34' of porous element 21' in order to take full advantage of a sequential concentrating followed by a washing step intended to remove contaminants not otherwise permitted to follow with flow across surface 34'.

Forced inward convection of wash solution into and across the concentrated cell mass tends to displace the cellular material radially inward away from the interior surface of porous outer ring 184, i.e., floated or "levitated" off the surface. Each cell that remains with the first fraction finds a new point of equilibrium (at some radial position within the gap) where convective drag on the cell (a force which is controlled by wash solution flux) is in balance with centrifugal force on the cell. Any particle which cannot find new equilibrium, e.g., broken cell stroma, will be washed out. It should be understood that the portion of boundary 48' between the facing porous surfaces of rings 170 and 184 will become somewhat displaced radially inward from its position as shown in FIG. 6A and less clearly defined because the population of cells has a distribution of settling velocities. Some perturbation of reference boundary 48' must occur in zone E due to the change in equilibrium conditions previously established in zones RC' and RD'.

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Liquid component M2 which flows through the porous cylinder 21', as indicated by flow arrows 46', moves radially inwardly into inner region R' and then upwardly through such region and into passages 199 formed in the upper common walls 198 (Fig. 6) of the inner and outer shells and then upwardly through a space 201 between the outer surface of drive tube 104' and the inner surface of support tube 41' into a collection chamber 202 between combination bearing and O-ring seals 203 and 204 to be discharged through a conduit 205. It should be understood that during operation of this form of the apparatus, sterile solution is forced through conduit 91' into the housing neck 107' so as to cool the bearings and seals disposed in the drive support member 106' and the housing neck in the same manner described hereinbefore with respect to the apparatus of FIG. 3. It should also be understood that the sterile solution entering through conduits 91' and 130' follows a sterile path which includes the interior of the housing H' and the exterior of the rotating cylindrical assembly A, and is maintained at a higher static pressure than the fluids M, M1, M2, and M3 so as to protect the fragile components of these fluids by preventing them from entering the seals as described in detail hereinbefore. Moreover, the introduction of sterile solution through porous element 184 makes it possible to re-liquify or otherwise render axially flowable any packed cells of the liquid component M1 within the lower portion of gap G'.

Reference may now be made to FIGS. 13 - 15 for a description of the general mode of operation of the present invention as applied to previously described separator apparatus.

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It is important to note:

a) the separation of particles is occurring as a result of differences or changes in "settling rate", see FIG. 15, i.e., a dynamic condition; and not due to separation after the particles have arrived at their static bands, as shown in the classical separation bands of FIG. 14.

b) Settling rate in a given medium is a function of particle size, shape, concentration, and density. It is also a function of fluid viscosity and is generally proportional to the term $r\ \omega^2$, where r = distance of particles from spin axis; ω = spin angular velocity, which is selected to achieve dynamic settling rate separation of different particles. FIG. 15 is a plot of the population distribution for several formed elements of blood with respect to their settling rates divided by the multiplier $r\ \omega^2$. Dilute concentrations are assumed and the Stokes approximation is used for these plots. There is good agreement with observation for all blood particles except concentrated red blood corpuscles (RBC).

Note that in FIG. 15, the separation of platelets from other particles, as a function of settling rate, is much greater than in FIG. 14, which is a plot of the population distribution as in FIG. 15 but, in this case, with respect to particle density only, wherein the platelet band overlaps (i.e., is not spaced from) the lymphocyte particle band. The density bands of FIG. 14 illustrate the end point distribution of essentially fully settled particles.

c) In accordance with the present invention, decanting occurs while particulate is settling out, and not after settling is completed into bands as shown in FIG. 14.

d) Further, in accordance with the present invention, decanting can occur after some particles

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have settled out according to density to form distinct bands, however prior art centrifugal separators employ means to extract material from these formed "layers", which is radically different from and inferior to that which is used in the present invention partly due to the fact that in the present invention, decanting occurs in a direction parallel to the force field (i.e., in the direction of vector 300 in FIG. 11), and not at an angle to the force field, thereby eliminating otherwise obligatory and destabilizing shear to achieve decanting. The latter effect reduces the effectiveness of all known prior art devices; and

e) particles separate even while they are still physically mixed in suspension not otherwise possible when separating particles from "formed" layers.

As a consequence of these novel principles, it is possible to separate platelets from lymphocytes, RBC, and granulocytes in apparatus designed in accordance with the present invention by selecting the appropriate operating parameters as described above. Separation is in accordance with differences in settling rate, (FIG. 15) not density, (FIG. 14). Decanting flow velocity and spin rate determine which components follow the several possible liquid fractions. These are fully selectable for many diverse applications as hereinafter described.

Application of these inventive principles to important blood component separation problems may be illustrated by first referring to FIGS. 13, and 14 which show a summary of published data on the population distribution of effective diameters and densities, respectively, of four important classes of human blood components, namely, red blood corpuscles (RBC), platelets, lymphocytes, and granulocytes. Except in regions of high concentration of components,

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the settling rate of that component in human plasma may be computed or at least characterized from these data using the Stokes drag equation:

$$V_s = \frac{D^2 \Delta\rho}{18 \mu} r \omega^2$$

V_s - settling velocity (cm/sec);

D - equivalent particle diameter (cm);

$\Delta\rho$ - density difference, particle minus medium

μ - viscosity, medium

$\frac{r \omega^2}{g}$ - g's of centrifugal force if g = acceleration of gravity.

Equivalent particle diameter refers to that diameter that gives the experimentally observed or "correct" settling velocity according to the Stokes equation which is more useful to show how settling velocity varies with design and operating parameters r and ω, respectively. To this purpose calculations based on the Stokes equation are plotted in FIG. 15 as velocity per unit of centrifugal acceleration. Note that granulocytes, due to size as well as density, settle much faster than other particles, and the lot settles at least eight times faster than platelets.

Consequently, platelets which could not be separated from lymphocytes by density (see FIG. 14), which is a very significant problem in achieving the desired lymphocytes-free platelets required for therapy, can be separated by settling rate using the teachings of the present invention.

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In the operation of the apparatus of FIGS. 3, 4, and 5, as a separator for blood components, liquid mixture M is blood which enters the upper portion of the rotating cylindrical assembly A through drive tube 104 and enters gap G. This form of the apparatus is particularly adapted for use as a collector of cell free or platelet rich plasma.

In the usual blood-bank setting a typical donor can be "bled" at a rate of about 100 ml/min. At an average hematocrit (Hct) of 45% (i.e., percent of whole blood by volume comprising cellular material), 55 ml/min of the 100 ml/min is plasma, the suspending medium, which, incidentally, is over 90% water, the rest being dissolved complex organic molecules, lipids, and salts. Because the device illustrated in FIG. 3 is capable of decanting as much as 90% of the plasma, leaving the remainder to support fluidity of the concentrated portion, one can use, for purposes of this example, the removal, i.e., decanting, of 50 ml/min of plasma uniformly distributed over 50 cm^2 of porous flow distributing surface. Hence, the inward radial convective decanting velocity is 1.0 cm/min or 0.0167 cm/sec, that is, 50 ml/min divided by 50 cm^2.

For operating and design purposes, one might pick a settling rate for red blood corpuscles to be 0.02 cm/sec which exceeds the convective velocity by enough

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to prevent red blood corpuscles from approaching the porous surface. Referring to FIG. 15, one has

$$0.8 \times 10^{-7} \times r\,\omega^2 = 0.02 \text{ or } r\,\omega^2 = 2.5 \times 10^5.$$

A practical example for the diameter of a blood film could be 1.5 inch. With an $r\,\omega^2$ of 2.5×10^5 the r.p.m. would be 3486 giving 255 g's of centrifugal force. Inserting these values into the Stokes equation and solving for V_s, the corresponding settling rate of the fastest platelets is only

$$0.2 \times 10^{-7} \times 2.5 \times 10^5 = 0.005 \text{ cm/sec}$$

or far less than the convective velocity of 0.0167 by a factor of 0.30. Hence platelets are easily carried with the plasma to yield what is referred to as platelet rich plasma (PRP) but without, it should be noted, the presence of any leukocytes.

This calculation assumes a relatively low concentration of red blood corpuscles near the porous surface for the Stokes equation or, more to the point, a narrow well defined range of settling velocities to apply. The initial impregnable zone makes this possible as follows:

Suppose the blood film thickness is nominally 0.1 cm, which, as will be shown herein, is well within the allowable range. When the red blood corpuscles and lymphocytes travel about 0.05 cm, they are nearly fully settled out as together they comprise nearly half the volume of the initially whole blood. They

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travel nearly this entire distance, or about 0.04 cm in 2 seconds, in the absence of a radial convective velocity such as obtains over the initial impregnable zone. Since the feed rate of 100 ml/min is 1.667 ml/sec, a hold-up volume of 3-1/3 ml of blood film over this zone (which may, for example, be obtained by using a gap G thickness of 0.1 cm and a first encountered impregnable surface area of 33-1/3 cm^2) will cause the blood to have a residence time of 2 seconds over the impregnable area and 6 seconds over the 50 cm^2 of porous surface 21. The latter value is due to the fact that half of the 100 ml/min is withdrawn resulting in an effective axial flow of 50 ml/min through a hold-up volume of 5.0 ml over 50 cm^2 of porous surface. The total residence time is 8 seconds in the operative blood film.

As just seen, the red blood corpuscles are nearly settled out before they even get to the porous surface 21 and settle even further thereafter. It is therefore reasonable to conclude that throughout the proximity of the porous surface, the concentration of red blood corpuscles is low and the Stokes settling rate is obeyed.

On the other hand, in 2 seconds, the platelets move away from the surface by, at most, 0.005 cm or barely 1/10th of the distance they would otherwise travel to their settled position absent convective

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decanting. They retrace this entire displacement in less than 1/3rd second after encountering radial inward convective flow upon first reaching the porous surface 21 and continue to be drawn through the porous flow distributing surface for the remaining 5.67 seconds of residence time over that surface.

These simple calculations demonstrate a device that yields nearly all the available plasma completely rich in platelets and absent all other cellular material. The size of the device for the application example indicates that it could easily have been made smaller say 1.0 inch diameter, and ω increased to 4270 r.p.m. to achieve the same effect. On the other hand, there is another use for the device wherein the larger device can be used to advantage, that is, where one wants to either concentrate the collected platelet rich plasma in a second stage (see FIG. 12) or simply collect cell-free plasma.

In the latter case, assume again that the decantation rate is 50 ml/min over 50 cm^2 of porous surface or a convective velocity of 0.0167 cm/sec. For completely cell-free plasma the settling rate of platelets must exceed this value, say 0.02 cm/sec or greater. Then, because platelets are so sparsely concentrated to begin with, (i.e., their concentration has no affect on the validity of the Stokes calculation) one may use:

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$r\ \omega^2 \times 0.5 \times 10^{-8} \geq 0.02$ or, for a 2.0 inch diameter blood film, the r.p.m. must be 12,077. This rotation speed can be achieved with proper bearing design and balancing of the apparatus.

By way of example, FIG. 16 illustrates the manner in which two separator apparatus A-1 and A-2 of the type shown in FIG. 3 may be operated simultaneously to produce platelet concentrate (PC) using positive displacement peristaltic roller pumps commonly available for the pumping of blood or other sterile fluids.

In the operation of the apparatus of FIGS. 6, 6A, and 7 as a separator for blood components, liquid M would be blood which enters the upper portion of the rotating cylindrical assembly A through drive tube 104' and enters gap G'. This form of the apparatus is particularly adapted for use as a rapid PC collector in certain surgical settings where high platelet loss is expected. If a fully therapeutic dose of platelets could be obtained from the surgical patient in the O.R. during surgical preparation and returned to that patient following surgery, significant clinical benefits (related to control of bleeding, i.e. clotting mechanisms) would be expected. Having reference to FIGS. 6, 6A, and 7, such a procedure can be carried out in one step in the apparatus shown. Because access to venous circulation is substantial in

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this case it is possible to obtain, for example, about 300 ml/min of blood flow, at least half of which, 150 ml/min, will be plasma available for collection or processing. Of that, 30 ml/min will carry the concentrated platelets and 120 ml/min would be the cell-free plasma to be decanted first. Referring to FIG. 6, with blood entering gap G' at the top, such blood first encounters impervious entrance member 66' and then porous sections 21' and 170 in succession. For purposes of the present example, the area of porous surface 34' of porous element 21' is fixed at 200 cm^2. 120 ml/min of cell free plasma flowing radially inward through the porous element produces a radial convective velocity of 0.01 cm/sec, i.e. 2 ml/sec divided by 200 cm^2. In order to collect only cell-free plasma as the second liquid fraction M2, the Stokes velocity for platelets must exceed the convective velocity by at least 25%. In the present example $r\ \omega^2 x\ 0.5\ x\ 10^{-8} \geq 0.0125$ represents the required condition. See FIG. 15. For a 2.0 inch diameter blood film the r.p.m. is 9548. Larger diameters or more porous surface area would reduce the r.p.m. requirement.

The plasma remaining in zone E after decantation of cell free plasma from zone RC' contains PC which can, in sequential decantation across the outer surface of porous element 21' be largely removed from

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zone E through porous ring 170 as third liquid fraction M_3, the remainder rejoining the concentrated material from zone 83' at passage 144' where the recombined material, now first fraction M_1, is led away at conduit 86'. In order to prevent RBC or lymphocytes from being decanted along with the platelets it is necessary to choose a convective radial velocity which exceeds the settling velocities of platelets but is less than those for RBC. Referring to FIG. 15 it is seen that such a velocity would be adequately represented by $r\ \omega^2 \times 2 \times 10^{-8}$ which, for the specified blood film and rotation rate, is 0.05 cm/sec. Given the decantation rate for M_3, (i.e. PC), that is, 30 ml/min or 0.5 ml/sec, the area of the exterior surface of porous ring 170 must be 10 cm^2 to enable the convective inward velocity of 0.05 cm/sec at that surface. Thus, the second porous element 170 is much smaller than the first porous element 21 in area and axial extension.

Referring again to Figs 6, 6A, and 7, yet another application of the invention has great utility in the washing and concentrating of red blood corpuscles either in connection with frozen blood storage or, perhaps more importantly, for application to blood cell salvage in what is termed auto-transfusion of the surgical patient's own blood during surgery. In the latter instance, it is the removal of excess heparin

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and return of concentrated protein and clotting factors for the purpose of clotting function regulation that has the greatest clinical importance. The processing of high volumetric rates can be useful. Cell washing should involve a concentration step followed by the simultaneous addition, separation and removal of wash solution, usually saline. If concentration precedes washing, the amount of wash solution required to displace cell stroma dispersed in the original suspending medium is minimized.

With particular reference to FIG. 6A, when cylindrical valve ring 182 is raised, a saline wash solution, indicated by flow arrows 189 from space 93' flows radially inwardly through porous rings 184 and 170, respectively, at a rate of flow effective to enable an inward radial velocity of controllable and uniform value across the gap and into passages 174, space 176, and through discharge conduit 178 (see FIG 6). The inward radial convective velocity associated with wash solution flow should be higher than that of prior flow across surface 34' of porous element 21' in order to take full advantage of a sequential concentrating followed by a washing step intended to remove contaminants not otherwise permitted to follow with flow across such surface. Using the criteria above described, assume the apparatus of the present invention is capable of removing 200 ml/min from a

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blood flow that would be typically 300 to 400 ml/min. Also, assume surface 34' has an area of 200 cm^2 so that the inward radial convective velocity is 0.0166 cm/sec. In order not only to salvage most of the red blood corpuscles, especially the youngest and healthiest cells, which are generally the least dense, but further, to prevent smaller contaminants such as cell stroma which have settling velocities comparable to platelets, from following with the protein comprising the second liquid fraction, one would again consult FIG. 15 where the minimum Stokes velocity for platelets is about $5 \times 10^{-9} \times r \omega^2$ and set this value at or above 0.02. Using a 2.0 inch diameter blood film, the required r.p.m. is 12,080. It remains only to use a higher radial velocity than that used to decant liquid from zone RC' to decant wash solution, after deciding how much wash solution is required, bearing in mind it can always be adjusted to fit whatever operating conditions prevail and that the example here is for maximal conditions. The operative parameter is about 10 ml/min of wash solution for each 1.0 cm^2 of exterior and interior porous surface of porous elements 170 and 184, respectively, in order to maximize the washing effect (i.e. displacement of cell stroma) while still retaining all RBC in the first fraction. Because the pre-concentration step removed so much protein containing liquid which does not now

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have to be displaced by an approximately equal amount of wash solution, it is estimated that 20 to 50 ml/min of wash solution would be sufficient to process about 100 ml/min of packed RBC. Using the upper value, the surfaces of porous elements 170 and 184 and could be as little as 5 cm^2. However, if one doubles the area and rate of wash solution flow, the design is virtually identical to that for the PC collector. It will be understood that operation of cylindrical valve ring 182 to block and unblock access of saline solution to porous elements 184, as shown in FIG. 6A, converts the FIG. 6 apparatus from PC collector to a cell washer and concentrator.

It is noted that the washing process operative in the example herein described displaces rather than mixes with the original suspending medium as in prior art cell washing methods. Consequently, washing is more thorough per unit volume of wash solution because, as in the comparison between a shower and a bath, the wash solution is not substantially diluted. It is further noted that the crystalloid portion of the first separated protein containing liquid (i.e. plasma) can be removed as by ultra filtration in separate apparatus so that protein concentrate can also be returned to the patient. See FIG. 17.

Figure 17 is a schematic illustration of the operation of separator apparatus embodying the present

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invention which is convertible from a platelet concentrator to a cell washer/concentrator in accordance with principles of the invention. Whole blood or a solution containing blood components is delivered by pump P6. As a PC collector or cell washer/concentrator, pump P7 removes concentrated blood while pump P8 removes cell-free and stroma-free liquid. The difference, that is, the volumetric pumping rate of P6 less the sum of rates of P7 and P8 is a net flow which is PC or contaminated wash solution in the cases of platelet collector and cell washing/concentrating, respectively. In the former, cell-free plasma is recombined with concentrated blood to form reconstituted blood for return to the patient. In the alternate, cell-free liquid, containing plasma proteins and crystalloid material including water, follows a different path as indicated by the dotted lines at the left portion of FIG. 17 to a separate device incorporating membrane filtration to remove a large part of the water and crystalloid to form concentrated plasma protein. The latter is recombined with concentrated blood for return to the patient.

Saline circulation is handled in each case as follows: Pump P9 delivers saline to each end of the apparatus while pump P10 removes saline from the central port 190 simultaneously, and at a slightly slower volumetric rate, in the case of platelet

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collection, in order to force some saline across the seals.

For cell washing, pump P10 is slowed further. Pump P10 removes saline from the apparatus A at a volumetric rate which is less than the volumetric rate of pump P9. The difference is the volumetric rate at which saline wash solution is delivered across the gap. It is understood that fluids other than saline may be used for the purpose described above. When the cylindrical valve ring 182 (FIG.6) is raised, saline solution enters the porous ring 170 and outlet conduit 178 to wash contaminants picked up by the saline solution for disposal, as indicated by the dotted lines at the right portion of FIG. 17.

Referring now to FIGS. 8 and 9, there is shown the major components of a third form of apparatus embodying the present invention. This form of the invention is similar to the form of the invention shown in FIGS. 3, 4, and 5, with the exception that the outer cylinder O is provided with a porous element 193 over a portion of its axial extension. Like parts bear double primed reference numerals. The upper part of the apparatus of the third form of the invention is provided with an electro-magnetic armature drive, like that shown in FIG. 3 arranged to effect rotation of the inner and outer cylinders I'' and O'' within stationary housing H''. A sterile solution is

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introduced into the conduit 91'' at top of drive support member 104'', and is discharged through an outlet conduit 92'' at the lower right-hand portion of housing H''. The liquid component M to be fractionated enters through the upper end of drive tube 104'' and flows downwardly through the lower end of the drive tube into the entrances of radially outwardly extending passages 196 formed between the upper walls of the inner and outer cylinder members. The radially outer ends of these passages empty into the upper end of gap G''. The lower end of the gap G'' is in communication with the radially outer ends of radially extending passages 209 found between the lower walls of inner and outer cylinders I'' and O''. The radially inner ends of these passages are connected to the upper end of lower tube 150'' to discharge liquid fraction M1 through the lower end of the housing H''. A circular baffle 210 is arranged coaxially between support tube 41'' and inner cylinder I'' to define inner region R''. Inner region R'' receives liquid fraction M2 which permeates through porous element 21'' of the inner cylinder I'' by a pressure differential created between the gap G'' and inner region R'', as fully described hereinbefore. Passages 211 formed in the lower portion of the cylindrical assembly A'' transfer liquid component M2 into a space 212 from which the liquid is discharged

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through the lower portion of housing H''. The lower portion of the housing H'' is provided with bearings and O-ring bearing seals (not shown) through which a sterile, cooling solution is circulated as with the apparatus of FIGS. 3 and 6.

Assuming the liquid mixture is blood, for cell washing purposes, blood entering drive tube 104'' at the top of the apparatus usually consists of concentrated cells (i.e., 90+% cells in a liquid medium or "carrier"). The blood cell concentrate is led via flow path 207 to a gap entrance region 208 at the upper end of the separation gap G''. The gap is defined by interior surfaces of the inner and outer shell's axial sections. Sterile solution, such as a saline wash solution, enters the upper and lower ends of housing H'' by means of positive displacement volumetric pumping, follows a flow path through conduits designed to cool the bearings and seals and prevent blood component leakage and enters exterior region space 93'' between housing H'' and outer cylinder O'' at a substantially uniform pressure throughout the exterior region. It further enters and crosses (i.e., permeates) porous element 193 of the outer cylinder under the influence of the uniform pressure at a uniform volumetric rate over the entire exterior surface of such porous element, thus establishing an inward radial flow velocity of wash

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solution across the axial extent of gap G" enclosed by porous element 193, as described hereinbefore. The flux velocity is determined by the volumetric rate at which wash solution crosses porous element 193 divided by the inner surface area 213 of such porous element. The portion of wash solution that enters space 93'' in excess of that which crosses porous element 193 leaves the apparatus via port 92''.

Wash solution which crosses porous element 193 nearest the top of the gap enters the concentrated blood cell mixture at gap region 218 and operates to dilute the mixture (provided wash solution is miscible with carrier fluid) even as the cells migrate radially outwardly under the influence of centrifugal force. The cells form a concentrated cell mass exterior to imaginary boundary 48''. Wash solution accumulates in gap region 219 and flows axially downwardly along with the concentrated cell mass in gap region 218. Gap region 219 is formed by impervious entrance element 216 which comprises an axially extending portion of the inner shell at the latter's top, which portion is tapered radially inwardly or away from boundary 48'' in the downward direction. Consequently, gap region 219 increases in thickness downwardly to accommodate the addition of wash solution to the mixture.

Wash solution enters gap region 220 at a flux velocity identical to that at which it enters region

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218. However, wash solution is simultaneously crossing the outer surface of porous element 21'' at the same rate thus removing wash solution from gap region 221 as fast as it enters. The net effect is that wash solution crosses the gap in a radially inward direction with no net accumulation of wash solution in the gap for the axial extent of the gap which is defined and enclosed by the common axial overlap (i.e., axially co-extensive portions) of porous elements 21'' and 193 acting together. The axial extensions of porous elements 21'' and 193, where they do not face each other, serve purposes described separately herein. The gap-defining surfaces of the porous elements, where they face each other, remain concentric and parallel to boundary 48'' and to each other. The latter is the principal washing region of the gap.

The washing method is practiced by causing the wash solution flux velocity to be greater and less than the settling velocities of particles and/or cells to be washed out and cells to be retained in the gap, respectively. Clearly, continuous phase will be washed out and virtually replaced with wash solution, provided the two liquids are miscible. If they are not, it is not possible to predict with certainty the behavior just described.

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Wash solution that was added to gap regions 218 and 219 is an excess volume not removed from gap region 221 and must flow axially toward exit region 209. However, the bottom portion of the outer cylinder is comprised of an impervious element 222 having an inner gap defining surface 223 for approximately the same axial extent as the impervious upper element 216 of the inner shell. Impervious surface 223 is a continuation of porous element 193 wherefore wash solution flows out of gap region 224 without simultaneous replenishment from gap region 225. Consequently, porous surface 226 of element 21'' is tapered outwardly and downwardly toward boundary 48'' to account for the diminishing amount of continuous phase. Cells in gap region 225 become more concentrated until they reach the level of concentration at which they entered, thus canceling the dilution introduced in gap regions 218 and 219. Surface 226 is tapered outwardly and downwardly to boundary 48'' to aid in the flow of concentrated cells toward exit region 209.

The described method of dilution and re-concentration has the effect of increasing the distance between imaginary boundary 48'' and the inner shell's porous outer surface 226. The additional distance operates to maintain dilute concentration of cells in the mixture most proximate the porous

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"separation" surface 226. The main concentration of cells is radially exterior of boundary 48''.

The "environment" in which biologically valuable cells exist in gap regions 220 and 221 is unique in the present invention and, being sustainable indefinitely, has not been so achieved in apparatus heretofore. The opposing forces on a biological cell, operative in the gap, are centrifugal force urging the cell to seek the inner porous surface of the outer shell and the drag force of radially inwardly flowing media tending to carry the cell toward the outer porous surface of the inner shell. All cells remaining in the gap find a point of balance between these forces or "rest" on the inner surface of the outer shell which contains pores through which the cells cannot pass, not necessarily because the pores are too small in "size" for cells (some of which are sufficiently deformable to enter pores smaller than their normal cross-section) to enter but, rather, because the pore-open to pore-matrix solid volume is sufficiently low to substantially increase the wash solution inward radial flux velocity obtaining within the porous element volume to overcome the outward radial migration velocity of all relevant cells. Again, "filtering", understood as a sieving process, is not the operative feature here, nor does the outer porous element operate as a physical barrier, absent

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the radially inward flow of wash solution, to effect separation of components.

For every collection of cells there exists a wash solution flow rate corresponding to an inward radial flux velocity in the gap in combination with a centrifugal force, determined in the apparatus by rpm, that can easily be found experimentally to produce a cell concentration gradient most dilute near the inner shell and most concentrated near the outer shell wherein every cell is surrounded by wash solution flowing continuously over its surface and wherein every cell no longer moves radially in either direction. In effect, the cells can be levitated and maintained in suspension even while the suspending phase is being continuously ex changed. The cell mass exists under conditions which are analogous to a "liquified bed". Such apparatus can superimpose a controlled axial flow or operate without axial flow by deleting gap regions 218, 219, 224, and 225 along with the associated impervious elements. Once stasis is achieved, it can be maintained indefinitely. Wash solution can carry nutrients and oxygen to the cells and simultaneously remove CO_2 and other waste products. It can be used to control temperature, enzymes and drug delivery to the cell. It is clearly a novel cell culturing method that does not subject the cell to the damaging effects of mechanical shear and filtration or

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substrate interaction as used in some prior cell culturing methods.

Furthermore, given the indefinitely extended time scale, separation as between cells with very closely matched sedimentation properties could be carried on very gradually over long periods of time. These novel techniques suggest promising new possibilities for further biological and medical research involving in vitro cell studies.

As a more immediate practical application of the cell washing method of the present invention, FIG. 19 illustrates a simple pumping arrangement for washing stored blood using the separator apparatus of FIGS. 8 and 9. Blood is pumped via pump P15 while washed cell concentrate is pumped via pump P16 into a separate washed-blood bag. Because of the normal time delay required for some chemicals such as ethylene glycol (typically used to store frozen blood) to leave the red blood corpuscles (RBC) one would allow the first washed blood to re-enter the original storage bag, after all blood is cycled through the cell washer, by opening a valve between the two bags. After a period of time, the cycle is repeated for as many cycles as may be required to rid the stored blood of objectionable chemical. The last cycle leaves the clean blood in the washed-blood bag. Pumps P18 and P19 provide circulation and positive pressure on the

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seals of the apparatus A5 for controlled leakage as described hereinbefore, but the difference in their volumetric rates, i.e., the pressure of pump P18 minus the pressure of pump P19 is now also used to provide the positive definite flow of wash solution. The volumetric rates of pumps P15 and P16 match at all times so that there is never any difference in blood volume. Consequently, all excess flow, i.e., flow from pump P18 minus flow from pump P19 must leave the separator apparatus A5 via the waste wash path.

Another use of the cell washing method and apparatus of FIGS. 8 and 9 permits a major departure in extracorporeal blood oxygenation not possible heretofore. FIG. 20 illustrates such general method. The first stage employs a plasma separator apparatus A6 of the type shown in FIGS. 8 and 9 yields two outlet streams, one being highly concentrated RBC bearing de-oxyhemoglobin, that is, red cells poor in oxygen and saturated with carbon dioxide, RBC-D, the other being most (90% to 95%) of the plasma which is returned to the patient. The concentrated RBC-D (not pumped in order to minimize hemolysis), is led to a mixing chamber 400 through conduit 402 where it is thoroughly mixed with concentrated oxygen rich artificial blood particles, AB-O. The resulting mixture contains RBC bearing oxyhemoglobin, RBC-O, and spent AB saturated with CO_2 or AB-D. The mixing

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chamber output rate of flow is determined by the rate of pump P20 (PR1) minus the rate of pump P21 (PR2) plus the rate of pump P25 (PR6), which flow enters the cell washer A7 through conduit 403. The difference of pump rates, PR1 minus PR2 is determined by the hematocrit of the patient blood (i.e., cell volume fraction, Hct.). The rate of pump P25 (PR6) will necessarily be related to that difference which correlates with the mass flow of hemoglobin, Hb., that is:

$$PR6 = f\ (PR1 - PR2)$$

where f is some factor depending upon the AB product used.

The wash solution flow rate is the rate of pump P23 (PR4) minus the rate of pump P24 (PR5) even though the wash solution is led serially through the plasma separator A6 (which draws off very little wash solution) before entering the cell washer A7, as shown in FIG. 20. Again, the concentrated RBC-O is not pumped in order to protect the cells but pump P22 draws waste wash solution out of the system. So long as PR3 = PR6 + (PR4 - PR5) or PR3 = (PR4 - PR5) + f (PR1 - PR2), the cellular output of RBC-O from the cell washer A7 will match that of the plasma separator A6, i.e., PR1 - PR2. This preserves the RBC cell mass. The wash rate PR4 - PR5 is controlled to provide the necessary wash-out of AB particles and

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suspending medium. In order to prevent repeated dilution of plasma protein with each pass of blood through the oxygenator, the wash solution in this example should be the patients own plasma or donated plasma. This is both possible and practical because very little wash solution is required per pass to remove AB particles from the concentrated RBC cell mass in accordance with the method of the present invention. Finally, the RBC-O is recombined with the plasma from the plasma separator to reconstitute the blood, i.e., plasma with, now, oxygen-rich, CO_2-regulated, RBC. The reconstituted whole blood must flow into sufficient positive pressure so that neither pumps P21 nor P22 apply suction to the fluids. This provision is important to prevent fluid outgassing or cavitation. The suction side of pump P22 is the lowest pressure in the system, but it need not be below atmospheric if there is adequate resistance in the patient return line 404.

Having described the system, it is important to note that there are many varieties of artificial blood generally consisting of particles of extraordinary solubility relative to gases such as O2 and CO_2. Many are very compatible with blood and organ tissues. A typical example is Perfluorooctyl Bromide, PFOB, sold by Nippon Mektron Ltd. The ability of these particles to rapidly transfer oxygen and remove CO_2 from the body

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tissues and blood cells, with no apparent toxicity, is well established. Consequently, direct mixing of PFOB with concentrated RBC-D converts the latter immediately to RBC-O. The problem has always been separating the spent PFOB from the blood before returning the latter to the patient. Wholesale injection of PFOB into the patient is not approved.

Complete separation of entrained PFOB particles by filtration has not been possible because such particles are only about 0.1 micron in diameter. Separating them by prior centrifugation techniques is equally difficult because the particles have a specific gravity approaching 2.0 and would form a thin dense layer under the RBC which would defeat any reasonable method of skimming. On the other hand, the settling velocities of the particles are a small fraction of the settling velocity of RBC due to their small size. The settling velocity of a PFOB particle is about 0.006 the settling velocity of an RBC. Consequently, they are easily washed out using the present invention.

In summary, the oxygenator system of the present invention as described immediately hereinabove includes a plasma separating step (so as not to require separating PFOB particles from plasma) followed by a step which mixes RBC with AB, followed by a step which washes AB and any other stroma out of

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the RBC and finally recombination of clean, oxygenated RBC with the plasma for return to the patient. These steps run continuously and simultaneously in a closed extracorporeal circuit as will be clear from FIG. 20.

With reference to porous elements disposed in the inner shells I, I', and I" of FIGS. 1 through 9, their necessary properties may be summarized as follows. They should have:

1) pore diameters of sufficient size to pass formed or particulate supernatant constituents without restriction, but not substantially larger than that size; and

2) resistance to flow of the supernatant fluid medium so that pressure loss experienced by supernatant crossing the porous barrier is substantially greater than pressure loss experienced by the remaining suspension as the latter flows from entrance to exit of the device; and

3) because axial movement of the blood within the blood film must be under conditions of viscous boundary flow in order to remain stable, the outermost layer of the porous cylinder or outer diameter surface must be "wettable" by

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the suspending medium, hydrophilic in the case of blood.

Examples of how these properties can be achieved in a practical device are as follows:

First, it should be noted that the porous flow distributors are essentially tubular and can be comprised of multi-layers of concentric cylinders of various properties which, acting in combination, achieve the desired results.

Once the outer surface is "wetted", the interior remainder of the porous structure need not obey this condition (i.e., hydrophobia) which is one way of significantly increasing flow resistance.

It is further desirable, although not as fundamentally required, that the outer diameter of the porous cylinder have a high "open" to "solid" volume ratio or stated in other terms, a high concentration of pores per unit surface area. This condition should exist for a depth of at least several pore diameters in order to prevent local concentration of supernatant flow velocity at a microscopic level. Once the supernatant becomes trapped within the porous structure and removed from the bulk blood film, the high open to solid ratio need not be maintained. Consequently, inner layers of the continuously open porous structure can be comprised of lower open to solid ratios or lower concentration of pores. This

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further adds to flow resistance without affecting the requisite blood contact surface properties of the porous flow distributor. Of course, simply adding layers, or pore structure thickness, further adds to flow resistance.

In summary, three ways to establish the desired flow resistance of the porous flow distributor are:

1. Decreasing the open to solid volume toward the interior of the pore structure.
2. Increasing the depth or thickness of the pore structure.
3. Changing the "philic" nature of the surface in contact with the suspension to a "phobic" condition toward the interior.

In practice, one may achieve these alterations of pore structure properties by employing concentric multi-layers.

It should be understood with respect to the aforedescribed apparatus and method of the present invention, that the fluid film, (e.g., blood) being separated must be thin enough that secondary flows which would disturb settling may not arise. The only flows permitted are the bulk rotation of the fluid film trapped between two surfaces rotating at the same angular velocity, the axial laminar streamline viscous boundary layer flow within that film from top entrance to bottom exit, and the forced convective radial

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inward flow through one or more porous flow distributing surfaces.

In general, flow in a rotating system is characterized by very strong secondary flows that arise as a consequence of the rotational effects. Briefly, the Coriolis force balances the centrifugal pressure force in any regions of the fluid flow that are unaffected by viscosity such as would obtain sufficiently distant from a wall or surface containing the flow. In these regions where the flow is termed "geostrophic", the fluid velocities are nearly zero because the force results in no driving forces to move the fluid. Thus, if there is a global flow occurring in the system, the flow must occur in a region where viscosity can upset the geostrophic force balance to allow a fluid velocity. In many systems, viscosity is important only near the walls of the rotating container and, as a result, the bulk of the flow occurs only in thin layers near the wall. The layer where viscosity is important is called the Ekman layer when the wall surface normal vector is approximately parallel to the axis of rotation, and the Stewartson layer when the wall surface normal vector is nearly perpendicular to the axis of rotation.

A non-dimensional parameter that can be used to measure the importance of these boundary flows is the Ekman number given by

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$$\epsilon_k = \upsilon/\omega L^2$$

where υ is the kinematic viscosity of the fluid medium, ω is the rotational angular velocity, and L is a system characteristic length measured along the rotation axis. The Ekman number is a ratio of the viscous force to the Coriolis force in a rotating system. In systems rotating at high speed, ϵ_k, is typically very small, suggesting that geostrophic flow dominates the character of the flow. Using the viscosity of blood plasma and the approximate dimensions of a device suitable for separating platelets, the Ekman number is tabulated below for several rotation speeds.

TABLE I

Speed (rpm)	Ekman Number (ϵ_k)
5,000	1.71×10^{-7}
10,000	8.56×10^{-8}
15,000	5.70×10^{-8}
20,000	4.28×10^{-8}

It is evident that geostrophic flow will dominate in a typical centrifugal separator used heretofore with blood because the Ekman number is so small. Consequently, all significant fluid flow will occur in a region very close to the walls of the processing volume which goes to the heart of the reason for keeping the blood film "thin" in the instant invention. Incidentally, this problem plagues all

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prior continuous centrifugal separators attempting to decant formed layers during rotation in a bulk or batch separator. Estimates of the thickness of the boundary layers where the flow actually occurs can be made based upon the Ekman number and the length scale. The thickness of the Ekman layer (on walls perpendicular to a vertical axis of rotation, i.e., horizontal surfaces) is estimated by:

$$t_{\epsilon k} = (\epsilon k)^{0.5} L$$

The thickness of the more important Stewartson layer (on walls parallel or at some small angle to a vertical axis of rotation, i.e., vertical or nearly vertical walls) is estimated by:

$$t_{st} = (\epsilon k)^{0.25} L$$

Using these formulas, the estimated thickness of the layers are indicated in Table II below:

TABLE II

speed (rpm)	$t_{\epsilon k}$ (horizontal)	t_{st} (vertical)
5,000	0.0019 inch	0.096 inch
10,000	0.0014 inch	0.081 inch
15,000	0.0011 inch	0.073 inch
20,000	0.0010 inch	0.068 inch

Clearly the blood film perpendicular to the rotation axis, that is, blood flow along horizontal surfaces in a vertically oriented device, are subject to instabilities and geostrophic flow. More important, however, is the fact that the operative

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separation chamber, namely, the "thin" blood film flowing parallel to the vertically oriented rotation axis is within the Stewartson boundary layer thickness provided the blood film is limited to those thicknesses listed in Table II under t_{st}. These values define maximum claimed blood film thickness, at least for the entering whole blood.

As the blood becomes more concentrated and viscosity increases toward the blood exit, dramatically in some cases, one may wish to permit a thickening of the blood film by as much as 20% to 30%, relative to the entrance value. It is noted that film thickness varies only as the 1/4th root of viscosity.

For most applications a blood film thickness of 0.060 inch at the whole blood entrance is adequate for the purpose of limiting axial pressure gradients, even for flows on the order of 1 to 2 liters/min.

Provided that the blood film thickness for the entire volume, where layering and separation is intended to occur, is within the Stewartson layer, as defined herein, no geostrophic region with zero flow velocity will exist. Consequently, undesirable secondary flows are very unlikely. In short, the radial thickness of the processing chamber is so small that the entire region can be thought of as a boundary flow.

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As a check on the potential for instabilities due to the forced convective flow radially inward toward the porous flow distributor, it is appropriate to examine the influence of inertial effects in rotating systems. This can be estimated by computing the Rossby number given by:

$$R_o = \upsilon / \omega L$$

where υ is a characteristic velocity in the plane perpendicular to the axis of rotation. Using the estimated convective velocity of 0.0167 cm/sec, the Rossby number was calculated for radial plasma flow in whole blood as shown in Table III below:

TABLE III

speed (rpm)	R_o
5,000	6.4×10^{-7}
10,000	3.2×10^{-7}
15,000	2.1×10^{-7}
20,000	1.6×10^{-7}

Even at 20 times the convective velocity, as may obtain in surgical cell salvage and concentration, and as is evident in Table III, the Rossby number is very small indicating that inertial effects are much smaller than Coriolis effects in this flow. Hence, the convective velocity does not contribute instabilities even approaching those which limit the thickness of the Stewartson layer. Other instabilities which might give rise to inertial waves

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could occur at the entrance to the processing chamber but are quickly damped due to supporting vanes which separate walls defining entry to the blood film, and to the stabilizing influence of the initial impregnable zone which quickly establishes the Stewartson viscous boundary flow.

Finally, it is important to consider the influence of rotation on the settling of the particles in question. This will be done for platelets and red blood corpuscles.

The first issue is the particle Taylor number, T_ϱ. This parameter is a measure of the ratio of the size of the particle compared to the thickness of the Ekman layer, or, alternatively, the ratio between the Stokes drag force on the particle and the Coriolis force. The particle Taylor number is given by:

$$T_\varrho = 0.2 \frac{a^2 \omega}{\upsilon}$$

where a is the particle radius. The particle Taylor numbers for platelets and red corpuscles are listed below in Table IV.

TABLE IV

speed (rpm)	t_ϱ (platelets)	t_ϱ (RBC)
5,000	1.09×10^{-4}	7.08×10^{-4}
10,000	2.18×10^{-4}	1.41×10^{-3}
15,000	3.27×10^{-4}	2.12×10^{-3}
20,000	4.36×10^{-4}	2.83×10^{-3}

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If the particle Taylor number is large, which is not the case here, rotational effects can strongly influence the Stokes drag on the particle. This would have introduced error in the calculation of settling rates presented in FIG. 5(c), which can now be safely relied upon. In the case of red blood corpuscles, the Stokes drag is strongly dependent upon particle concentration, such as hematocrits typical of whole blood. However, it will be seen in specific examples to follow that red corpuscles sediment very quickly leaving only platelet rich plasma for which particle concentration effects on the Stokes drag is minimal due to very low concentration of platelets on a volume percentage basis.

A second non-dimensional parameter related to the settling of a particle is the time ratio λ. The time ratio is the ratio of separation time for a particle to the spin-up time for that particle. The spin-up time is the time for the particle to reach the system rotational speed after it enters the rotating system. The time ratio is given by:

$$\lambda = \epsilon_k^{0.5}/\epsilon T_\varrho \ (L/r)$$

ϵ is the density ratio defined by:

$$\epsilon = (\varrho_d - \varrho_c)/\varrho_c$$

where ϱ_c is the density of the continuous phase, in this case, plasma, and ϱ_d is the density of the dispersed phase, namely, platelets or red blood

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corpuscles. Table V below lists the time ratios for these particles:

TABLE V

speed (rpm)	λ (platelets)	λ (RBC)
5,000	13.0	1.20
10,000	4.6	0.43
15,000	2.5	0.22
20,000	1.6	0.15

This indicates that the separation of either red blood corpuscles or platelets is a relatively fast process. In fact, it may happen so quickly that the cells are not up to the rotational speed of the device (for $\lambda << 1.0$). This would be a problem for red corpuscles at very high speeds. Potentially, red blood corpuscles could sediment to the outer wall before they have reached approximately the same rotational speed as the wall. This could tend to cause high shear on the red blood corpuscles with the possibility of hemolysis which must be avoided. Therefore, conduits and vanes at the blood entrance to the device serve not only to space and support the walls defining the blood film but are indeed crucial in the design to force, especially the red blood corpuscles to spin-up to match device rotational speeds. Supporting vanes are both shaped and angled in such a manner as to accomplish the imparting of system rotational speed to the red blood corpuscles

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with a minimum of trauma, i.e., shearing of the red blood corpuscles among the spin-up surfaces. As seen in Table V, the time ratio for platelets is about 10 times that for red blood corpuscles and, consequently, red blood corpuscles sediment about 10 times faster than platelets as was seen in the several examples previously presented.

In summary:

1) The appropriate blood film thickness has been computed and must be limited by viscous boundary flow or the Stewartson layer.

2) Inertial instabilities are small, particularly in connection with the forced convection which decants the supernatant, i.e., the Rossby number is very small.

3) Turbulence is not an issue because the Reynolds number is less than 10 in this system.

4) The particle Taylor number indicates that, apart from concentration effects which influence only red blood corpuscles, the Stokes model for the drag on a particle is valid.

5) The time ratio is such that the settling of particles can be relatively fast in comparison with their spin-up time so that entry vanes are essential to force particle spin-up and should be designed with a minimum of turbulence and shearing of the particles.

In practicing the present invention, the details

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may be replaced with other technically equivalent elements; furthermore, the materials used, and the shapes and dimensions, may be any selected ones to meet individual requirements without departing from the scope of the present invention.

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WE CLAIM:

1. Apparatus for fractionating a liquid mixture substantially into first and second liquid fractions whose components have settling velocities which are under identical conditions of centrifugal force, higher and lower, respectively, than a selected value, said apparatus comprising:

a rotary assembly for rotation about a central axis and including inner and outer shells defining therebetween an axially extending tubular gap and an inner region radially inwardly of said inner shell;

said inner shell including a flow resistive porous structure to provide for permeation therethrough of said second fraction at a radially inward entrance velocity below said selected value and to restrict flow of the residual of said fluid mixture therethrough;

an inlet for introducing said liquid mixture into said gap at one axial end thereof;

a frame for mounting said frame for rotation about said axis;

a drive for rotating the assembly at a predetermined fractioning speed effective to impart centrifugal force to said liquid mixture within said sufficient gap to cause said second fraction to flow radially inwardly through said porous structure and to prevent said first liquid fraction from permeating said porous structure; and

an outlet for drawing said first fraction from said inner region.

2. The apparatus of Claim 1 that includes:

a residual outlet at one axial end of said gap for withdrawing said second fraction therefrom.

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3. The apparatus of Claim 1 that includes:

a pump for controlling pressure in said gap to control the pressure differential across said first porous structure.

4. The apparatus of Claim 3 wherein:

said pump is operative to maintain the pressure of said liquid in said gap at a predetermined pressure and wherein said apparatus includes:

a tank enclosing said assembly and cooperating therewith to form a pressure chamber;

encapsulating fluid in said pressure chamber; and

means for maintaining the pressure of said encapsulating fluid in said pressure chamber at a selected pressure higher than said predetermined pressure.

5. The apparatus of Claim 4 for use in fractioning a said mixture including blood components and wherein:

said encapsulating fluid is sterile.

6. The apparatus of Claim 1, wherein:

said inner shell includes an impervious cap between said inlet and said inner porous structure, the outside surface of said cap being tapered gradually radially inwardly and away from said inlet to gradually increase the annular flow area in said gap.

7. The apparatus of Claim 1 for fractionating a liquid mixture of the type having a predetermined ratio of first to second fractions and which, during rotation of said assembly at said predetermined fractioning speed, builds up an inner

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layer on the outer surface of said porous structure leaving an outer layer including said first fraction and wherein:

said assembly is axially elongated; and

said inner shell adjacent said mixture inlet tapers radially inwardly and away from said inlet at an angle to reduce said outer surface thereof sufficiently so that as said drive rotates said assembly at said predetermined fractionating speed said inner and outer layers will flow axially at substantially the same axial velocity.

8. The apparatus of Claim 1 for fractionating a blood mixture and wherein:

said inner and outer shells are concentric to form said gap with a radial thickness of between at least 5 and 150 millimeters.

9. The apparatus of Claim 1 for treating a blood mixture including plasma and wherein:

said porous structure is constructed for, at said predetermined fractioning speed, permeation therethrough of said plasma.

10. The apparatus of Claim 1 for treating said second fraction with a selected fluid and wherein:

said porous structure is constructed for, at said predetermined fractioning speed, permeation therethrough of said selected fluid; and

said outer shell includes an inlet for introduction of said selected fluid for flowing through said second fraction.

11. The apparatus of Claim 1 for fractionating a liquid mixture of blood with plasma

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defining said second fraction and red blood cells defining said first fraction and wherein:

said porous structure is constructed for, at said predetermined fractioning speed, permeation therethrough of said plasma.

12. The apparatus of Claim 11 for drawing blood from a patient and which further includes:

an inlet conduit for connecting said inlet to a patient's blood circulatory system for drawing said blood therefrom.

13. The apparatus of Claim 11 wherein:

said rotary assembly includes a residual outlet for withdrawing said red blood cells as said second fraction from said gap; and

a blood outlet conduit connected to said residual outlet for withdrawing said red blood cells therefrom for infusion back into said patient's blood circulatory system.

14. The apparatus of Claim 1 for fractionating a liquid mixture, including blood components susceptible to forming packed components which are reliquefiable by a selected fluid and that includes:

rotary seal means configured to allow for some fluid seepage of said selected fluid;

an encapsulating housing around said outer shell to be pressurized by said selected fluid to a pressure sufficient to cause said selected fluid to seep through said seals into said gap to reliquefy said packed components which might form in said assembly.

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15. The apparatus of Claim 1 wherein:

said porous structure is axially elongated and said apparatus includes, and is configured to, and has a thickness and pore diameter effective to, when said fluid mixture fully covers the surface thereof and a predetermined pressure drop is formed radially across said porous structure, establish a predetermined rate of permeation; and

a pump coupled with said fluid mixture inlet for maintaining said predetermined pressure drop across said porous structure.

16. The apparatus of Claim 1 that includes:

a tank enclosing said assembly and cooperating therewith to form a pressure chamber;

bearings mounting said assembly from said tank;

cooling fluid in said pressure chamber; and

circulation means for circulating said cooling fluid in heat exchange relationship with said bearings.

17. The apparatus of Claim 1, wherein:

said rotary assembly is axially elongated, said inlet disposed at one end of said gap and that includes:

a residual outlet at the opposite end of said gap; and

inlet and outlet pumps connected with the respective said inlet and residual outlet to control the rate of fluid flow through said gap.

18. The apparatus of claim 1 for fractionating said fluid mixture of the type having a predetermined ratio of said first to second fractions

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and predetermined viscosity characteristics and wherein:

said gap is axially elongated, said inlet disposed at one end thereof and that includes a residual outlet disposed at the opposite end thereof;

said inner shell and porous structure is so configured that, at said predetermined fractionating speed, said assembly is operative to form an outer layer including said first fraction in said gap surrounding an inner layer including said second fraction on the outer surface of said inner shell; and

a pump connected with said inlet for controlling flow of said mixture at a predetermined steady flow rate axially through said gap to cause said inner and outer layers to flow axially at substantially the same velocity.

19. The apparatus of Claim 1 for treating said second fraction with a treatment solution and wherein:

said assembly is axially elongated with said inlet disposed at one end of said gap and that includes:

an outlet disposed at the opposite end of said gap;

a porous treatment structure in said inner shell spaced axially toward said outlet from said inner porous structure for flow of said first fraction axially in said gap past the outer surface thereof; and

a treatment solution tank surrounding said outer shell and formed with a treatment port for introducing said treatment solution into said gap adjacent said porous treatment structure whereby said treatment solution may be introduced to said tank to

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flow radially inwardly over said second fraction of said liquid mixture to pass radially inwardly through said porous treatment structure.

20. The apparatus of Claim 19 that includes:

valve means for controlling flow of said treatment solution to said wash port.

21. Apparatus of Claim 1 for use with an encapsulating fluid compatible with said fluid mixture and that includes:

a pump for maintaining the pressure in said gap at a predetermined pressure;

seals for sealing said assembly against uncontrolled escape of said fluid mixture and constructed to, upon application of said encapsulating fluid at a selected pressure, provide for seepage inwardly therethrough to flow said fluid mixture away from said seals;

an encapsulating tank surrounding said assembly for receipt of said encapsulating fluid; and

a pump connected with said tank for applying said encapsulating fluid at said selected pressure thereto.

22. The apparatus of Claim 1 that includes:

means for pressurizing the liquid mixture within said gap during such rotation of said rotary assembly to positively compel flow of said second fraction radially inwardly through said porous structure into said inner region.

23. The apparatus of Claim 1 for fractionating a liquid mixture containing red blood cells and plasma and wherein:

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said porous structure at said fractionating speed provides flow resistance to radial inward flow of said red blood cells while allowing said plasma to flow freely therethrough.

24. A method for fractionating a liquid mixture into first and second liquid fractions and including the following steps:

selecting an assembly of the type including inner and outer shells constructed for equal angular velocity rotation about a common central axis, said inner shell including a porous structure for at least a part of its extent and a space interior of said porous structure;

introducing said liquid mixture into said gap between facing surfaces of said inner and outer shells;

compelling flow of said second fraction through said porous structure; and

rotating said shells at a speed effective to prevent the first liquid fraction from inclusion in said flow causing said first and second fractions to form on opposite sides of said porous structure.

25. The method of claim 24 that includes:

distributing the flow of said mixture substantially uniformly over the outer surface of said porous structure.

26. The method of claim 25 that includes:

distributing said flow over said porous structure to cause the radial inward velocity of entry of said flow into said porous structure to be substantially uniform over its outer surface.

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27. A method for fractionating a liquid mixture substantially into first and second liquid fractions whose components have settling velocities which are, under identical conditions of centrifugal force, higher and lower, respectively, than a selected value, which includes the steps of:

selecting an assembly of the type having inner and outer shells defining therebetween an axially extending tubular gap, and a radially inward inner region, the inner shell including an axially extending porous structure disposed radially outward of said inner region for permeation therethrough of said second fraction at a radially inward entrance velocity substantially equal to said selected value and to resist radial inward flow of the residual of said fluid mixture;

introducing said liquid mixture at a predetermined rate into said gap at one end thereof;

rotating said assembly at a predetermined fractioning speed effective to impart sufficient centrifugal force to said liquid mixture within said gap to apply a radially outward velocity to said first liquid fraction to resist permeation of said porous structure; and

pressurizing said liquid mixture within said gap during such rotation of said assembly to compel flow of said second liquid fraction radially inwardly through said porous structure into said inner region while retaining said first fraction in said gap.

28. The method of Claim 27 that includes:

rotating said assembly at a sufficient speed and pressurizing said gap with sufficient pressure to maintain a portion of said fluid mixture, including said first fraction, flowing along the exterior

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surface of said inner shell in a substantially uniform flow pattern.

29. The method of Claim 28 that includes:

rotating said assembly at a sufficient speed and maintaining said pressure in said gap at a sufficient level to maintain said residual of said fluid mixture flowing along said inner shell in a sufficiently thin layer to maintain laminar axial flow throughout the depth thereof.

30. Fractionating apparatus for treating a selected fraction suspended in a suspension medium of a liquid mixture with a selected treatment solution, said treatment solution and selected fraction formed by respective components having settling velocities which are, under identical conditions of centrifugal force, higher and lower, respectively, than a selected value, said apparatus comprising:

an axially elongated rotary assembly adapted for rotation about a central axis, said assembly having inner and outer shells defining therebetween an axially extending tubular gap and an inner region disposed radially inwardly of said inner shell;

said inner shell including a flow resistant porous structure for at least a part of its axial extension to provide for permeation therethrough of said treatment solution and to present resistance to radially inward flow of said suspension fluid;

a liquid mixture inlet to one end of said gap;

a treatment solution inlet for introducing said treatment solution into the radially outward portion of said gap;

a frame rotatably supporting said rotary assembly for rotation about said axis;

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a drive coupled with said rotary assembly to rotate said assembly at a predetermined fraction speed sufficient to, when said mixture is introduced to said gap through said mixture inlet and said treatment solution is introduced through said solution inlet, apply a settling velocity to said predetermined fraction sufficient to hold it suspended within said gap while said treatment solution is introduced through said treatment solution inlet causing it to flow radially inwardly through said suspension fluid and second fraction.

31. The apparatus of Claim 30 for use in washing a mixture of the type including red blood cells with a saline wash solution and that includes:

a saline tank encapsulating said rotary assembly and formed with said treatment solution inlet port; and

a treatment pump to pump said saline treatment solution into said tank and through said treatment solution inlet port.

32. The apparatus of Claim 30 wherein:

said inner shell is formed adjacent said fluid mixture inlet with a frusto-conical shape to slope gradually radially inwardly and away from said fluid mixture inlet to gradually increase the radial thickness of said gap.

33. The apparatus of Claim 30 that includes:

bearings interposed between said housing and assembly; and

circulation means connected with said treatment solution inlet for flowing said treatment

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solution in heat exchange relationship with said bearings.

34. Fractionating apparatus for fractionating a first fraction suspended in a suspension medium of a liquid mixture including a second fraction, said fractions formed by respective components having settling velocities which are, under identical conditions of centrifugal force, higher and lower, respectively, than a selected range of settling velocities, said apparatus comprising:

an axially elongated rotary assembly adapted for rotation about a central axis, said assembly having inner and outer shells defining therebetween an axially extending tubular gap and an inner region disposed radially inwardly of said inner shell;

said inner shell including a flow resistant porous structure for at least a part of its axial extension to provide for permeation therethrough of said first fraction and to present resistance to radially inward flow of the remainder of said fluid mixture;

a liquid mixture inlet to one end of said gap;

a frame rotatably supporting said rotary assembly for rotation about said axis; and

a drive coupled with said rotary assembly to rotate said assembly at a predetermined fractioning speed sufficient to, when said mixture is introduced to said gap through said mixture inlet, apply settling velocities in said selected range of settling velocities to hold said second fraction in said gap while flowing said first fraction through said flow resistant porous structure into said inner region.

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AMENDED CLAIMS

[received by the International Bureau on 17 February 1994 (17.02.94);
original claims 1,2,15,18,24,27-30,32 and 34 amended;
other claims unchanged (13 pages)]

1. Apparatus for fractionating a liquid mixture substantially into first and second liquid fractions whose components have settling velocities which are under identical conditions of centrifugal force, higher and lower, respectively, than a selected value, said apparatus comprising:

a rotary assembly for rotation about a central axis and including concentric inner and outer shells having a common axis defining therebetween an axially extending tubular gap and an inner region radially inwardly of said inner shell;

said inner shell including a flow resistive porous structure to provide for permeation therethrough of said second fraction at a radially inward entrance velocity substantially uniform over the outer surface of said inner porous structure and below said selected value and to restrict flow of the residual of said fluid mixture therethrough;

an inlet for introducing said liquid mixture into said gap at one axial end thereof;

a frame for mounting said frame for rotation about said axis;

a drive for rotating the assembly at a predetermined fractioning speed effective to impart centrifugal force to said liquid mixture within said sufficient gap to cause said second fraction to flow radially inwardly through said porous structure and to prevent said first liquid fraction from permeating said porous structure; and

an outlet for drawing said second fraction from said inner region.

2. The apparatus of Claim 1 that includes:

a residual outlet at one axial end of said gap for withdrawing a residual liquid fraction.

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3. The apparatus of Claim 1 that includes:

a pump for controlling pressure in said gap to control the pressure differential across said first porous structure.

4. The apparatus of Claim 3 wherein:

said pump is operative to maintain the pressure of said liquid in said gap at a predetermined pressure and wherein said apparatus includes:

a tank enclosing said assembly and cooperating therewith to form a pressure chamber;

encapsulating fluid in said pressure chamber; and

means for maintaining the pressure of said encapsulating fluid in said pressure chamber at a selected pressure higher than said predetermined pressure.

5. The apparatus of Claim 4 for use in fractioning a said mixture including blood components and wherein:

said encapsulating fluid is sterile.

6. The apparatus of Claim 1, wherein:

said inner shell includes an impervious cap between said inlet and said inner porous structure, the outside surface of said cap being tapered gradually radially inwardly and away from said inlet to gradually increase the annular flow area in said gap.

7. The apparatus of Claim 1 for fractionating a liquid mixture of the type having a predetermined ratio of first to second fractions and which, during rotation of said assembly at said

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predetermined fractioning speed, builds up an inner layer on the outer surface of said porous structure leaving an outer layer including said first fraction and wherein:

said assembly is axially elongated; and

said inner shell adjacent said mixture inlet tapers radially inwardly and away from said inlet at an angle to reduce said outer surface thereof sufficiently so that as said drive rotates said assembly at said predetermined fractionating speed said inner and outer layers will flow axially at substantially the same axial velocity.

8. The apparatus of Claim 1 for fractionating a blood mixture and wherein:

said inner and outer shells are concentric to form said gap with a radial thickness of between at least 5 and 150 millimeters.

9. The apparatus of Claim 1 for treating a blood mixture including plasma and wherein:

said porous structure is constructed for, at said predetermined fractioning speed, permeation therethrough of said plasma.

10. The apparatus of Claim 1 for treating said second fraction with a selected fluid and wherein:

said porous structure is constructed for, at said predetermined fractioning speed, permeation therethrough of said selected fluid; and

said outer shell includes an inlet for introduction of said selected fluid for flowing through said second fraction.

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11. The apparatus of Claim 1 for fractionating a liquid mixture of blood with plasma defining said second fraction and red blood cells defining said first fraction and wherein:

said porous structure is constructed for, at said predetermined fractioning speed, permeation therethrough of said plasma.

12. The apparatus of Claim 11 for drawing blood from a patient and which further includes:

an inlet conduit for connecting said inlet to a patient's blood circulatory system for drawing said blood therefrom.

13. The apparatus of Claim 11 wherein:

said rotary assembly includes a residual outlet for withdrawing said red blood cells as said second fraction from said gap; and

a blood outlet conduit connected to said residual outlet for withdrawing said red blood cells therefrom for infusion back into said patient's blood circulatory system.

14. The apparatus of Claim 1 for fractionating a liquid mixture, including blood components susceptible to forming packed components which are reliquefiable by a selected fluid and that includes:

rotary seal means configured to allow for some fluid seepage of said selected fluid;

an encapsulating housing around said outer shell to be pressurized by said selected fluid to a pressure sufficient to cause said selected fluid to seep through said seals into said gap to reliquefy

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said packed components which might form in said assembly.

15. The apparatus of Claim 1 wherein:

said porous structure is axially elongated and said apparatus includes, and is configured to, and has a thickness and pore diameter effective to, when said liquid mixture fully covers the surface thereof and a predetermined pressure drop is formed radially across said porous structure, establish a predetermined rate of permeation; and

a pump coupled with said fluid mixture inlet for maintaining said predetermined pressure drop across said porous structure.

16. The apparatus of Claim 1 that includes:

a tank enclosing said assembly and cooperating therewith to form a pressure chamber;

bearings mounting said assembly from said tank;

cooling fluid in said pressure chamber; and

circulation means for circulating said cooling fluid in heat exchange relationship with said bearings.

17. The apparatus of Claim 1, wherein:

said rotary assembly is axially elongated, said inlet disposed at one end of said gap and that includes:

a residual outlet at the opposite end of said gap; and

inlet and outlet pumps connected with the respective said inlet and residual outlet to control the rate of fluid flow through said gap.

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18. The apparatus of claim 1 for fractionating said liquid mixture of the type having a predetermined ratio of said first to second fractions and predetermined viscosity characteristics and wherein:

said gap is axially elongated, said inlet disposed at one end thereof and that includes a residual outlet disposed at the opposite end thereof;

said inner shell and porous structure is so configured that, at said predetermined fractionating speed, said assembly is operative to form an outer layer including said first fraction in said gap surrounding an inner layer including said second fraction on the outer surface of said inner shell; and

a pump connected with said inlet for controlling flow of said mixture at a predetermined steady flow rate axially through said gap to cause said inner and outer layers to flow axially at substantially the same velocity.

19. The apparatus of Claim 1 for treating said second fraction with a treatment solution and wherein:

said assembly is axially elongated with said inlet disposed at one end of said gap and that includes:

an outlet disposed at the opposite end of said gap;

a porous treatment structure in said inner shell spaced axially toward said outlet from said inner porous structure for flow of said first fraction axially in said gap past the outer surface thereof; and

a treatment solution tank surrounding said outer shell and formed with a treatment port for

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introducing said treatment solution into said gap adjacent said porous treatment structure whereby said treatment solution may be introduced to said tank to flow radially inwardly over said second fraction of said liquid mixture to pass radially inwardly through said porous treatment structure.

20. The apparatus of Claim 19 that includes:

valve means for controlling flow of said treatment solution to said wash port.

21. Apparatus of Claim 1 for use with an encapsulating fluid compatible with said fluid mixture and that includes:

a pump for maintaining the pressure in said gap at a predetermined pressure;

seals for sealing said assembly against uncontrolled escape of said fluid mixture and constructed to, upon application of said encapsulating fluid at a selected pressure, provide for seepage inwardly therethrough to flow said fluid mixture away from said seals;

an encapsulating tank surrounding said assembly for receipt of said encapsulating fluid; and

a pump connected with said tank for applying said encapsulating fluid at said selected pressure thereto.

22. The apparatus of Claim 1 that includes:

means for pressurizing the liquid mixture within said gap during such rotation of said rotary assembly to positively compel flow of said second fraction radially inwardly through said porous structure into said inner region.

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23. The apparatus of Claim 1 for fractionating a liquid mixture containing red blood cells and plasma and wherein:

said porous structure at said fractionating speed provides flow resistance to radial inward flow of said red blood cells while allowing said plasma to flow freely therethrough.

24. A method for fractionating a liquid mixture into first and second liquid fractions and including the following steps:

selecting an assembly of the type including inner and outer shells constructed for equal angular velocity rotation about a common central axis, said inner shell including a porous structure for at least a part of its axial extent to resist radial inward flow of said liquid mixture substantially uniformly over the outer surface of said porous structure;

introducing said liquid mixture into said gap between facing surfaces of said inner and outer shells;

compelling flow of said second fraction through said porous structure; and

rotating said shells at a speed effective to prevent the first liquid fraction from inclusion in said flow causing said first and second fractions to form on opposite sides of said porous structure.

25. The method of claim 24 that includes:

distributing the flow of said mixture substantially uniformly over the outer surface of said porous structure.

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26. The method of claim 25 that includes:

distributing said flow over said porous structure to cause the radial inward velocity of entry of said flow into said porous structure to be substantially uniform over its outer surface.

27. A method for fractionating a liquid mixture substantially into first and second liquid fractions whose components have settling velocities which are, under identical conditions of centrifugal force, higher and lower, respectively, than a selected value, which includes the steps of:

selecting an assembly of the type having inner and outer shells defining therebetween an axially extending tubular gap, and a radially inward inner region, the inner shell including an axially extending porous structure disposed radially outward of said inner region for permeation therethrough of said second fraction at a radially inward entrance velocity substantially uniform along said axial extension equal to said selected value;

introducing said liquid mixture at a predetermined rate into said gap at one end thereof;

rotating said assembly at a predetermined fractioning speed effective to impart sufficient centrifugal force to said liquid mixture within said gap to apply a radially outward velocity to said first liquid fraction to resist permeation through said porous structure; and

pressurizing said liquid mixture within said gap during such rotation of said assembly to compel flow of said second liquid fraction radially inwardly through said porous structure into said inner region while retaining said first fraction in said gap.

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28. The method of Claim 27 that includes:

rotating said assembly at a sufficient speed and pressurizing said gap with sufficient pressure to maintain a portion of said liquid mixture, including said first fraction, flowing along the exterior surface of said inner shell in a substantially uniform flow pattern.

29. The method of Claim 28 that includes:

rotating said assembly at a sufficient speed and maintaining said pressure in said gap at a sufficient level to maintain said residual of said liquid mixture flowing along said inner shell in a sufficiently thin layer to maintain laminar axial flow throughout the depth thereof.

30. Fractionating apparatus for treating a selected fraction suspended in a suspension medium of a liquid mixture with a residual and a selected treatment solution, said treatment solution and selected fraction formed by respective components having settling velocities which are, under identical conditions of centrifugal force, higher and lower, respectively, than a selected value, said apparatus comprising:

an axially elongated rotary assembly adapted for rotation about a central axis, said assembly having inner and outer shells defining therebetween an axially extending tubular gap and an inner region disposed radially inwardly of said inner shell;

said inner shell including a flow resistant porous structure for at least a part of its axial extension to provide for permeation therethrough of said treatment solution and to present flow resistance to said residual of said liquid mixture substantially

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uniformly along the outer surface of said porous structure;

a liquid mixture inlet to one end of said gap;

a treatment solution inlet for introducing said treatment solution into the radially outward portion of said gap;

a frame rotatably supporting said rotary assembly for rotation about said axis;

a drive coupled with said rotary assembly to rotate said assembly at a predetermined fraction speed sufficient to, when said mixture is introduced to said gap through said mixture inlet and said treatment solution is introduced through said solution inlet, apply a settling velocity to said predetermined fraction sufficient to hold it suspended within said gap while said treatment solution is introduced through said treatment solution inlet causing it to flow radially inwardly through said suspension liquid and second fraction.

31. The apparatus of Claim 30 for use in washing a mixture of the type including red blood cells with a saline wash solution and that includes:

a saline tank encapsulating said rotary assembly and formed with said treatment solution inlet port; and

a treatment pump to pump said saline treatment solution into said tank and through said treatment solution inlet port.

32. The apparatus of Claim 30 wherein:

said inner shell is formed adjacent said liquid mixture inlet with a frusto-conical shape to slope gradually radially inwardly and away from said

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fluid mixture inlet to gradually increase the radial thickness of said gap.

33. The apparatus of Claim 30 that includes:

bearings interposed between said housing and assembly; and

circulation means connected with said treatment solution inlet for flowing said treatment solution in heat exchange relationship with said bearings.

34. Fractionating apparatus for fractionating a first fraction suspended in a suspension medium of a liquid mixture including a second fraction, said fractions formed by respective components having settling velocities which are, under identical conditions of centrifugal force, higher and lower, respectively, than a selected range of settling velocities, said apparatus comprising:

an axially elongated rotary assembly adapted for rotation about a central axis, said assembly having inner and outer shells defining therebetween an axially extending tubular gap and an inner region disposed radially inwardly of said inner shell;

said inner shell including a flow resistant porous structure for at least a part of its axial extension to provide for permeation therethrough of said first fraction and to present flow resistance to said residual of said liquid mixture substantially uniformly along the outer surface of said porous structure;

a liquid mixture inlet to one end of said gap;

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a frame rotatably supporting said rotary assembly for rotation about said axis; and

a drive coupled with said rotary assembly to rotate said assembly at a predetermined fractioning speed sufficient to, when said mixture is introduced to said gap through said mixture inlet, apply settling velocities in said selected range of settling velocities to hold said second fraction in said gap while flowing said first fraction through said flow resistant porous structure into said inner region.

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STATEMENT UNDER ARTICLE 19

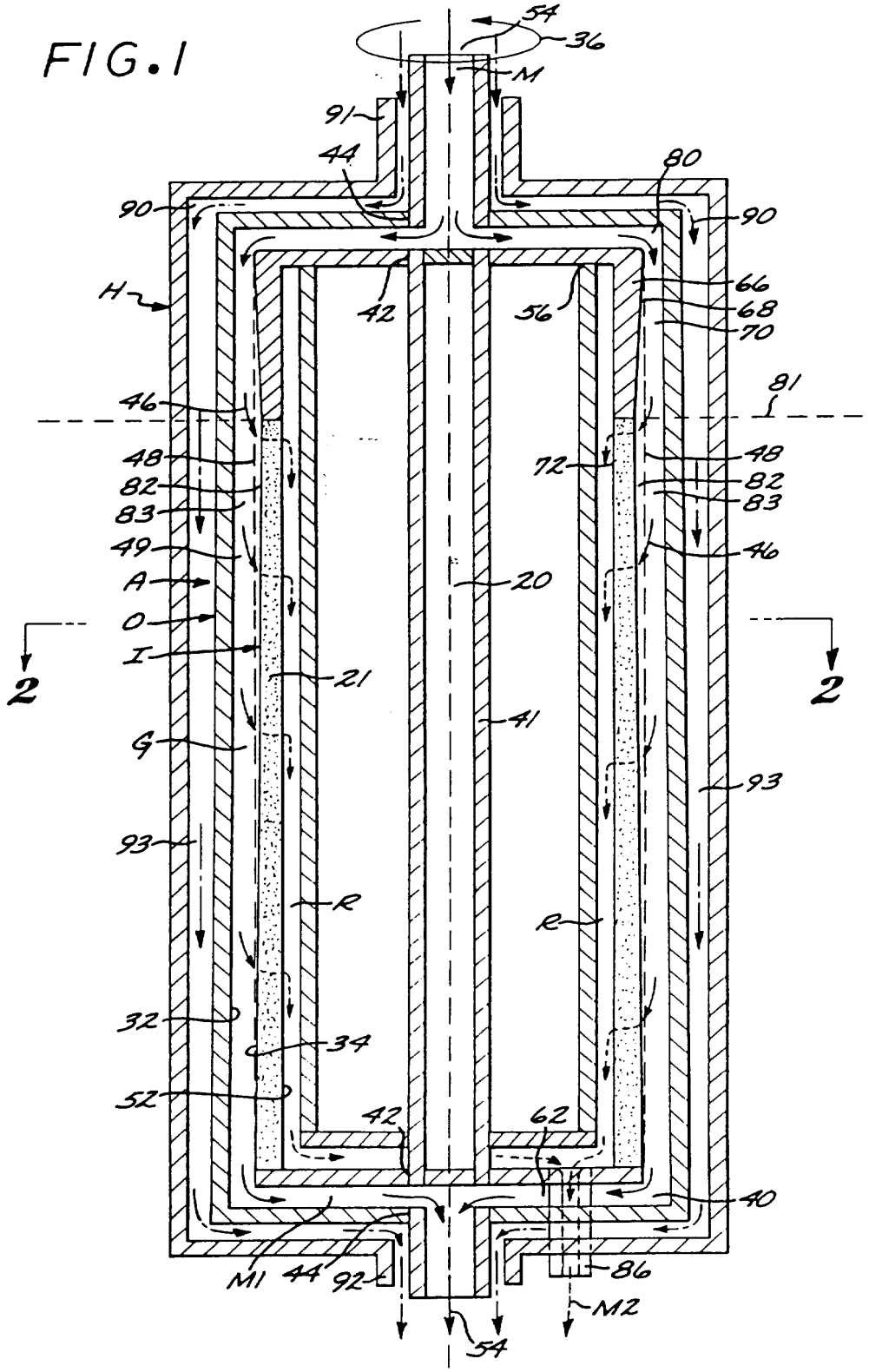
Claims 1, 2, 15, 18, 24, 27, 28, 29, 30, 32 and 34 have been amended to more particularly claim the matter for which protection is sought and are being submitted in accordance with PCT Article 19.

The amended claims are fully supported by the description and do not go beyond the disclosure in the international application as filed. None of the references in the International Search Report, alone or in combination, suggest the present invention as now claimed.

In conclusion, the amended claims more specifically claim the present invention disclosed in the international application. The present invention as now specifically claimed is not suggested by the international search authority references, alone or in combination.

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FIG. 1



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FIG. 1A

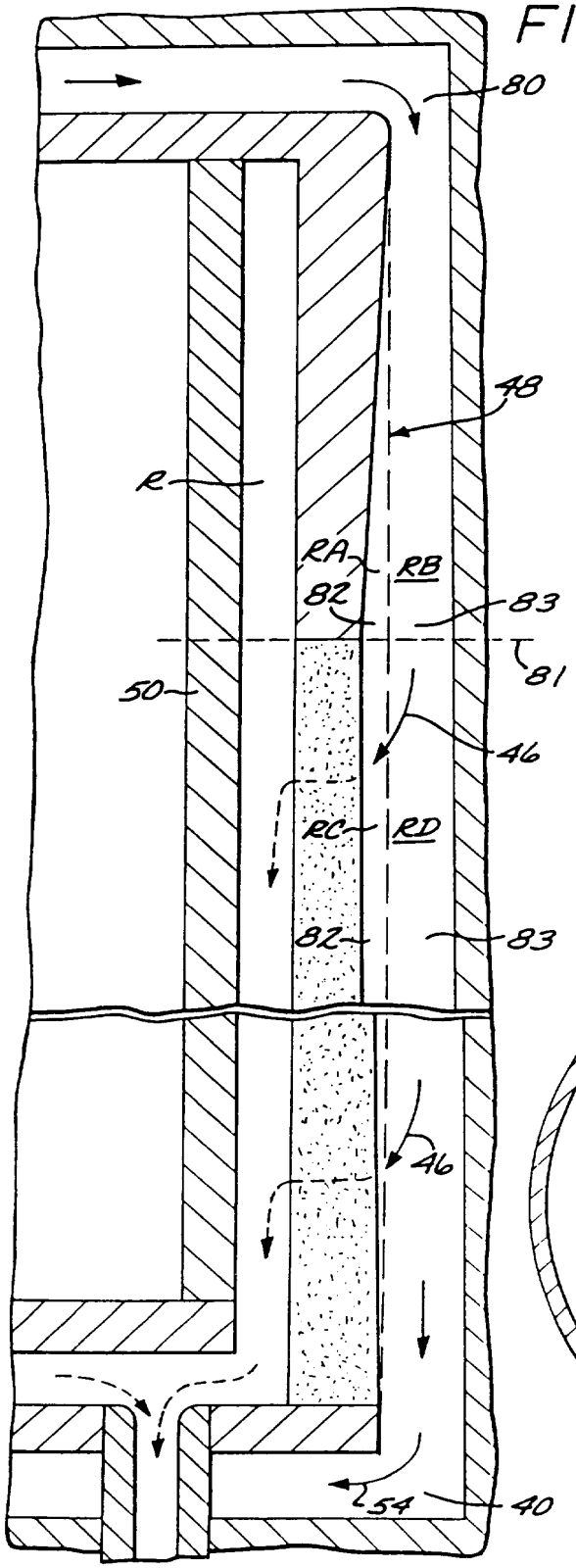
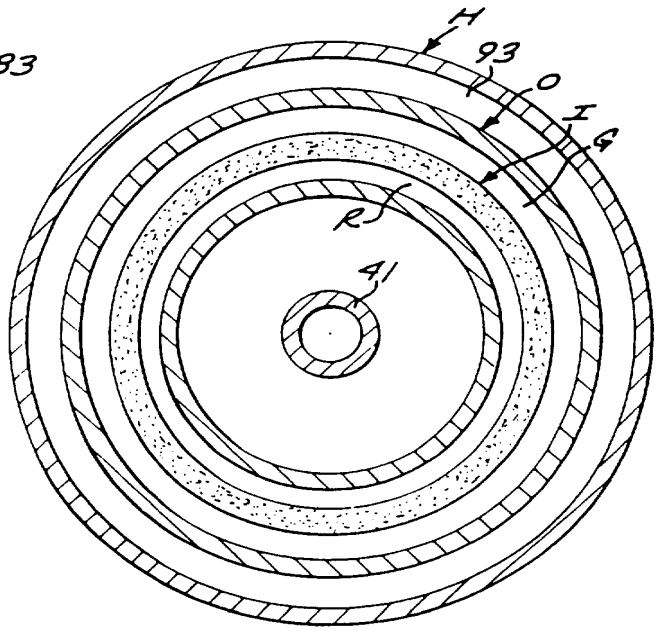
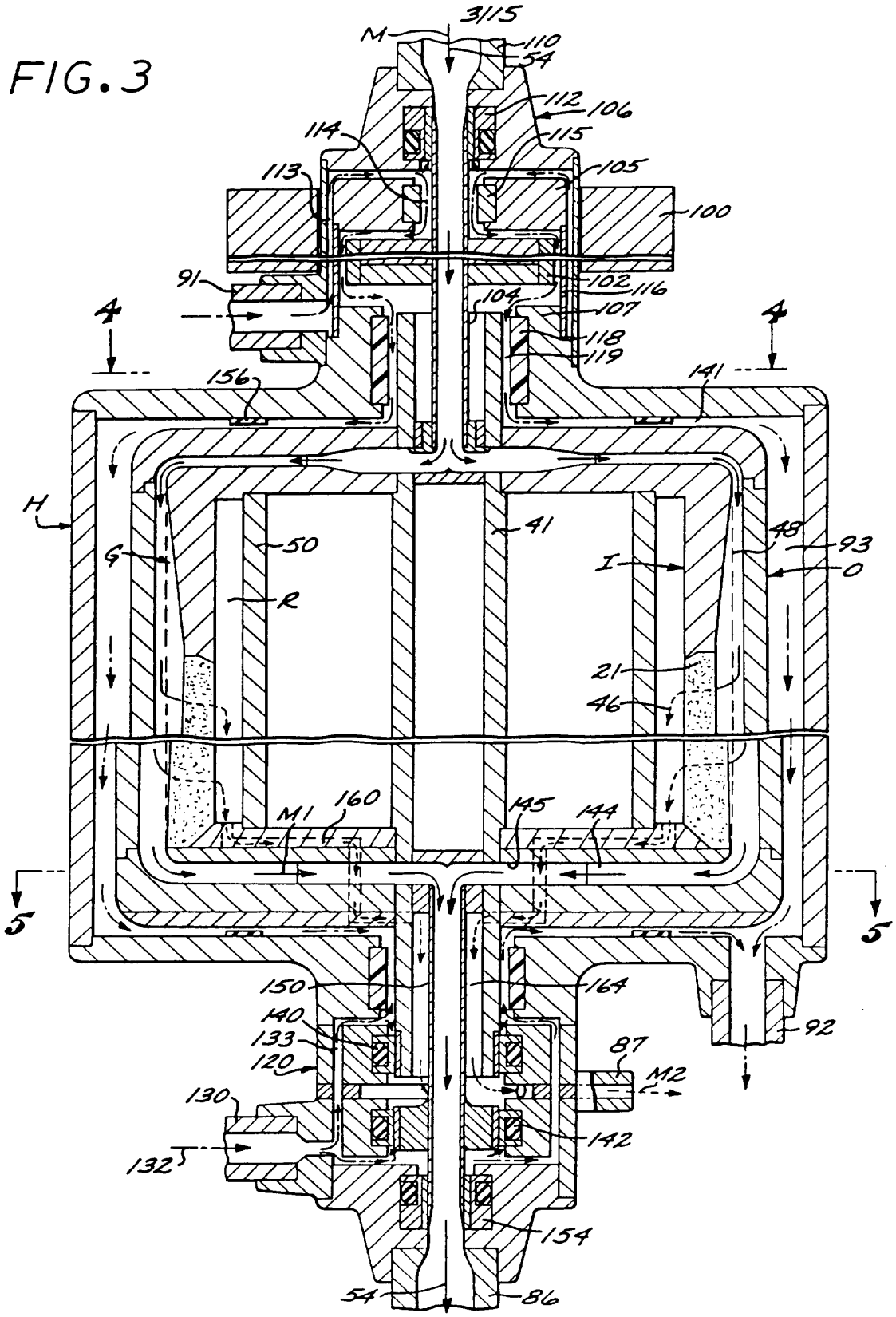


FIG. 2



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FIG. 3



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FIG. 4

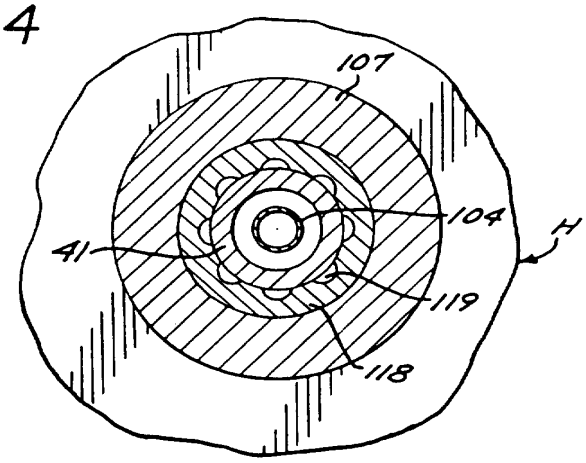
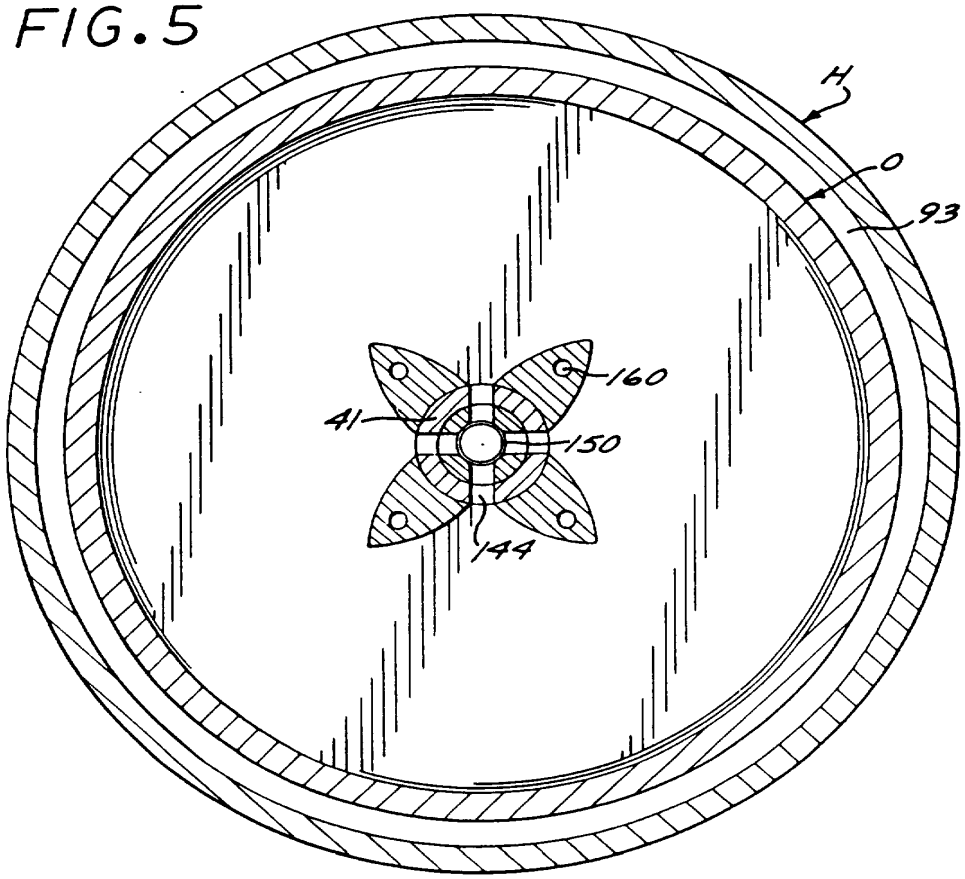


FIG. 5



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FIG. 6

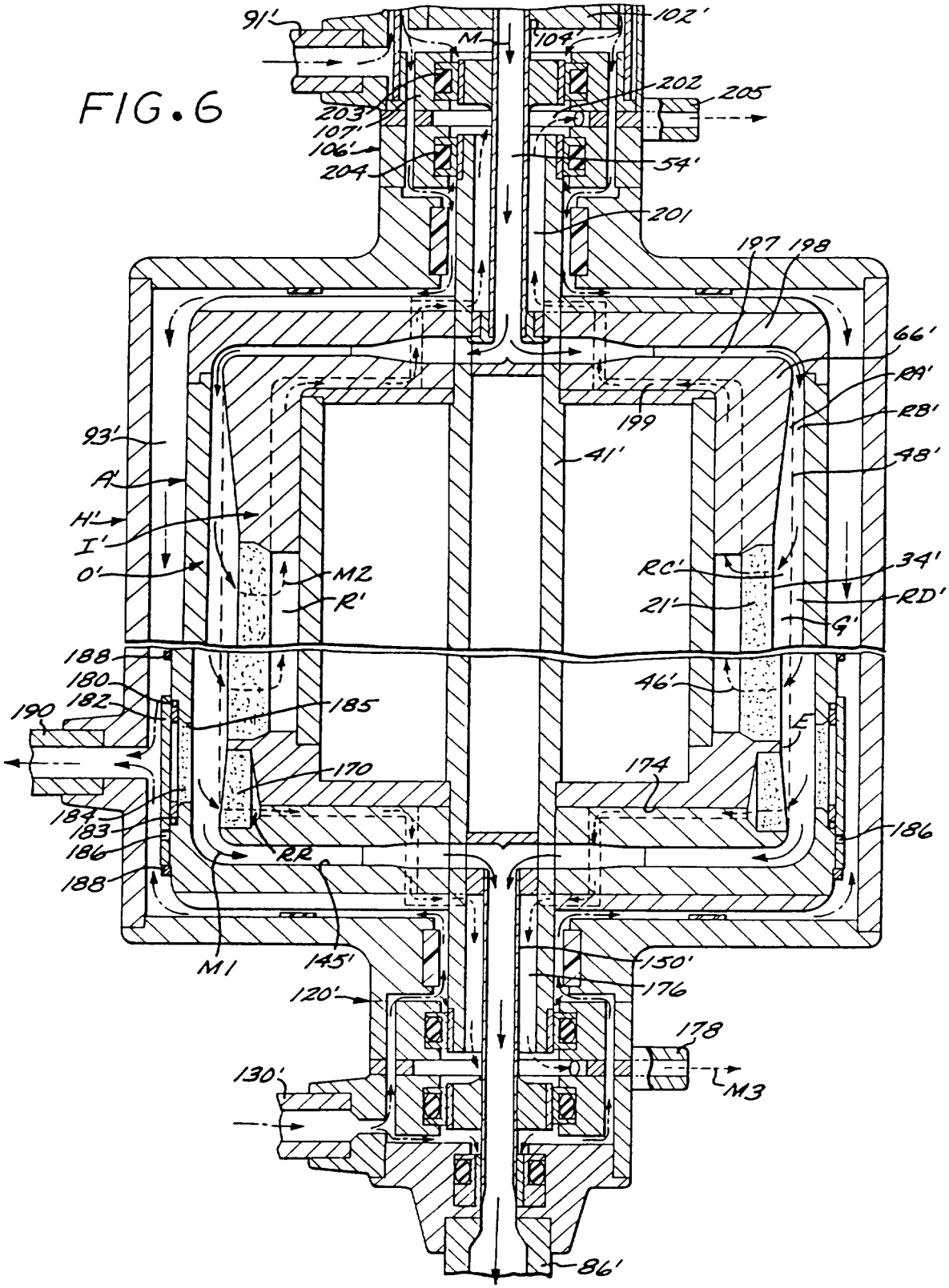

91'
M
104'
102'
202
205
203'
107'
106'
204
54'
201
197
198
66'
RA'
RB'
199
41'
48'
93'
A'
H'
I'
O'
M2
R'
RC'
34'
21'
RD'
G'
188
180
182
190
185
46'
E
170
174
184
183
186
188
RR
186
M1
145'
150'
176
120'
178
130'
M3
86'

FIG. 6A

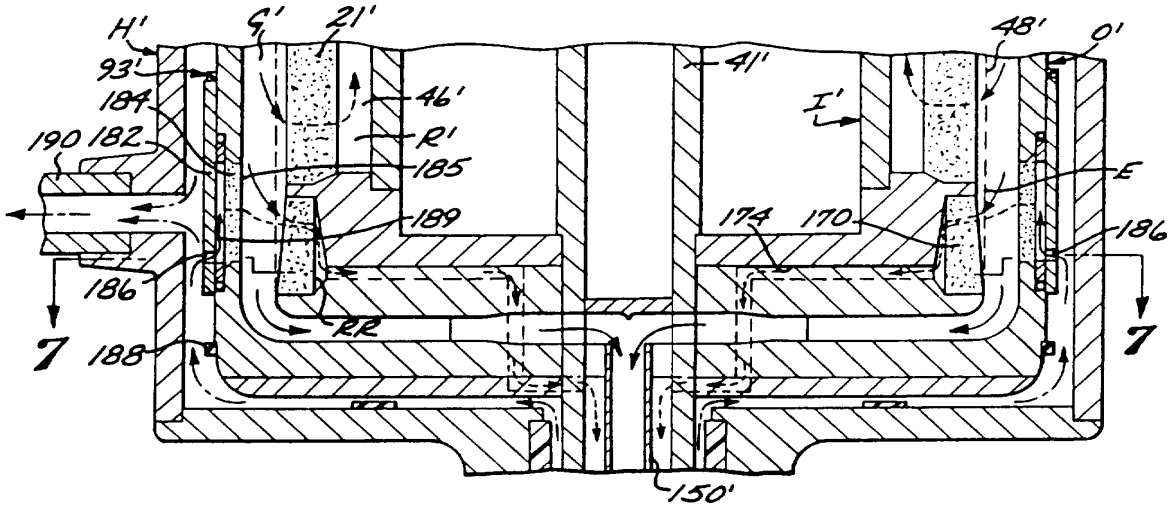
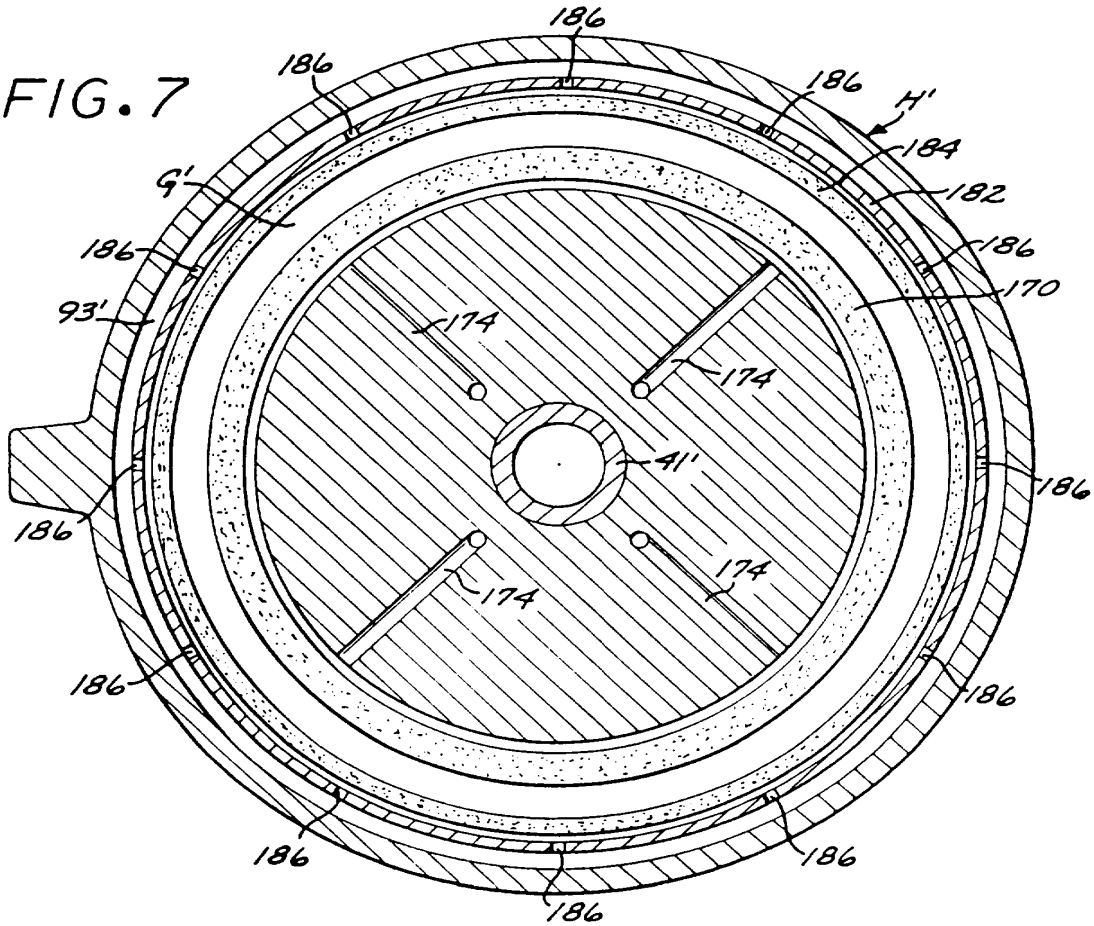
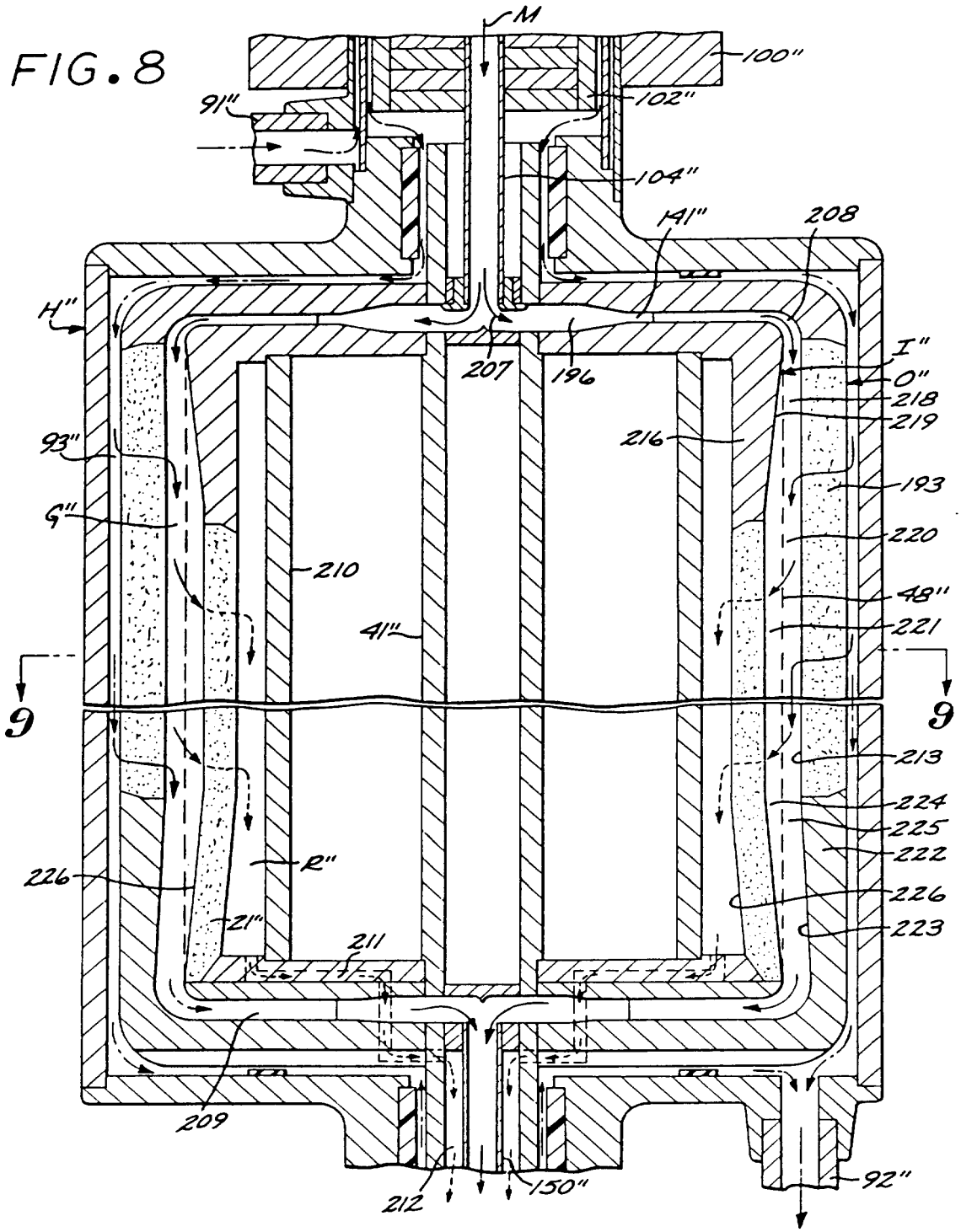


FIG. 7



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FIG. 8



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FIG. 9

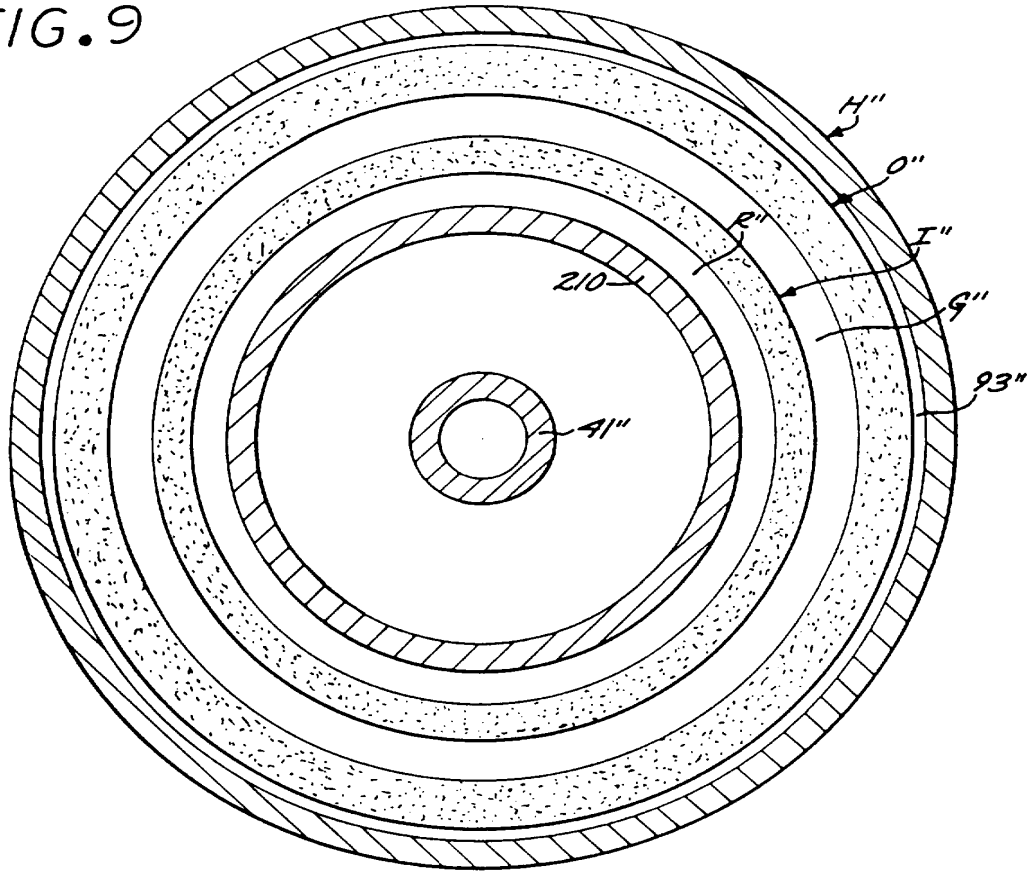
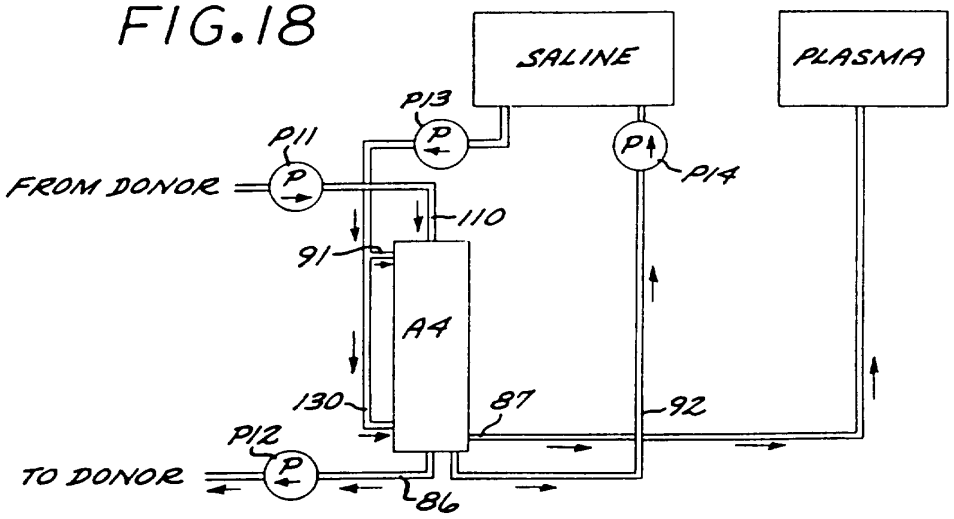

H"
O"
R"
I"
210
S"
93"
41"

FIG. 18


SALINE
PLASMA
P13
P11
P
P14
FROM DONOR
110
91
A4
130
87
92
P12
TO DONOR
86

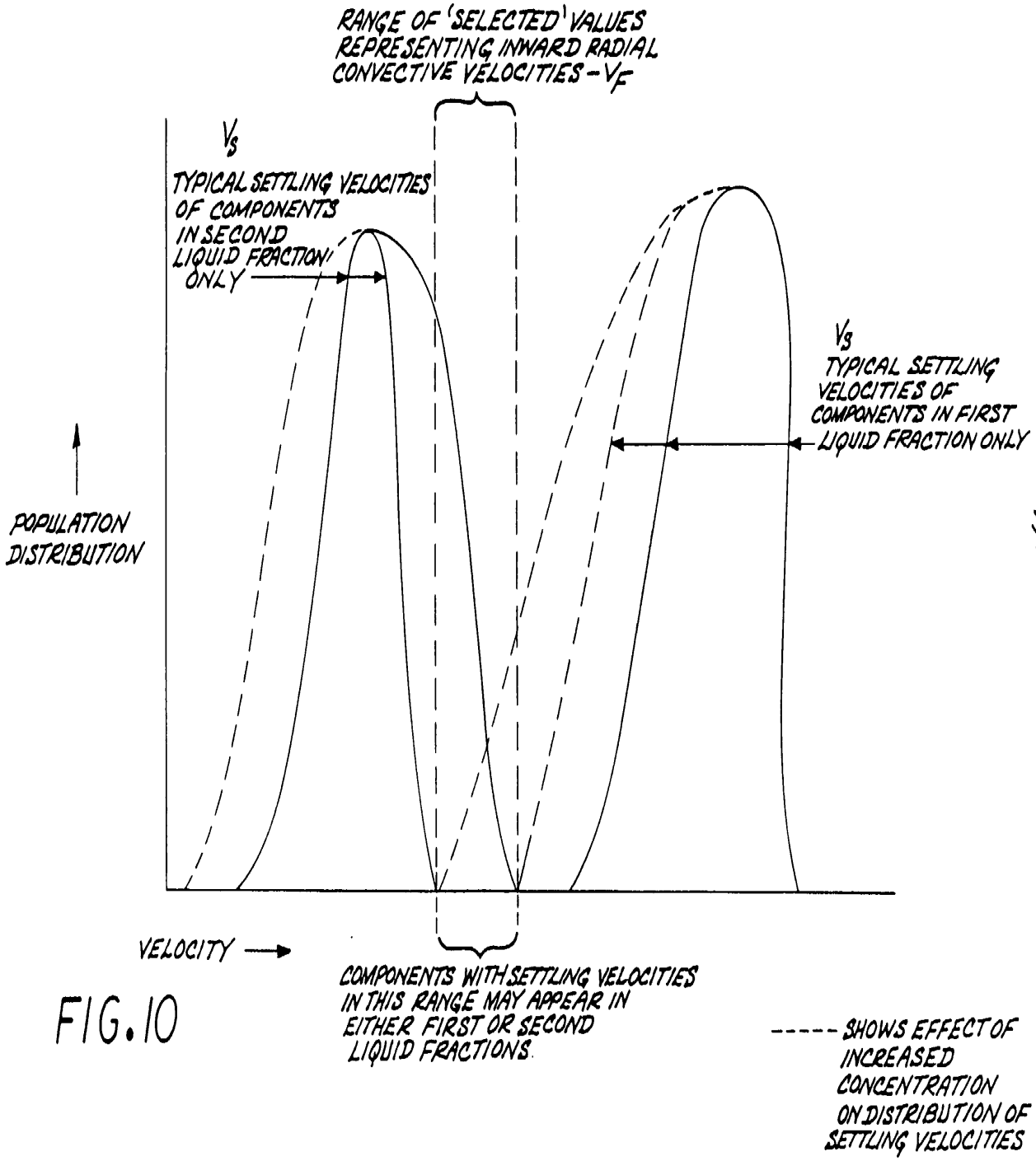


FIG. 10

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FIG.11

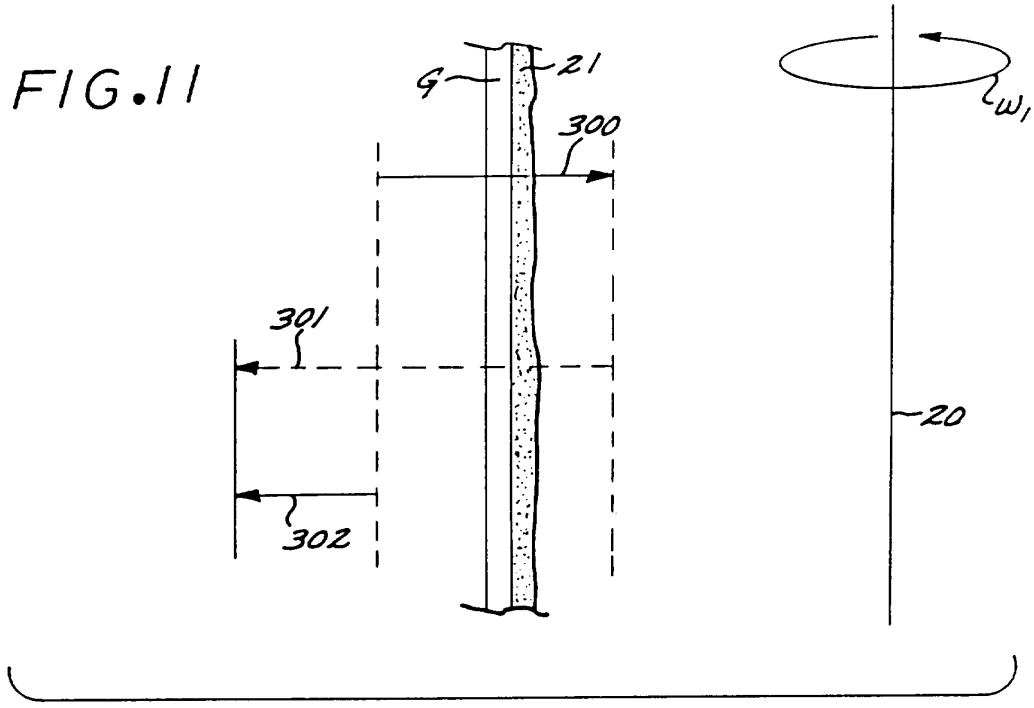
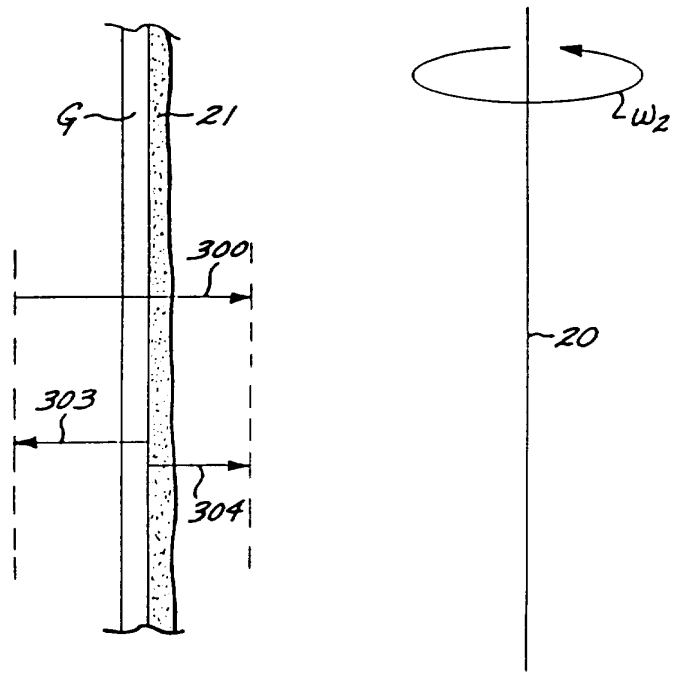


FIG.12



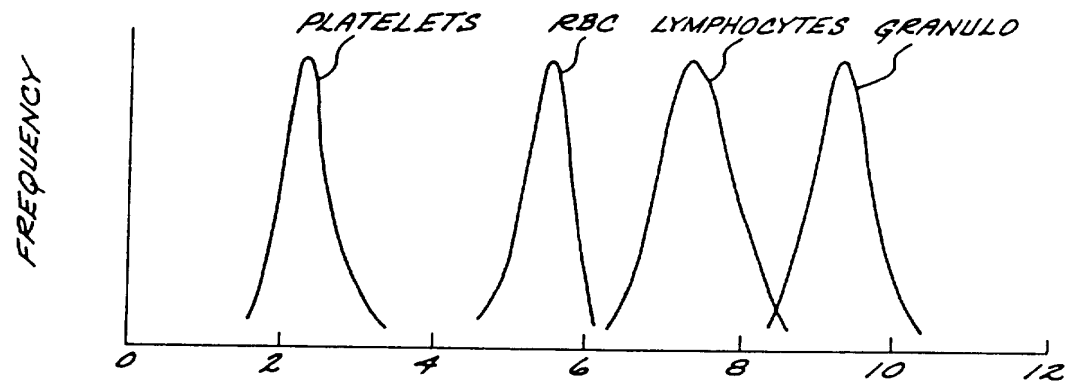


FIG.13

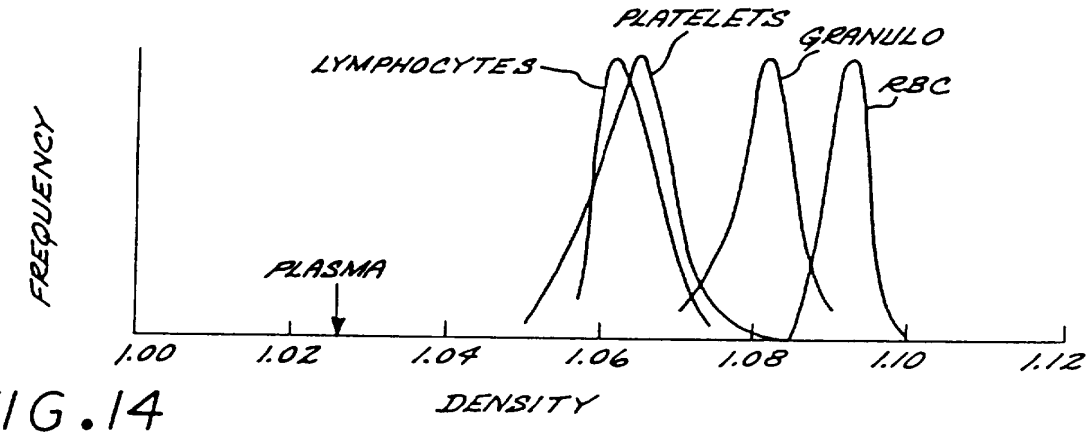


FIG.14

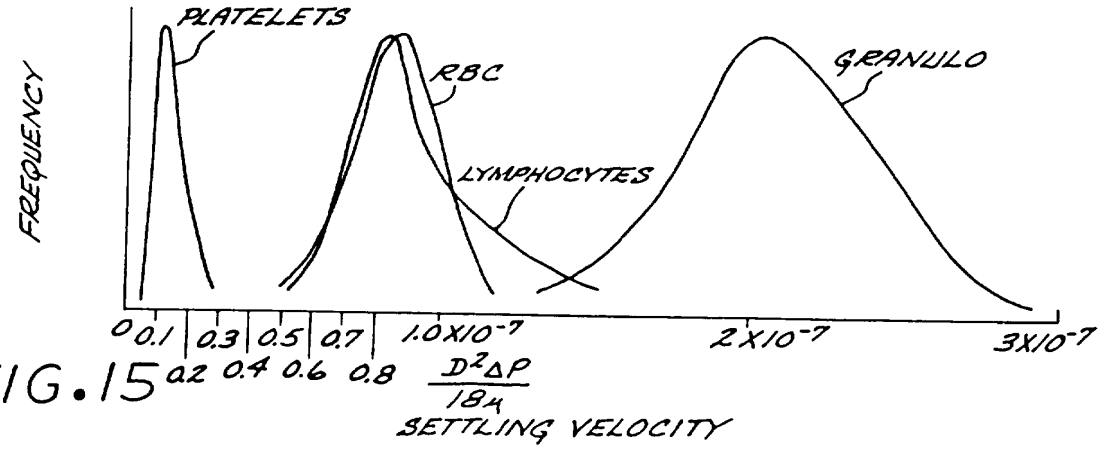


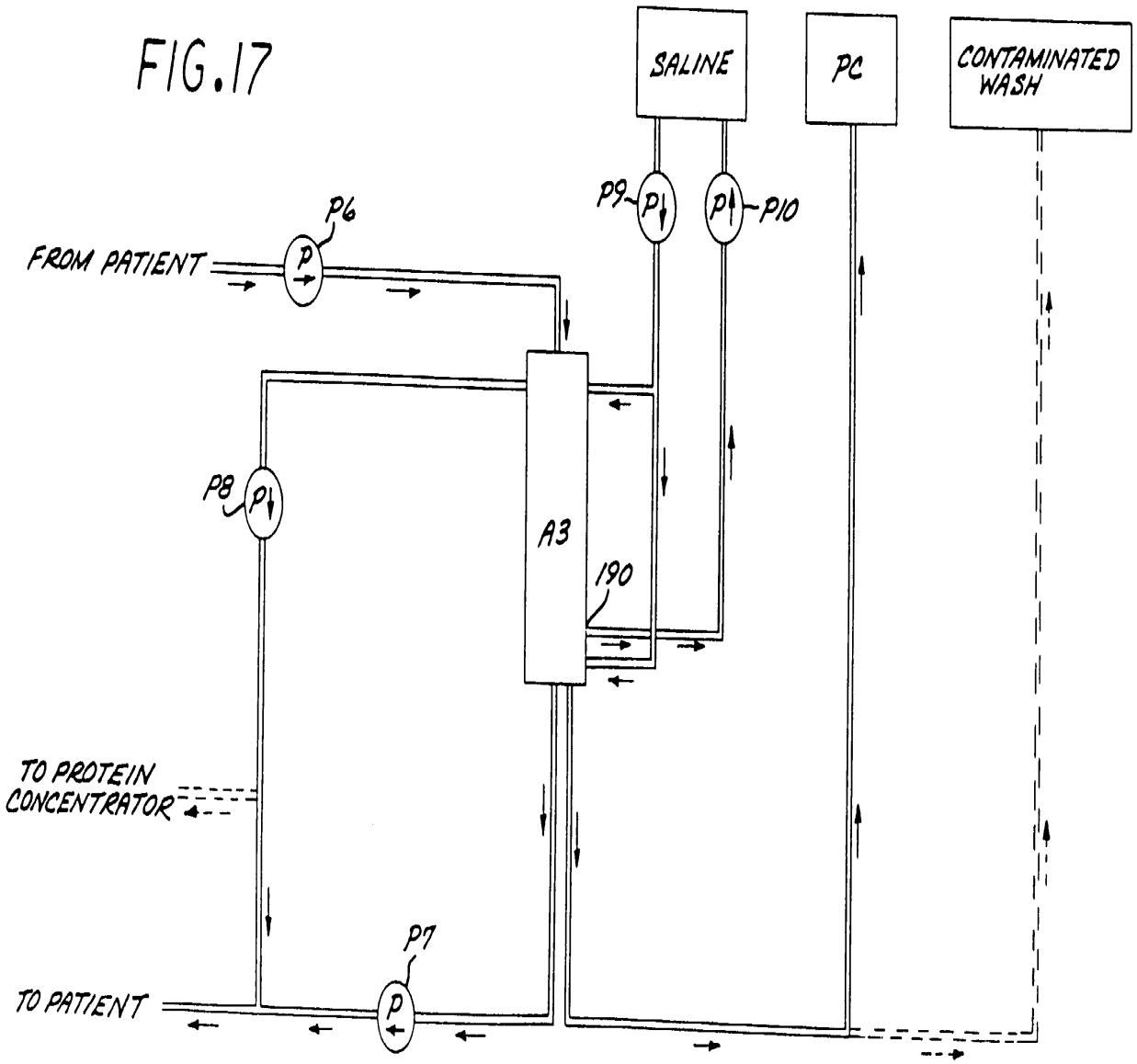
FIG.15

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FIG.16

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FIG.17

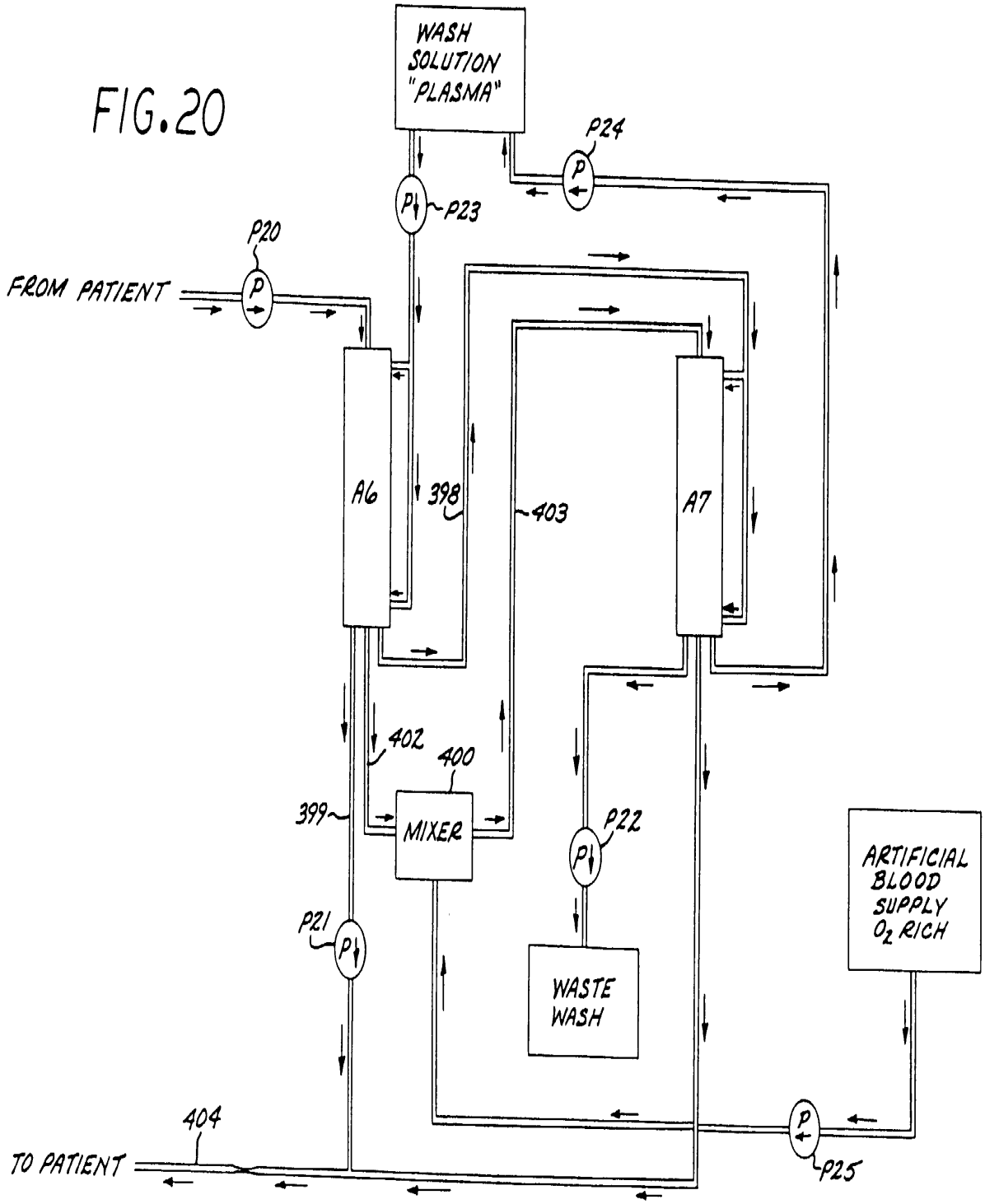


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FIG.19

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FIG.20



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/08523

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :B01D 33/00, 61/00
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US, A, 5,034,135 (Fischel) 23 July 1991 See entire document	1-5,8-19,21-31,33-34 --- 20
X -- Y	US, A, 4,871,462 (Fischel et al.) 3 October 1989 See entire document	1-3,6-7 --- 32

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 DECEMBER 1993	Date of mailing of the international search report 16 DEC 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer SUN UK KIM Telephone No. (703) 308-2350

Form PCT/ISA/210 (second sheet)(July 1992)*

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Petitioner Terumo Exhibit 1021-0793

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/08523

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

210/87, 90, 97, 134, 177, 178, 195.2, 216, 252, 258, 321.67, 321.68, 321.87, 324, 359, 360.1, 483, 497.01, 497.3, 512.1, 650, 651, 782, 787; 436/177, 178; 604/4, 5, 6

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

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BLOOD PROCESSING SYSTEM

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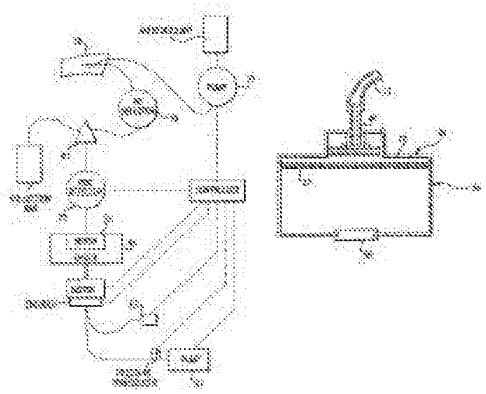
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Abstract of WO9611747 (A2)

A rotor (2a-2e) for collecting and centrifuging biological fluids in a range of volumes. The rotor includes an elastic impermeable diaphragm (31) which defines at least a portion of a variable-volume processing chamber (30), where the fluid is centrifuged. The rotor includes a rigid mounting member (28), to which the diaphragm is mounted and which is held and spun by a chuck. Preferably, this rigid mounting member includes a boundary wall (10) which together with the elastic diaphragm defines the



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chamber. The boundary wall may be a substantially imperforate circular wall which extends to the periphery of the processing chamber but defining one opening, preferably near the axis of rotation, permitting a conduit (13) or conduits (83, 93, 163, 165, 188) to pass therethrough so as to be in fluid communication with the processing chamber. The rotor may include a separate structure (40, 190, 244) for controlling the flow of liquid out of the chamber into the conduit. In a preferred embodiment, this outlet-control structure is a perforate, substantially rigid wall or plate (40), located within the processing chamber and mounted adjacent the rigid boundary wall. In an alternative embodiment, the outlet-control structure for controlling flow from the processing chamber to the conduit may include at least one tube or preferably a set of tubes (190), wherein each tube provides fluid communication between the chamber and the conduit. In one preferred embodiment, grooves (244) in the boundary wall may be used as the outlet-control structure.

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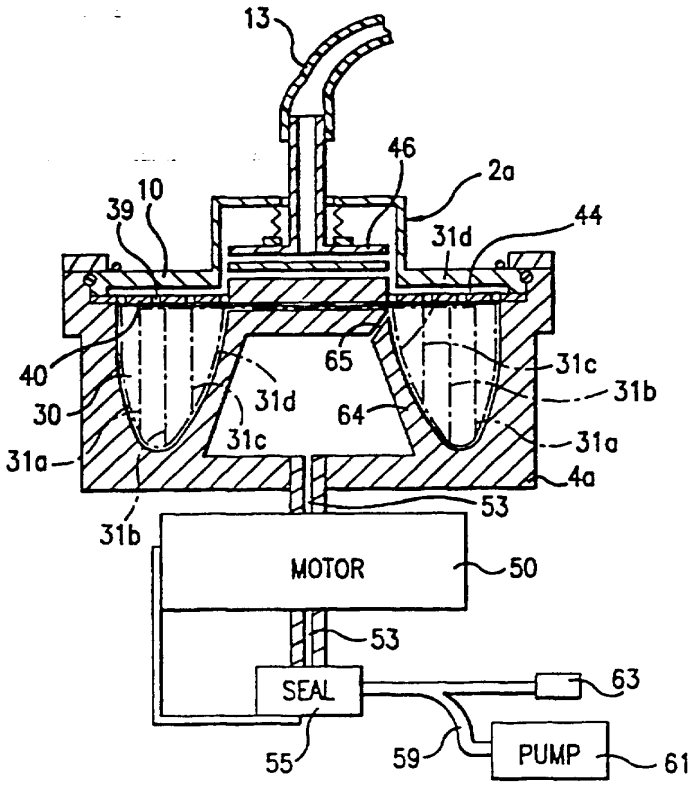
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(57) Abstract

A rotor (2a-2e) for collecting and centrifuging biological fluids in a range of volumes. The rotor includes an elastic impermeable diaphragm (31) which defines at least a portion of a variable-volume processing chamber (30), where the fluid is centrifuged. The rotor includes a rigid mounting member (28), to which the diaphragm is mounted and which is held and spun by a chuck. Preferably, this rigid mounting member includes a boundary wall (10) which together with the elastic diaphragm defines the chamber. The boundary wall may be a substantially imperforate circular wall which extends to the periphery of the processing chamber but defining one opening, preferably near the axis of rotation, permitting a conduit (13) or conduits (83, 93, 163, 165, 188) to pass therethrough so as to be in fluid communication with the processing chamber. The rotor may include a separate structure (40, 190, 244) for controlling the flow of liquid out of the chamber into the conduit. In a preferred embodiment, this outlet-control structure is a perforate, substantially rigid wall or plate (40), located within the processing chamber and mounted adjacent the rigid boundary wall. In an alternative embodiment, the outlet-control structure for controlling flow from the processing chamber to the conduit may include at least one tube or preferably a set of tubes (190), wherein each tube provides fluid communication between the chamber and the conduit. In one preferred embodiment, grooves (244) in the boundary wall may be used as the outlet-control structure.



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BLOOD PROCESSING SYSTEM

DESCRIPTION

Technical Field

This invention generally relates to systems for processing blood and other biological fluids.

Background Art

Centrifugal biological-fluid-processing systems have been in existence for some time. Some are used to collect high concentrations of certain components of a person's blood while others are used to further process blood components by washing, concentrating or otherwise purifying the blood component of interest. Some of these systems are used to process biological fluids other than blood. Filtration systems are also used for processing blood and other biological fluids.

The centrifugal systems (hereinafter called blood-processing systems) generally fall into two categories, continuous-flow devices and discontinuous-flow devices.

In continuous-flow systems, whole blood from the donor or patient flows through one conduit into the spinning rotor where the components are separated. The component of interest is collected and the unwanted components are returned to the donor through a second conduit on a continuous basis as more whole blood is being drawn. Because the rate of drawing and the rate of return are substantially the same, the extracorporeal volume, or the amount of blood that is out of the donor or patient at any given time in the procedure, is relatively small. These systems typically employ a belt-type rotor, which has a relatively large diameter but a relatively small (typically 100 ml or less) processing volume. Although continuous-flow systems have the advantage that the amount of blood that must be outside the donor or patient can be relatively

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small, they have the disadvantage that the diameter of the rotor is large. These systems are, as a consequence, large; furthermore, they are complicated to set up and use. These devices are used almost exclusively for the collection of platelets.

In discontinuous-flow systems, whole blood from the donor or patient also flows through a conduit into the rotor where component separation takes place. These systems employ a bowl-type rotor with a relatively large (typically 200 ml or more) volume that must be filled with blood before any of the desired components can be harvested. When the bowl is full, the drawing of fresh blood is stopped, and the unwanted components are returned to the donor or patient through the same conduit intermittently, in batches, rather than on a continuous basis. When the return has been completed, whole blood is again drawn from the donor or patient, and a second cycle begins. This process continues until the desired amount of component has been collected.

Discontinuous-flow systems have the advantage that the rotors are relatively small in diameter but have the disadvantage that the extracorporeal volume is large. This, in turn, makes it difficult or impossible to use discontinuous systems on people whose size and weight will not permit the drawing of the amount of blood required to fill the rotor. Discontinuous-flow devices are used for the collection of platelets and/or plasma, and for the concentration and washing of red blood cells (RBCs). They are used to reconstitute previously frozen RBCs and to salvage RBCs lost intraoperatively. Because the bowls in these systems are rigid and have a fixed volume, however, it is difficult to control the hematocrit of the final product, particularly if the amount of blood salvaged is insufficient to fill the bowl with RBCs.

One RBC-washing system marketed by Cobe Laboratories is made almost entirely of flexible PVC. It has the advantage of being able to vary the volume of the rotor to control the final hematocrit but has the disadvantage of being limited

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to a rather flat, wide pancake-like shape due to manufacturing constrictions. The Cobe system controls the rotor volume by pumping a hydraulic fluid--a liquid--in or out of a bladder that rotates with and squeezes the blood out of rotor. The Cobe system takes up a fairly large amount of space, and its flexible pancake-shaped rotor is awkward to handle. The Cobe system does not permit blood to flow into and out of its rotor at the same time. The Cobe system also does not permit blood to be pulled into the rotor by suction. The Cobe rotor is usually filled with blood by gravity, although the blood may be pumped into the rotor. After the blood has been separated, it is squeezed out of the rotor by pumping hydraulic fluid into the bladder.

Haemonetics Corp. and others have provided systems to collect blood shed during surgery, concentrate and wash the RBCs, and return them to the patient. Existing systems typically use a 3 liter reservoir to collect and coarse filter the blood vacuumed from the surgical site and a separate processing set including a special centrifugal processing chamber to wash and concentrate the red blood cells in order that they may be safely reinfused to the patient. Because of their cost and complexity of use, these systems are used only in operations where relatively large blood loss is expected. The prior-art rotors used for processing blood collected during an operation, made by Haemonetics Corp. and others, must be completely filled with RBCs before any processing can occur, and thus the process takes more time and is not appropriate for use with small people or for an operation with low blood loss. Because the volume of the processing chamber is fixed, the final concentration of the RBCs in the last cycle of the process cannot be easily controlled.

Solco Basel AG makes a filter-based system for wound drains. This wound-drain system has the disadvantage that the blood returned to the patient contains, in addition to the RBCs, substances that may be deleterious to the patient.

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There exists the need, therefore, for a centrifugal system for processing blood and other biological fluids, that is compact and easy to use and that does not have the disadvantages of prior-art discontinuous-flow systems. There is also a need for improving the way that blood is processed in a variety of applications, such as apheresis, intraoperative blood-salvage systems, and wound drains, so that the blood processing takes less time, requires less cumbersome equipment, and/or reduces harmful side effects in the patient or donor.

Summary of the Invention

The present invention provides a container, referred to herein as a rotor, which may be used for collecting and centrifuging biological fluids in a range of volumes. The rotor includes an elastic impermeable wall (diaphragm) which defines at least a portion of a variable-volume processing chamber, where the fluid is centrifuged. The rotor includes a rigid mounting member, to which the diaphragm is mounted and which is held and spun by a chuck. Preferably, this rigid mounting member includes a wall which together with the elastic diaphragm defines the chamber.

This diaphragm and rigid wall are both referred to herein as boundaries, since each defines a portion of the boundary of the variable-volume processing chamber and each has one side which does not come into contact with the biological fluid. In some embodiments, the diaphragm may be located inside other walls on the exterior of the rotor, such as the rigid boundary wall or an exterior shell.

The rigid boundary wall may be large enough to surround the maximum volume that may be taken up by the chamber, or the rigid mounting member may be only large enough to provide a place where the diaphragm may be mounted and where a chuck can hold and spin the rotor. In a preferred embodiment, the rigid boundary wall is a substantially imperforate circular wall which extends to the periphery of the processing chamber, so as to define the top of the

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processing chamber; the diaphragm is attached to the perimeter of the wall and defines the remainder of the processing chamber.

As noted above, the rigid wall in one embodiment surrounds the chamber, and the diaphragm is located inside a portion of the rigid boundary wall. In one version of this embodiment, the rotor includes a core located inside the rigid boundary wall and the chamber, and the diaphragm is mounted about the core.

In a preferred embodiment, the rigid boundary wall is substantially imperforate but defines one opening, preferably near the axis of rotation, permitting a conduit or conduits to pass therethrough so as to be in fluid communication with the processing chamber. In another alternative embodiment, the rigid boundary wall has a plurality of openings for controlling the flow into and/or out of the rotor while the rotor is being spun.

Preferably, the rotor includes a separate structure for controlling the flow of liquid out of the chamber into the rotor's (outlet) conduit. In a preferred embodiment, this outlet-control structure is a perforate, substantially rigid wall or plate, located within the processing chamber and mounted adjacent the rigid boundary wall. Since it is located within the processing chamber, and both of its sides come into contact with the biolcgical fluid, this perforate wall is referred to as an interior wall. The perforate interior wall preferably extends substantially to the periphery of the chamber, although in other embodiments it may have a smaller diameter. Although in a preferred embodiment the perforate wall has many holes, in alternative embodiments the perforate wall may have holes located only at a discrete radius or at discrete radii from the axis of rotation. The interior wall may also serve the purpose of protecting the elastic membrane from being abraded from a non-rotating portion of the rotor while the body of the rotor is spun.

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In an alternative embodiment, the outlet-control structure for controlling flow from the processing chamber to the conduit includes at least one tube or preferably a set of tubes, wherein each tube provides fluid communication between the chamber and the conduit. The tubes used as the outlet-control structure may have holes along their length to provide additional points of entry for fluid from the processing chamber. In some versions of the rotor, the tube or tubes provide fluid communication from a variety of radii within the chamber; in other versions, the tube or tubes provide fluid communication from a discrete radius or discrete radii within the chamber.

In another preferred embodiment, the outlet-control means may include vertical walls that define channels. These channels may be grooves formed in the interior surface of the rigid boundary wall. As long as the vertical channel walls are spaced close enough to each other (i.e., as long as the grooves are narrow enough), the channels (grooves) will remain open even though the processing chamber is at its lowest volume and the elastic membrane is pressed against the bottom of the vertical walls. Such channels can provide fluid communication to the rotor's outlet conduit from the periphery of the processing chamber to the innermost radius of the processing chamber and all the points in between. The grooves can be shortened so as to provide fluid communication to the outlet conduit from just those points between two radii within the chamber.

In one embodiment of the rotor, a single conduit passes through a portion of the rotor that does not rotate during centrifugation--i.e., the rotor's fixed portion. The fixed portion passes through the rigid boundary wall, and the rigid boundary wall is rotatably mounted around the fixed portion. In another embodiment, two or more conduits pass through a portion of the rotor that does not rotate during centrifugation. This embodiment permits unseparated fluid to flow into the spinning rotor through one conduit, while separated fluid can flow out of the rotor through the other

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conduit. This embodiment of the rotor may further include a substantially imperforate interior wall, mounted between the boundary wall and the perforate interior wall and around the fixed portion, so as to provide a channel permitting fluid to flow from the rotor's input conduit to the chamber's periphery. This substantially imperforate interior wall does define a center hole through which the rotor's fixed portion passes. The substantially imperforate interior wall may be considered an inlet-control structure which controls the flow of fluid into the rotor--in this case directing the fluid to the rotor's periphery.

Alternative embodiments of the rotor do not have a fixed portion. The conduits extending from these embodiments of the rotor thus spin with the rest of the rotor during centrifugation. A rotary seal may be located at some point in the tubing connecting the rotor with the rest of the processing set. Alternatively, a skip-rope system may be used in lieu of a rotary seal.

The embodiments of the rotor having a fixed portion preferably include a rotary seal that has a base, a spring member, first and second seal faces, which spin in relation to each other, and a flexible seal member. The spring is mounted on the base, and the first seal face is mounted on the spring member so that the spring member presses the first seal face against the second seal face. The seal member prevents flow between the first seal face and the base. Preferably, the flexible seal member and the first seal face are disposed so that the force with which the spring member presses the first seal face against the second seal face is not adversely affected by pressure within the rotor. In a preferred embodiment, the flexible seal member and the spring member are separate members, although they may be made out of different portions of the same piece of material. Alternatively, if the flexible seal member is resilient and rigid enough to apply the proper force between the first and second seal faces, a separate spring member may not be necessary.

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In one embodiment, the rotary seal's base is part of the rotor's fixed portion, and the rotary seal's second seal face is attached to the rigid mounting member, which is part of the rotating portion of the rotor. Alternatively, the rotary seal's base may be part of the rotor's rigid mounting member, and the rotary seal's second seal face is attached to the rotor's fixed portion.

The rotor may be spun in a centrifuge system that includes a chuck for holding and spinning the rotor and a pressurized fluid supply for supplying a pressurized control fluid--preferably gas--adjacent the rotor's diaphragm, while the rotor is being spun. The pressurized gas may be used to force fluid out of the rotor's processing chamber. The system preferably includes means for applying a vacuum to the exterior side of the diaphragm (i.e., the side that does not come into contact with the fluid being processed), so as to draw fluid into the processing chamber. In one embodiment, for use with a rotor where the diaphragm is mounted along the bottom of a substantially flat, circular boundary wall, the chuck has extending from a rotatable base an outer peripheral wall, so as to define a cylindrical cavity into which the diaphragm may expand. In one version of this chuck embodiment, the chuck also has extending from its base a core, so that the chuck defines an annular cavity into which the diaphragm may expand. In another embodiment, for use with a rotor that has a core in the rotor's interior, the chuck has extending from a rotatable base a nozzle, through which the pressurized gas is provided through the rotor's core to an area adjacent the rotor's diaphragm. Another embodiment of the chuck holds the rotor from inside a rigid core in the rotor.

In order to make the rotor more portable while biological fluid is being collected in the rotor, a rigid, airtight exterior shell may be attached and sealed to the rigid boundary wall. In one embodiment, the shell may be removably attached to the rotor. The shell permits a vacuum to be applied to the exterior side of the diaphragm when the

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rotor is not in a chuck. Thus, fluid may be drawn into the processing chamber when the rotor is not in a chuck. A spring bellows may also be used to create a vacuum against the diaphragm.

The system may also include a control system for controlling the rotational speed of the chuck and the gas pressure provided by the gas supply to achieve the most advantageous combination of centrifugal force for separation and gas pressure against the diaphragm required to force fluid out of the rotor. The control system may be programmed to determine the volume of the processing chamber based on the rotational speed of the chuck and the air pressure provided by the chuck.

The rotor and centrifuge systems of the present invention may be used in many different processes involving biological fluid. A method for using the rotor would generally include the steps of introducing an unseparated fluid into the rotor's processing chamber, spinning the rotor so as to separate the fluid into denser and lighter components, and applying pressure to the diaphragm's exterior side so as to force a fluid component--usually the lighter fluid components--through the conduit.

Further aspects of the present invention will be apparent from the following description of specific embodiments, the attached drawings and the appended claims.

Brief Description of the Drawings

FIG. 1 is a top plan view of a rotor according to the present invention.

FIG. 2 shows a cross-section of the rotor shown in FIG. 1.

FIG. 3 shows a cross-section of the FIG. 2 rotor and a chuck for holding and spinning the rotor.

FIG. 4 shows a cross-section of the rotor and chuck system of FIG. 3 showing the shapes of the diaphragm with varying volumes of blood in the rotor.

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FIG. 5 is a perspective view of a system that may use the rotor in post-operative salvage (i.e., with a wound drain).

FIG. 6 is a schematic of a system to utilize the rotor as a donor-connected apheresis system for the collection of plasma or RBC.

FIG. 7 shows a cross-section of a rotor with an exterior shell.

FIG. 8A shows a cross-section of a rotor with an alternative exterior shell.

FIG. 8B shows a cross section of the rotor shown in FIG. 8A mounted on a chuck located within the core of the rotor's shell.

FIG. 9 shows a cross-section of the FIG. 2 rotor in an alternative chuck.

FIG. 10 is a top plan view of a two-conduit rotor.

FIG. 11 shows a cross-section of the FIG. 10 rotor.

FIG. 12 shows the FIG. 11 rotor mounted in a chuck.

FIG. 13 shows a cross-section of the FIG. 12 rotor and chuck system showing the shapes of the diaphragm with varying volumes of blood in the rotor.

FIG. 14 is a perspective view of a system used in RBC apheresis.

FIG. 15 is a schematic of a system for RBC apheresis.

FIGS. 16-18 show cross-sections of several alternative rotors having varying configurations of interior walls and fixed portions.

FIGS. 19A-19D show how an alternative rotor may be used to collect platelets.

FIG. 19E shows a rotor that may be used to collect the separated fluid component with the greatest density.

FIG. 20 shows a cross-section of an alternative rotor having a balloon-shaped diaphragm mounted around a core.

FIG. 21 shows a cross-section of the FIG. 20 rotor mounted in a chuck.

FIG. 22 shows a cross-section of the FIG. 21 system centrifuging blood.

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FIG. 23 shows a cross-section of an alternative two-conduit rotor.

FIG. 24 shows a cross-section of a modified version of the FIG. 23 rotor.

FIG. 25 shows cross-section of the FIG. 24 rotor mounted in a chuck.

FIG. 26 shows a cross-section of the FIG. 25 system centrifuging blood.

FIG. 27 shows a cross-section of the FIG. 25 system after centrifuging blood.

FIG. 28 is a schematic showing how an alternative rotor may be used to process blood.

FIG. 29 is a cross-section of the rotor shown in FIG. 28 and a portable device for applying a vacuum.

FIG. 30 shows an alternative rotor having a set of tubes, in lieu of a perforate interior wall, for controlling the flow from the processing chamber.

FIG. 31 shows a variation of the rotor shown in FIG. 30, wherein the tubes leading from the processing chamber remain separate.

FIG. 32 is a top plan view of a rotor having a set of radially mounted tubes in lieu of a perforate interior wall.

FIG. 33 shows a cross-section of the FIG. 32 rotor.

FIG. 34 shows a cross-section of a rotor having a fixed portion and a set of radially mounted tubes in lieu of a perforate interior wall.

FIGS. 35 and 36 show respectively a cross-section and a top plan view of a rotor having a fixed portion, a set of radially mounted tubes and a diaphragm that covers most of the top of the rotor.

FIG. 37 shows a cross-section of a rotary seal representative of prior-art rotary seals.

FIG. 38 shows a cross-section of an improved rotary seal, which may be used in the rotors disclosed herein that have fixed and rotating portions.

FIG. 39 shows a detail of an alternative rotary seal, wherein the spring and the flexible seal member and the

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spring are formed out of different portions of the same piece of material.

FIG. 40 shows an alternative rotor having a hemispherical boundary wall.

FIG. 41 shows a bottom view of a preferred rotor embodiment without its diaphragm.

Fig. 42 shows a cross-section of the FIG. 41 rotor with its diaphragm.

Description of Specific Embodiments

FIGS. 1 and 2 show a version of the centrifuge rotor **2a** according to the present invention. The rotor **2a** has an elastic boundary, i.e., an impermeable diaphragm **31**, which is sealed to a rigid, imperforate boundary wall **10** by an O-ring **35** or other means. The diaphragm **31** is preferably made of an elastic, stretchable and resilient material, such as latex or silicone rubber. A perforate interior wall **40**--also referred to as a plate--having holes **39** is attached under the rigid boundary wall **10**. Preferably, the boundary wall **10** and the interior wall **40** are made out of a rigid thermoplastic. The perforate interior plate **40** is held a short distance away from the imperforate boundary wall **10** by standoffs (not shown), thereby forming a passage **44**.

The rotor **2a** also has a collector assembly **46**, which is attached to tube **13**, and a rotary seal **48**, which maintains the sterile environment in the rotor **2a** but allows the rotor to turn even while the collector assembly is held stationary. The rotary seal **48** provides a seal between the collector assembly **46** and that portion **28** of the boundary wall **10** that surrounds the collector assembly **46**, while permitting the boundary wall **10** to spin around the collector assembly **46** while the collector assembly **46** is held in place.

Tube **13** is attached to the rest of the disposable processing set (tubing set), which may include a cassette (see item **15a** in FIG. 5). The tube **13** and the collector

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assembly **46** are held fixedly in place, while the rest of the rotor **2a**--the rigid boundary wall **10**, the diaphragm **31**, the plate **40** and any fluids in the variable-volume processing chamber--is spun. Although otherwise imperforate, the boundary wall **10** does of course define a central opening through which the collector assembly **46** can extend to connect with the tube **13**.

A variable volume is defined in the rotor **2a** between the boundary wall **10** and the diaphragm **31**. This variable volume is the processing chamber where the blood is centrifuged and separated. The processing chamber is sealed in by the boundary wall **10** and the diaphragm, so that during centrifugation the only fluid communication between the interior of the processing chamber and outside of the rotor **2a** is through the conduit leading to tube **13**--or in the embodiments of the rotor having multiple conduits into and out of the rotor (such as those shown in FIGS. 11, 16-18, 19A-19D and 23) through the multiple conduits. The conduit or conduits providing fluid communication with the processing chamber pass through the rotor's fixed portion, which includes the collector assembly **46**.

The plate **40** is located within the processing chamber. It is desirable to minimize the volume of the processing chamber above the plate **40** (including the channel), so that as much fluid as possible can be forced out of the processing chamber when the diaphragm **31** is forced against the plate **40**. Nevertheless, the passage **44** needs to be wide enough so as to permit sufficiently unrestricted flow from the periphery to the center of the passage **44**, even when the diaphragm **31** is forced against the plate **40**.

The interior plate's holes **39** allow fluid communication between the areas of the chamber above and below the plate **40**. The holes **39** should be small enough to prevent the diaphragm **31** from protruding too far into the passage **44**. If they are too large, protrusions of the diaphragm **31** through the plate's holes **39** could restrict flow from the

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processing chamber's periphery to the center of the channel. The size and placement of the holes **39** may be varied in order to regulate the flow out of the rotor **2a** as the rotor **2a** is emptied.

If the holes **39** are too large and too close to the collector assembly **46**, the portions of the diaphragm could touch the fixed portion's collector assembly **46**. Allowing the diaphragm **31** to touch the collector assembly **46** can cause abrasion of the diaphragm if the body of the rotor **2a** is being spun while the collector assembly **46** is being held in place, and continual abrasion may cause the diaphragm **31** to eventually rupture. Thus, the plate **40**, as well as the top wall **10**, separate the spinning diaphragm **31** from the non-spinning tube **13** and the collector assembly **46**.

In use, the rotor **2a** is placed in a centrifuge chuck **4a** and held in place by clamp **8**, as shown in FIG. 3. O-ring **35** is pressed against an inside wall of the chuck **4a** to form an air tight seal. Of course, different configurations may be used in order to create a seal between the rotor **2a** and the chuck **4a**, such as the use of a lip seal **36** shown in FIG. 12.

In one preferred embodiment, the chuck **4a** has a core **64** which limits how far the diaphragm **31** can expand towards the rotor's axis of rotation. Holes **65** in the interior core portion **64** of the chuck **4a** allow a control gas, preferably air, to flow from a compressor/vacuum pump **61** to the area of the chuck **4a** exposed to the elastic wall **31** of the rotor **2a**. Channels extending from the holes **65** may be provided on the inner surface of the chuck, so as to allow air to flow from the holes **65** to various points adjacent the diaphragm **31** when the diaphragm is fully extended (as shown by line **31d** in FIG. 4). The chuck **4a** is turned by a motor **50** and shaft **51**. The shaft **51** has an axial through hole **53** and protrudes below the motor **50**. A rotary pneumatic seal **55** is attached to the shaft **51** and is held stationary by a brace **57**. The pneumatic rotary seal **55** is connected by tubing **59** to the

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compressor/vacuum pump **61** and to a controllable exhaust valve **63**.

Instead of a rotary pneumatic seal, the tubing **59** may be connected to a compartment attached and sealed to the bottom of the motor **50**, so that the bottom of the shaft **51** extends into the compartment; if the motor forms a substantially air-tight barrier enclosing the compartment, this arrangement can be used instead of the rotary pneumatic seal. Instead of using a dual-purpose pump to provide both positive and negative pressure, a separate compressor and vacuum pump may be used to create positive and negative pressures respectively. Alternatively, the negative pressure may be provided by the hospital's vacuum source, which may be supplied to the housing by a vacuum line, while the pump **61** creates the positive pressure.

In the rotor shown in FIG. 2, the imperforate, rigid boundary wall **10** has a diameter substantially equal to the largest diameter of processing chamber, i.e., the space defined by the chuck **4a**. In an alternative embodiment, the diameter of the rigid boundary wall **10** may be as small as the collector/rotary-seal area **28**. In a rotor having an imperforate wall **10** with a smaller diameter than the perforated interior plate **40**, the elastic diaphragm **31** is bent around the periphery of the plate **40** in order to cover that portion of the top of the plate **40** not covered by the imperforate wall **10**. (See for example FIG. 35, which shows a rotor that uses tubes to control the flow out of the processing chamber instead of a perforate interior wall.) The chuck for holding and spinning such a rotor should have a lid in order to keep the portion of the diaphragm **31** above the interior plate **40** in the proper shape when the rotor is spun and in order to maintain an air-tight seal. It is desirable that the rigid rotatable portion of the rotor be large enough so that the diaphragm **31** may be mounted on it and so that the chuck **4a** may grasp the rigid rotatable portion in order to spin the rotor. In rotors having small-

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diameter boundary walls, the perforate interior wall **40** or other structure for controlling the flow out of the processing chamber may be modified to fold out of the way when the rotor is being built or stored. During centrifugation, the perforate interior plate **40** should--in a preferred embodiment--extend to the periphery of the processing chamber in order to ensure that fluid can flow from the periphery of the processing chamber to the collector assembly **46**, even when the processing chamber is at its smallest volume.

It will be appreciated that using a rotor having a rigid boundary wall extending all the way to the largest diameter of the processing chamber, like that shown in FIG. 2, has the advantages of being easier to use and not requiring the use of a lid on the chuck.

FIG. 4 shows the rotor **2a** while it is spinning and while blood flows into the rotor **2a** from the rest of the disposable set. While the body of the rotor **2a** is spun by the chuck **4a**, the collector assembly **46**, including the conduit connected to tube **13**, is held in place by a brace (such as brace **11** shown in FIG. 5). When the blood touches either the boundary wall **10** or the interior plate **40**, it is propelled by centrifugal force towards the perimeter of the rotor **2a**. As more blood enters, it continues to be propelled to the perimeter eventually flowing through the holes in the interior plate **40**. As the volume of the blood and the processing chamber **30** increases, the diaphragm stretches to allow the blood to reach the furthest diameter and at some point takes on a shape shown by line **31a**. As blood enters the rotor, the air in the chuck **4a** that is displaced by the blood escapes through hole **65**, down the shaft hole **53** and out exhaust valve **63**. If necessary, the blood flow rate can be increased by a vacuum in the chuck **4a** generated by the pump **61** or a separate vacuum supply (such as a separate vacuum pump or the hospital vacuum provided through a vacuum line). As more and more blood enters the

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rotor **2a**, the diaphragm changes shape to accommodate the blood. As it is filled further, the diaphragm takes on the shapes shown by line **31b** and line **31c** and finally, when the rotor is full, takes on the shape of the chuck interior, as shown by line **31d**.

As the diaphragm stretches to accommodate the expanding size of the processing chamber **30**, it comes into contact with the chuck in a sequential manner. As successive portions of the diaphragm come into contact with the chuck, they may become immobilized and cease to stretch, while those portions of the diaphragm that have not yet come into contact with the chuck continue to stretch, with the consequence that portions of the diaphragm may be subjected to greater stretching than other portions. In order to avoid rupturing of the diaphragm when the processing chamber **30** is filled with blood, the chuck **4a** may be shaped so as to minimize variations in the amount of stretching between different portions of the diaphragm.

FIG. 5 shows a system, according to the present invention, for recovering blood drawn by vacuum into a tube **17** from a wound drain. A filter **26** may be provided in the tube **17**. This type of system is known as post-operative salvage. A preferred embodiment of the system includes a housing **6**, having a small footprint of approximately 8 inches by 11 inches and a height of only about 10 inches. For some applications, even smaller systems, with smaller rotors, may be used. The rotor **2a** is held in the chuck, such as the chuck shown in FIGS. 3 and 4, by chuck clamp **8**. A vacuum is provided through the chuck to the exterior side of the diaphragm. Because the diaphragm is pulled downward by the vacuum in the chuck, fluid is drawn into the rotor **2a** through the rotor tube **13**. The blood is thus drawn from the wound-drain site through the tube **17** then through a cassette **15a**, which provides valving to control the flow of fluids through the various lines, and then through the rotor tube **13** to the rotor **2a**. Standard valves or valving techniques

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(e.g., pinching a tube) may be used to control fluid flow in the system instead of a cassette **15a**. Anticoagulant may be added to the drained blood at some point during the process.

An intermediate wound-drain canister may be placed in the line **17** between the patient and the cassette **15a**. The filter **26** may be located adjacent to or in this canister, and anticoagulant may be added to the blood in the canister. Such a canister can hold the whole blood pulled from the patient until the blood is to be processed; at that time, the vacuum generated in the chuck or a pump may be used to pull the blood from the canister to the rotor **2a**.

When it is desired to separate the blood in the rotor **2a**, the chuck spins the body of the rotor **2a**. In a preferred version of the post-operative salvage process using the present invention, blood flow to the rotor **2a** is stopped when the desired or the available amount of blood has entered the rotor, or when it is full. Since, in the rotor of the present invention, the processing chamber has a variable volume, the rotor **2a** does not have to be filled to its capacity with blood for the process to be done properly. After the flow into the rotor is stopped, the blood is then subjected to centrifugal force as long as is appropriate to separate the various components. The portion of the rotor **2a** where the rotor tube **13** enters the rotor **2a** (i.e., the fixed portion, which as noted previously in connection with FIG. 4 includes the collector assembly **46**) is held and prevented from spinning by a brace **11**.

Referring to FIG. 4, when the separation is complete, the compressor begins to pump compressed air into the chuck **4a**. When the air pressure acting on the diaphragm's exterior (i.e., the side that does not come into contact with blood) exceeds the fluid head between the collector assembly and the inner vertical face of the diaphragm (lines **31a**, **31b**, **31c** and **31d**), fluid begins to flow from the processing area in the rotor through the holes **39** in the interior plate **40** into the area around the collector

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assembly **46**, through the collector assembly and out of the rotor **2a** into the rotor tube **13**. The fluid head between the collector assembly and the inner vertical face of the diaphragm is created by the centrifugal force acting on the fluid in the channel **44**. In order to minimize the amount of air pressure needed to overcome the centrifugal force of the rotor, the rotational speed of the rotor **2a** may be reduced--at some point during the process--to a level that is high enough simply to keep the blood components separated.

It should be noted that while the use of air is described herein to apply pressure to the diaphragm **31**, other fluids could be used as well. Preferably a gas is used, since a gas will have a lower specific gravity than the lightest separated fluid in the processing chamber and therefore will stay between the liquid being centrifuged and the rotor's axis of rotation. Air is preferred since it is readily available and easily disposed of. Nitrogen or carbon dioxide may be used instead.

The compressed air first pushes the blood element with the lightest specific gravity out of the processing area. the lighter fluid passes through those holes **39** in the plate **40** at the smallest radius not sealed by the diaphragm **31**. Each blood element in turn by specific gravity flows through the holes **39** in the plate **40** at the smallest radius not yet sealed by the diaphragm **31** and then out of the rotor.

Referring to FIG. 5 again, the blood elements exiting the rotor can be diverted as desired by the cassette **15a**. The fluid flowing out of the rotor's processing chamber may be diverted to a specific container (e.g., a waste bag or an RBC bag) or returned to a donor depending on the purpose of the process, on how the system is configured and on how the cassette **15a** or other tubing directs the fluids.

In a typical post-operative salvage process using the present invention, the lighter elements--most of the plasma and platelets--are considered waste and are sent through the cassette **15a** (or other valving mechanism) and the tube **24** to

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a waste bag. The remaining blood elements--mostly concentrated RBCs--may then be further processed in the rotor **2a** and then forced out of the rotor **2a** through the cassette **15a** and the tube **22** to an RBC bag. After a sufficient amount of RBCs are sent to the RBC bag, the RBC bag is disconnected from the cassette **15a** and may then be attached to the patient in order to return the patient's RBCs.

The emptying of the processing chamber **30** of the rotor **2a** can be stopped at any time by stopping the increase in the air pressure inside the chuck **4a**, while maintaining the rotational speed of the chuck. If the rotor is processing blood, one likely place to stop might be when the RBC layer begins to exit the rotor and another might be when the rotor is empty.

The cycle of sending fluids into the rotor, centrifuging and forcing fluids out of the rotor **2a** can be repeated, for instance for further processing of the blood components left in the rotor (for instance, washing the RBCs or ficol-hypaque separations). Other fluids can be allowed to flow into the rotor and back out again by inflating or deflating the diaphragm **31** and appropriately actuating the cassette **15a** (shown in FIG. 5). At the end of the last cycle in the post-operative salvage process, the air pressure in the chuck **4a** can be adjusted to the proper level to obtain the desired hematocrit in the final product.

The rotor speed may be changed at different times while the rotor is emptying, in order to achieve the most advantageous combination of centrifugal force for separation and air pressure inside the chuck required to force fluid out of the rotor. It is desirable to avoid applying too much air pressure against the outside of the diaphragm **31**, for safety considerations, and for reducing the size of the system components and the power consumed by the system.

Thus, in a preferred embodiment the rotor is emptied in the following manner, with reference to FIG. 4. Initially,

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the rotor **2a** is spinning at full processing speed--say for instance 5000 rpm. The gas in the chuck **4a** is positively pressurized, thereby causing fluid to flow out of the rotor's chamber **30** until an equilibrium is reached between the gas pressure in the chuck and the centrifugal force acting on the fluid in the channel **44** above the plate **40** between the outer edge of the collector assembly **46** and the inner vertical face of the diaphragm (lines **31a**, **31b**, **31c** and **31d**. The gas may continue to be pressurized until it reaches 2 psi--or whatever pressure limit is chosen. Then, the rotational speed of the rotor **2a** is reduced. The rotational speed may be reduced without affecting the separation of the fluids in the rotor if the speed is reduced smoothly and slowly, and as long as the rotational speed does not fall below the minimum speed necessary to maintain separation, which may for example be as low as 500-1500 rpm. Reducing the speed lowers the centrifugal force on the fluid in the channel **44**. Thus, additional fluid is forced out of the rotor until a new equilibrium is reached. By continuing to reduce the rotor's rotational speed, additional fluid is forced out of the rotor even though the gas pressure in the chuck **4a** is kept constant.

Alternatively, fluid may be forced out of the rotor **2a** with low gas pressure by first reducing the rotational speed of the rotor **2a** to the desired level--for instance, the lowest speed which will maintain separation--and then increasing the pressure in the chuck **4a**. It is also possible to reduce the rotational speed and increase the gas pressure at the same time. An advantage of this technique of emptying the rotor--namely, reducing the rotational speed of the rotor to assist in emptying--is that less gas pressure in the chuck is needed to force liquid out of the rotor.

The chuck's gas pressure and rotational speed may be controlled by a controller (preferably, a digital data processor located in the system housing **6**, which housing is

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shown in FIG. 5), which receives information from a pressure transducer for measuring the gas pressure in the chuck **4a** and from an encoder for measuring the rotational speed of the chuck **4a** and the rotor **2a**. The controller may control the compressor **61** and the motor **50**, in addition to valves in the rest of the disposable set. The controller may also be programmed to calculate the volume of liquid in the rotor's processing chamber based on the chuck's gas pressure and the rotational speed.

In order to avoid excessive vibration of the system as the rotor is being spun, the speed of rotation may be varied. For instance, instead of trying to maintain a constant speed of rotation of 5000 rpm, the motor may cycle through a range of speeds around 5000 rpm. This cycling will help avoid the motor staying at a rotational speed that puts the system into a resonant vibration. The rotational speed should be changed quickly enough so that the system does not have an opportunity to resonate at a given speed, yet the speed should not be changed so quickly that the separation of the fluid components is upset.

At some point in the emptying, only one component will remain in the rotor, for instance red blood cells (or only components whose separation is not required will remain in the rotor). At that point, the foregoing process may continue until the rotor **2a** is empty or, preferably, the spinning of the rotor **2a** may be stopped. The gas pressure necessary to push the remaining liquid out of the rotor **2a** when it is stopped must only be greater than the fluid head from the rotor **2a** to the highest point in the tubing between the rotor and the collection bag.

FIG. 6 is a schematic of a system to utilize the rotor **2a** described above in a donor-connected apheresis system for the collection of RBCs. A suitable anticoagulant is metered into the blood at the end of the needle which has been inserted into a vein in an arm of the donor **70**. The flow of anticoagulant is controlled by a pump or other metering

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device **77**. The anticoagulated blood flows through the donor tubing and into the rotor by the combination of gravity and venous pressure and, if needed, vacuum from compressor/vacuum pump **61** or a peristaltic pump. At this point during the process, valve **81** closes off the component collection bag and permits flow to the rotor.

After sufficient blood enters the rotor, the rotor is spun quickly enough and long enough to cause adequate separation. The valve **81** remains in the position where the donor tubing is open and the tubing to the collection bag is closed. While the chuck continues to spin the rotor in order to maintain separation (although the rotational speed may be reduced), the compressor **61** pumps air into the chuck forcing plasma to flow back to the donor. The plasma flowing back to the donor is checked for air bubbles by the air detector **79**. As the RBCs start to emerge from the rotor, as detected by RBC detector **75**, the valve **81** opens the tubing to the collection bag and closes the tubing to the donor. When the rotor is empty, the compressor stops and the pressure in the rotor is vented through vent **63**. The process can be repeated as desired.

If plasma is to be collected instead of RBCs, the valve **81** would first shunt the plasma exiting the rotor to the collection bag. Then, when RBCs were detected by the RBC detector **75** the valve **81** would open the donor tubing and permit the RBCs to be sent to the donor. The valve **81** may be placed in a cassette, like cassette **15a** (shown in FIG. 5), which may provide chambers for detecting RBCs and air bubbles and which may further provide supplemental pumping means.

FIG. 6 shows a controller regulating the anticoagulant pump **77**, the valve **81**, the chuck's motor, the vent **63** and the pump **61**. The controller is connected to an encoder or tachometer to monitor the motor's speed, and is connected to a pressure transducer to measure the gas pressure being applied to the exterior side of the rotor's diaphragm. The

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controller also monitors the air detector and the RBC detector. As discussed above in relation to FIG. 5, the controller may increase the gas pressure in the chuck and/or reduce the rotational speed of the chuck in order to force the blood components out of the rotor.

In this embodiment, no separate pump is required to move blood to or from the rotor (although pumps may be used). Standard peristaltic blood pumps can create a large amount of pressure or suction and therefore require special devices to protect the donor from excessive suction while drawing blood and from excessive pressure when returning blood. In this system, the draw and return pressures can be controlled exclusively by the air pressure from the chuck and therefore can be controlled and monitored much more safely and with less cost for both the equipment and the disposables. The potential for runaway blood pumps is also reduced by the system above.

The FIG. 2 rotor **2a** may also be used for recovering blood suctioned from the surgery site on a patient during an operation. This type of system is known as intraoperative salvage. A suction canister, which is attached to a hospital's wall vacuum (or which utilizes a vacuum pump in the system housing), draws blood from the patient's surgery site through a suction tube. Anticoagulant may be provided to the canister in order to prevent the blood from clotting. Normally, in the intraoperative salvage process, the suctioned blood has been diluted with saline which was used to irrigate the surgery site.

The blood that has collected in the canister is drawn from the canister through a cassette or other valving mechanism to the rotor tube **13** and finally to the rotor **2a**. Blood flow to the rotor is stopped when the desired or the available amount of blood has entered the rotor, or when it is full. (As noted above, since, in the rotor of the present invention, the processing chamber **30** has a variable volume, the rotor **2a** does not have to be filled to its capacity with blood for the process to done properly.) The

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rotor **2a** is spun so as to separate the blood into its components. When the separation is complete, like the post-operative process discussed above in relation to FIG. 5, the compressor (item **61** in FIGS. 3, 4 and 6) may begin to pump compressed air into the chuck, and the rotational speed of the rotor **2a** may be reduced to a level that is high enough simply to keep the blood components separated. As discussed above in relation to FIG. 4, when the air pressure acting on the exterior of the diaphragm **31** exceeds the fluid head from the inner radius of the diaphragm **31** to the skirt of the collector **46**, fluid begins to flow from the processing area in the rotor **30** through the holes **39** in the plate **40** into the area around the collector assembly **46**, through the collector assembly **46** and out of the rotor **2a** into the rotor tube **13**.

Like the post-operative salvage system discussed above in connection with FIGS. 4 and 5, in an intraoperative salvage process, the lighter components--primarily the saline and the plasma--are the first components to be pushed out of the rotor **2a** through the rotor tube **13**. In a typical intraoperative process, these components are considered waste and are shunted by the cassette to a waste bag. After the waste components are pulled from the rotor **2a**, the remaining blood components, which now have a higher concentration of RBCs, are pushed through the rotor tube **13** and then shunted by a cassette (or other valve means) to an RBC bag. After a sufficient amount of RBCs are sent to the RBC bag, the bag is disconnected from the cassette and connected to the patient in order to return the patient's RBCs. Alternatively, a tube may be connected directly between the patient and the bag so that blood may be returned directly to the patient by gravity without removing the bag.

FIG. 7 shows the rotor **2a** of FIG. 2 with an airtight exterior shell **3a** attached and sealed to the boundary wall **10**. The use of an exterior shell makes the FIG. 2 rotor **2a**

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especially convenient for use as a wound drain. In one embodiment, the shell **3a** may be removably attached to the rotor **2a**. The shell **3a** permits a vacuum to be applied to the exterior side of the diaphragm **31** (i.e., the side that does not come into contact with the blood) without placing the rotor **2a** in the chuck **4a**. A valve **68** is disposed in the shell **3a**. The valve **68** permits the shell **3a** to be attached to the hospital vacuum or a vacuum pump. A vacuum is thus introduced into the shell **3a**, and the vacuum in the shell **3a** draws blood from the wound drain. With the FIG. 7 configuration, the rotor **2a** can begin drawing blood from the wound drain as soon as the wound drain is placed in the patient--typically in the operating room--without mounting the rotor **2a** in the chuck **4a**. Later--when the patient is brought into the recovery room--the rotor **2a** can be placed in a chuck to process the drained fluid. If the shell **3a** is removable, it may be removed from the rotor **2a**, and the rotor **2a** may then be placed in the chuck **4a** shown in FIG. 3. If the shell **3a** is not removable, a different chuck may be used. Such a chuck would have means for opening valve **68** in order to permit fluid communication between the chuck and the interior of the shell **3a**. Preferably, such a chuck would provide a compressed gas in order to force fluid out of the rotor **2a**. In addition, such a chuck would also preferably be able to provide a vacuum to the interior of the shell **3a** in order to draw additional fluid into rotor **2a**. The shell **3a** also protects the diaphragm **31** from accidental abrasions.

An alternative shell **3b** is shown in FIG. 8A. This alternative shell **3b** has a core **66** that extends up from the bottom of the shell **3b** around the rotor's axis of rotation. Near the top of this core **66** is the valve **68**, which is normally closed but which may be opened for permitting either a vacuum or positive pressure to be introduced into the interior of the shell **3b**.

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If the shell **3a**, **3b** remains attached to the rotor **2a** during centrifugation, the shell may be shaped so as to reduce variations in the stresses in the diaphragm **31** (like the chuck shown in FIG. 3 for example). Also, if the shell **3a**, **3b** remains attached to the rotor **2a** during centrifugation, the diaphragm **31** may be attached to the bottom of the shell and/or to the core **66**.

As shown in FIG. 8B, using a rotor having a shell **3b** with a core **66**--or a rotor like rotor **2c** shown in FIG. 20 (discussed below) having a core **116** which is part of the rigid boundary wall **10**--permits the use of a chuck **4'** that fits inside the core **66**, so that the rotor **2a** and shell **3b** may be held from the inside of the core **66**, instead of the outside of the rotor like the chucks **4a** and **4c** shown FIGS. 3 and 21. Such an arrangement permits a smaller system housing to be used, and the motor **50'** and perhaps even part of the pump **61'** may be located within the rotor's core.

FIG. 9 shows the addition of a secondary elastic wall **67** in the chuck. This secondary elastic wall **67** is held in place by clamp **69**. This secondary elastic wall is a barrier between the air in the chuck and the diaphragm **31** of the rotor and would prevent pressurized air entering the rotor's processing chamber in the event of a tear in the diaphragm **31**. Operationally, this configuration of the system would work in a manner very similar to that described above except that before blood was allowed to flow into the rotor, the pump would inflate the secondary elastic wall **67** until it completely filled the chuck. The air in the chuck would be forced out holes **71**, which are covered by one-way valves **73** to prevent air from re-entering the chuck.

FIGS. 10 and 11 show respectively a top plan view and a cross-section of a two-conduit, edge-loading rotor, which permits flow into and out of the rotor **2b** at the same time. Like the rotor **2a** shown in FIG. 2, the FIG. 11 rotor **2b** has an elastic diaphragm **31**, a plate **40** with holes **39**, and a boundary imperforate wall **10**. (Most of the boundary

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imperforate wall, as in an alternative embodiment mentioned above in connection with rotor **2a**, can be substituted for with a portion of the diaphragm **31** extending over the top of the rotor and adapting the chuck to include a lid. See FIG. 35.) These portions of the rotor are spun by a chuck. Like the FIG. 2 rotor, the FIG. 11 rotor **2b** also has a collector assembly **46**, which is held in place while the rest of the rotor is spun. The FIG. 11 rotor may be modified so that the bottom rigid wall, i.e., the perforate interior wall **40**, is flat--like the perforate plate **40** shown in FIG. 2.

The FIG. 11 rotor further includes a second imperforate wall **87** (which is also referred to herein as an inlet-control structure or an imperforate interior plate) located between the top imperforate wall **10** and the perforate interior plate **40**, so as to form a channel **85** between the two imperforate walls. Like the rigid boundary wall **10**, the interior imperforate plate **87**, although otherwise imperforate, does define a central opening to permit the collector assembly **46** to pass through. This second plate **87** is also spun along with the perforate interior plate **40**, the top wall **10** and the diaphragm **31**. The rotor **2b** also has an umbrella deflector **91**, which directs the unseparated fluid along the top of the imperforate interior plate **87**. Instead of a single input/output tube **13** of the FIG. 2 rotor, the FIG. 11 rotor **2b** has an input tube **83** and a separate output tube **93**, which together with the collector assembly **46** are held in place during centrifugation while the rest of the rotor is spun.

In use, the rotor **2b** is placed in centrifuge chuck **4b**, as shown in FIG. 12. (The interior of chuck **4b** has a somewhat different shape from that of the FIG. 3 chuck **4a**. The shape of the chuck's interior may be varied depending on whether the rotor is usually filled while being spun by the chuck or while at rest.) The rotor **2b** is held in place by clamp **8**. Lip seal **36** interfaces with the rotor to form an air-tight seal. The centrifuge is turned by motor **50** and

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shaft **51**. The shaft **51** has an axial through hole **53** and protrudes below the motor **50**. A rotary pneumatic seal **55** connects tubing **59** to the shaft **51** and is held stationary by fixture **57**. (Alternative means for providing substantially air-tight fluid communication between the tubing **59** and the axial through hole **53** as discussed above may be used in lieu of the rotary pneumatic seal **55**.) The tubing **59** connects the rotary pneumatic seal **55** to the compressor/vacuum pump **61** and to a controllable exhaust valve **63**. Holes **65** in the chuck core **64** allow air to flow from the compressor into the space between the chuck and the diaphragm. (As noted above in connection with the FIG. 3 chuck **4a**, channels emanating from the holes **65** may be provided in the chuck so that fluid may flow to various points adjacent the exterior of the diaphragm even when the diaphragm is fully extended.)

FIG. 13 shows the rotor **2b** spinning. Blood flows into the rotor through tube **83**, then the blood flows off umbrella deflector **91** and is channeled to the outside edge of the rotor through channel **85**. As the volume of the blood in the rotor **2b** increases, the diaphragm **31** stretches to allow the blood to fill the processing area and at some point will take on a shape shown by line **31a**. As blood enters the rotor, the air in the chuck **4b**, which is displaced by the diaphragm **31** and the blood, escapes through hole **65**, down the shaft hole **53** and out exhaust valve **63**. As more and more blood enters the rotor, the diaphragm changes shape to accommodate the blood. The diaphragm will in turn take on the shapes shown by lines **31b**, **31c** and **31d**.

In the FIG. 11 rotor **2b**, unprocessed blood or fluids can flow into the rotor **2b**, while the lighter blood elements can simultaneously flow out of the rotor **2b**. This flow pattern is similar to the flow pattern in rotors marketed by Haemonetics, Electromedics and Shiley. One distinction between those prior-art rotors and the present invention is that when it is time to harvest the heavier components from

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the rotor **2b** (typically red blood cells) the compressor **61** turns on and increases the air pressure in the chuck **4b**, forcing any remaining lighter elements out of the rotor **2b** until the desired concentration of remaining products is achieved. Once the desired concentration is achieved, the remaining products can be harvested from the rotor **2b** by further increasing the air pressure in the chuck **4b**. Alternately, if the rotor **2b** is stopped, the remaining elements can be harvested with low air pressures in the chuck **4b** or even pumped out through either tube **93** or tube **83**.

A further distinction between the FIG. 11 rotor **2b** and prior-art rotors is that by controlling the air pressure in the chuck **4b** the increase in the volume of blood in the rotor **2b** can be stopped at any position such as **31a** in FIG. 13. At that time, the flow pattern of unprocessed fluids entering the rotor **2b** (via tube **83** and channel **85**) simultaneously with the lighter elements leaving the rotor **2b** (via channel **44**, collector assembly **46** and tube **93**) takes place but with a chosen rotor volume that is smaller than the rotor's maximum volume. One important advantage of this rotor **2b** and process described herein is that the variable volume of the rotor's processing chamber **30** makes it ideal for use for the intraoperative or post-operative salvage of shed blood. If the patient is small or if the blood loss has been gradual, it may be desirable to harvest the collected RBCs from the rotor **2b** before the rotor is completely full of RBCs. This cannot be done in the prior-art systems unless the operator is willing to accept a low hematocrit product. With the FIG. 11 rotor **2b**, the operator can keep the rotor's processing chamber **30** at the appropriate volume with air pressure in the chuck to suit the needs of the patient.

If the rotor **2b** is already fully expanded but there are not very many RBCs in the rotor when it is desired to harvest those RBCs, the compressor **61** is used to increase

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the air pressure in the chuck **4b**, thereby forcing out the lighter waste products until the desired concentration of RBCs is achieved. The RBCs can then be harvested from the rotor **2b** by one of the means described above.

Another important advantage of this rotor **2b** and system is that its variable volume makes it ideal for use in blood apheresis. Some apheresis blood collections such as platelet and RBC collections work better or faster if blood entering the rotor is forced to the edge of the rotor. These apheresis blood collections can be performed with less extracorporeal volume and therefore on smaller donors and from donors who are sensitive to blood volume changes. The extracorporeal volume is controlled by keeping the rotor's processing chamber **30** at the appropriate volume with air pressure in the chuck **4b**.

The FIG. 11 rotor **2b** may be used in a system, such as that shown in FIG. 14 for performing RBC apheresis. With this system, whole blood is drawn from the donor through tube **17'**, preferably with the assistance of a pump **95** to the cassette **15b**, which directs the whole blood to the input tube **83**. With the introduction of fluid into the rotor **2b**, the diaphragm **31** is distended in much the same way as shown in FIG. 13. Usually, the rotor **2b** is spinning while it is being filled. After separation is complete, while the rotor is still spinning, and while blood is still being introduced into the rotor **2b**, the plasma--the lighter blood component--can be forced, by air pressure in the chuck, through the plate's holes **39** (see FIG. 13) to the collector assembly **46** to the output tube **93** to the cassette **15b** (see FIG. 14) and finally to the tube **101** for returning the plasma back to the donor. A pump **103** may be used to assist in the return of plasma to the donor. Thus, the plasma may be returned to the donor while whole blood is still being taken from the donor and introduced into the rotor.

Once the desired volume of the processing chamber is established, the air pressure may be used to keep the volume

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constant; thus, the incoming whole blood will force out a corresponding volume of plasma. Preferably, however, the volume may be allowed to grow so that the volume of plasma exiting the rotor is the same as the volume of the plasma component of the whole blood entering the rotor. At some point the rotor's processing chamber may become filled with RBCs. At that point the pump **95** is turned off so that no more blood is drawn from the donor, and the RBCs are forced out of the rotor **2b** through the cassette into a line **22** connected to an RBC bag.

By using the FIG. 11 rotor **2b**--or the rotor **2d** shown in FIG. 23 and described below--for RBC apheresis, one does not have to wait for the rotor's processing chamber to be filled with whole blood before returning plasma to the donor. Likewise, the chamber does not have to be filled with RBCs before they can be forced out of the rotor's processing chamber through the cassette **15b** and into the RBC bag. This flexibility permits the plasma to be returned to the donor gradually, while the donor is still giving blood. This gradual return permits the plasma to be re-introduced to the donor over a longer period of time. This is desirable because the plasma contains most of the anticoagulant, for example, citrate. Citrate can cause an adverse reaction in some donors, especially if introduced into the donor too quickly. The rotor **2b**, **2d** also permits the processing of any given amount blood up to the maximum amount permitted by the rotor **2b**, **2d**. As noted previously, prior-art systems using fixed-volume rotors require that a fixed amount of blood be processed. With the variable-volume rotors **2b**, **2d**, a donor may be allowed to donate less than a standard unit of RBCs, which is advantageous in many situations, such as children and other donors with low body weight. These rotors **2b**, **2d** may also be used to minimize donor reactions caused by both the total amount of extracorporeal volume and the rate of change of extracorporeal volume.

FIG. 15 schematically represents a particular RBC apheresis process using rotor **2b**--or rotor **2d**. This process

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permits the collection of up to two-units of RBCs from a donor quickly and safely. (Donor monitoring and safety systems, such as bubble detection, are not shown in the FIG. 15 schematic for clarity. Likewise, a controller is not shown in FIG. 15. A digital data processor is preferably used for monitoring and controlling the various components of the systems in all of the various processes set forth herein.) Anticoagulant is pumped by pump **105** from bag **B1** down to needle **N1** which has been inserted in the donor's vein. The anticoagulant mixes with the blood at the needle hub and both are pumped by pump **95** to the rotor **2b**--or alternatively rotor **2d**. The rotor's processing chamber volume is initially held small by air pressure in the chuck, say at a volume of 100 ml. When plasma starts to emerge into tube **93**, the air pressure in the chuck is slowly decreased (by venting air through vent **63** shown in FIG. 13) thereby allowing the rotor's processing chamber to expand at the rate that the RBCs are entering the rotor as part of the whole blood. As the anticoagulated plasma emerges from the rotor, it flows to bag **B2** and then is pumped back to the donor by pump **103** via needle **N2** inserted in a different vein.

This procedure keeps all the RBCs in the rotor but continues to force the anticoagulated plasma out of the rotor **2b** so it can be returned to the donor on a continuous basis. The process continues until the desired amount of RBCs have been collected or until the rotor is full of RBCs. The air pressure in the chuck can then be increased by turning on compressor **61** (see FIG. 13) to achieve the desired concentration of RBC's. The RBCs are then harvested from the rotor and stored in bags **B3** and **B4** by stopping the rotor, maintaining the proper air pressure to push the RBCs out of the rotor **2b** and switching valve **81** to open the passageway to the bags **B3** and **B4**. If desired, RBC preservative solutions can be provided in bags **B3**, **B4**. This procedure results in plasma being returned to the donor

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sooner than is possible with the fixed-volume prior-art rotors and results in plasma being returned to the donor in a continuous stream. Therefore, the peak extracorporeal blood volume is lower and there is less extracorporeal volume fluctuation for the donor, thereby reducing the potential for adverse reactions.

One important factor in RBC apheresis is how long the donor is connected to the system. This factor is particularly important in mobile blood collections where donors are only available for a limited time, such as during blood drives at factories. The system shown in FIG. 15 is particularly fast because the plasma is being returned at the same time whole blood is being drawn and there are no stoppages to empty the rotor until the process is complete and the donor is disconnected from the system.

The plasma in the blood pathway of this FIG. 15 system is always in motion. In addition, the volume of the blood pathway filled with anticoagulated plasma is small, and the length of time any particular drop of plasma is out of the body is short and predictable. Therefore, since there is less propensity for the plasma to clot, the amount of citrate in the anticoagulant may be reduced from standard levels without danger of the plasma starting to clot. With less citrate in the system, the potential for donor citrate reactions is reduced further. (As noted above, the potential for citrate reactions is also reduced because, with the present invention, the anticoagulated blood may be returned to the donor over a longer period of time.)

Another advantage of this system is that it will allow the collection of RBCs from small donors and/or patients whose size or medical condition prevents them from donating with existing systems. Unlike the traditional bag systems and systems that use a fixed volume rotor, the FIG. 15 system causes only a low extracorporeal volume and can be stopped after any amount of RBCs have been collected. Further, the RBCs can be harvested as RBC concentrate. The operator simply stops the expansion of the diaphragm after

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the appropriate amount of RBCs have been collected, increases the air pressure in the chuck slightly to concentrate the cells and then harvests the RBCs.

It is sometimes desirable to replace the blood volume given by the donor. This can be accomplished simply in this process by pre-filling bag **B2** with an appropriate amount of an acceptable solution, such as 500 ml of saline. This replacement fluid is then simply reinfused along with the plasma.

Alternatively, the citrate required for proper anticoagulation can be further reduced and the donor can be kept isovolemic simultaneously by putting the replacement fluid such as saline or another injectable solution in bag **B1** along with the anticoagulant and increasing the ratio of anticoagulant/saline to blood by adjusting the relative rates of pumps **105** and **95**. Adding saline to the blood path in this manner will dilute the plasma, and the saline will travel intermixed with the plasma through the system. Diluting plasma with saline extends the clotting time so that less total citrate is needed to keep the plasma from clotting in the short time the plasma is outside of the donor's body. The same saline thus performs two functions: first, by helping to anticoagulate the plasma and, second, by being the replacement fluid as well. This arrangement has the additional advantage of reducing the percentage of plasma trapped in the RBCs because the plasma is diluted by the saline before it is trapped by the RBCs. The amounts of white blood cells and platelets trapped in the packed RBCs are also reduced because the saline provides a type of elutriation to wash them out with the plasma.

A variation of the above system that requires only one needle but has a longer processing time is achieved by connecting the tube from pump **103** into the tubing between needle **N1** and pump **95**. With this tubing arrangement and safeguards to insure both pumps are never on at the same time, the system can alternate between drawing blood with

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pump **95** and returning blood with pump **103** through the same needle **N1**.

In the FIG. 11 rotor **2b**, the spinning top wall **10** and interior plate **40**, as noted above, separate the spinning diaphragm **31** from the non-spinning input **83** and output **93** tubes and the top of the collector assembly **46**. It is important to keep rigid members that spin with the diaphragm **31** between the diaphragm and the non-spinning components of the rotor, so as to prevent the diaphragm **31** from touching a non-spinning component during centrifugation. (Some embodiments of the rotor do not have a fixed section and therefore do not have to use their interior walls to perform this function. See for example FIG. 28, discussed below.) In addition to preventing the diaphragm **31** from touching the rotor's fixed portion, the plate **40** also serves the important function of controlling flow out of the processing chamber to the collector assembly **46**. The interior walls **40** of the rotors **2a**, **2b** shown in FIGS. 2 and 11 (and of the rotors shown in FIGS. 20, 23, 28 and 39, which are discussed below) extend to the periphery of the processing chamber and thus keep a channel **44** open between the periphery of the interior wall **40** and the collector assembly **46**, no matter what the position of the diaphragm **31** is. If the interior wall **40** did not extend substantially all the way to the rotor's periphery and did not have holes **39** at the rotor's periphery, the fluid at the periphery of the spinning processing chamber **30** could be prevented from flowing to the collector assembly **46** by the diaphragm **31**.

FIG. 16 shows an example of a rotor with a perforate interior plate **40a** and a rigid imperforate interior plate **87a** that do not go all the way to the edge of the rotor. In the FIG. 16 rotor, the imperforate interior plate **87a** and the perforate interior plate **40a** shown extend about halfway to the edge of the FIG. 16 rotor as an example. These perforate and imperforate interior plates (walls) could extend to any desired radius, depending on the desired

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application of the rotor. With this configuration of interior plates, the channel between the perforate interior plate **40a** and the imperforate interior plate **87a** remains open during centrifugation as long as the volume of the processing chamber is greater than a defined amount. Once the processing-chamber volume drops below that amount, the diaphragm **31** blocks off further flow out of the processing chamber into the channel. This may be desirable during certain processes involving biological fluids. The imperforate plate **87a** does not have to have the same radius as the perforate interior wall **40a**. For instance, the imperforate interior wall may extend all the way to the rotor's periphery while the perforate interior wall extends only halfway to the periphery. Such a configuration would allow the rotor to be filled from the outer edge of the imperforate interior wall.

FIG. 17 shows another alternative rotor with a different configuration of interior plates **87a**, **87b**, **40b** and **40c**. In this rotor, fluids enter the processing chamber at different radii depending on how full the rotor is; likewise, fluids leave the rotor at different radii depending on how empty the rotor is.

As shown in FIG. 18, the interior walls **87**, **87'**, **40**, **40'** can be stacked and connected to inlets **83**, **83'** or outlets **93**, **93'**, so that fluids can enter or leave the processing chamber at different points. In the FIG. 18 rotor, fluids can enter and leave the rotor's processing chamber from multiple radii at the same time. Imperforate plate **87** defines one radius--near the rotor's periphery--where fluid enters the processing chamber, and imperforate plate **87'** defines a second, intermediate radius where fluid enters the processing chamber. In the FIG. 18 rotor, like the FIG. 16 rotor, a perforate wall **40'** does not extend all the way to the periphery of the processing chamber. Thus, the FIG. 18 rotor, like the FIG. 16 rotor, can prevent further flow over the top of the interior wall **40'** to a

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collector assembly at a particular point during emptying. The rotor in FIG. 18 has two inlets **83**, **83'** and two outlets **93**, **93'** allowing a multiplicity of flow patterns depending on how full the rotor is and which tubes connected to the inputs and the outputs are clamped or open.

Another way to use interior plates to accomplish the desired flow patterns is to strategically place holes in the plates. For instance, in FIG. 19A the fluid first exits the rotor in the middle through a set of holes **39'**, all of which are at a constant radius, even if the rotor is completely full. This configuration permits an intermediate-density fluid, such as platelets, to be emptied from the processing chamber while the lightest and heaviest fluids remain in the rotor.

FIG. 19B shows the FIG. 19A rotor mounted in a chuck **4b'**, which is similar to the chuck shown in FIG. 12. Anticoagulated whole blood may be pumped into the rotor through inlet **83**, while the chuck **4b'** and the rotor are being spun. Imperforate plate **87** directs the incoming whole blood towards the periphery of the rotor. The rotor is filled with blood, so as to occupy the entire space available in chuck **4b'**, causing plasma to be forced out of the rotor first, through holes **39'**. When a sufficient amount of RBCs is in the rotor, the platelet layer lines up with holes **39'**. One way for determining when the platelet layer lines up with holes **39'** is an optical detector, which detects the buff color of the platelet layer.

Once the platelet layer is lined up with holes **39'**, a valve (not shown) connecting the outlet **93** to a platelet-collection bag (also not shown) is opened. Compressor **61** then pumps air into the chuck **4b'**, causing the platelets to be forced through holes **39'**. As some of the platelets are forced out of the rotor, some of the plasma may be able to escape past the platelets through holes **39'**. However, the escaping plasma will entrain the platelets nearer the axis of rotation. If the platelet layer begins to move radially

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outward, away from the axis of rotation and away from holes **39'**, more whole blood may be added to the rotor so as to reposition the platelet layer directly under the holes **39'**.

A significant advantage of this platelet-collection process is that the plasma used to push the platelets out of the rotor comes from the center of the rotor instead of the rotor's periphery. Thus, the plasma pushes out the lightest platelets, which are the youngest platelets and which have the least amount of white blood cells intermixed with them. Prior-art platelet collection processes use fixed-volume rotors and use plasma coming from the periphery of the rotor to push platelets out of the rotor.

The system shown in FIG. 19C is similar to the system shown in FIG. 19B, except that the rotor has additional holes **39"** located at a smaller radius than holes **39'**. In using this rotor in the platelet collection process, the plasma flows out of holes **39"** as the rotor fills with RBCs. When the platelets are lined up with holes **39'**, whole blood flow into the rotor is stopped. Air is pumped into the chuck **4b'** causing plasma to flow through holes **39"** until the diaphragm covers the holes **39"**. When holes **39"** are covered, the platelets, which are lined up with holes **39'**, are forced out through holes **39'**.

FIG. 19D shows a system that permits platelet collection at various extracorporeal volumes. Sets of holes **39a**, **39b**, **39c**, **39d** and **39e** are arranged in circles and are spaced by some distances, such as 0.1 to 0.2 inches. There may be more or fewer sets of holes as desired. All of the holes in each set are located at the same radius. Platelets may be collected when there are sufficient RBCs in the rotor to position the platelets at any of the sets of holes.

For example, once the rotor shown in FIG. 19D is filled so that the platelets are located directly under holes **39b**, air may be pumped into the chuck **4b'** to force the plasma, which is located inside the layer of platelets, out first through holes **39e** (assuming that the rotor was completely

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filled before the platelets became located under holes **39b**), then holes **39d** and **39c** in turn. (The volume of the processing chamber may, of course, be set at less than its maximum volume by maintaining a positive air pressure in the chuck **4b'**; in such a case, the plasma would first be forced out through the holes at the smallest radius not covered by the diaphragm.) Once sufficient plasma has been forced out of the rotor so that all the holes located inside of the layer of platelets--holes **39c**, **39d** and **39e** in the example--are covered by the diaphragm, the platelets are forced out of the rotor through holes **39b**.

FIG. 19E shows a rotor that has as an outlet-control structure an imperforate interior wall **40"**, instead of a perforate interior wall (like plate **40** discussed above). This rotor has only one conduit **13**, which serves both as the inlet and outlet, at different times, to the rotor's processing chamber. This rotor may be used with a chuck, such as that shown in FIG. 3, or with an exterior shell, such as those shown in FIGS. 7 and 8A. Using an imperforate interior wall **40"** in this way permits the collection of separated fluid components having the greatest density first, before the collection of intermediate density and lighter density components. After the processing chamber has been filled with desired amount of blood (or other biological fluid) and the blood has been separated, the air pressure against the exterior of the diaphragm **31** is increased or the rotation of the rotor decreased so as to force the concentrated RBCs, which are located furthest away from the rotor's axis of rotation, past the outer edge of the imperforate interior wall **40"**. Since there may initially be separated blood components in the channel **44** between the boundary wall **10** and the interior wall **40"** after separation, there may be a small amount of lighter fluid components exiting the rotor before the concentrated RBCs. After this small amount of lighter blood components--plasma, platelets--are forced out of the channel **44**, all the RBCs

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may be collected before the remaining lighter blood components reach the periphery of the interior wall **40"**.

Thus, different configurations of the inlet-control and outlet-control structures allow rotors to be optimized for different types of blood-component collection processes, such as plasma collection or platelet collection, or other biological-fluid-component collection processes. In general, the placement of holes in the interior plates and the diameter of the plates can be manipulated in order to accomplish the desired flow patterns out of and/or into the rotor. As is discussed below in connection with FIGS. 30-36, tubes may be used instead of plates (e.g., plates **40**, **40'**, **40"**, **87**, **87'**, **87a** and **87b**) to achieve the desired flow patterns into and/or out of the rotor's processing chamber. It will be appreciated that various types of outlet-control structures, including tubes and plates that permit fluid to flow out of the processing chamber at a selected radius or selected radii (like the plates **40** shown in FIGS. 19A-19E), may be used with other types of rotor designs, such as the rotors shown in FIGS. 20 and 23.

For some of the blood-processing procedures which have been discussed in this application, such as post-operative and intraoperative salvage, and RBC and plasma apheresis (see for example the processes represented in FIGS. 6 and 15), it is desirable that the interior plates **40** have holes **39** located at varying and closely spaced distances from the center of the plate **40** to its periphery. This placement of holes **39** ensures that all of a lighter fluid element (e.g., plasma) is forced out of the processing chamber **30**, before a heavier fluid element (e.g. RBCs) begins to be forced out.

FIG. 20 shows an alternative rotor **2c**, which may be used in much the same way as the rotor **2a** shown in FIG. 2. Like the FIG. 2 rotor **2a**, the rotor **2c** shown in FIG. 20 allows fluids to flow in or out of the rotor in only one direction at a time. The boundary wall **10** of rotor **2c** includes a top portion **108**, a circumferential portion **110**

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and a bottom portion **112**, so that the boundary wall **10** forms a shell surrounding the processing chamber **30**. Note that the shell formed by the circumferential **110** and bottom **112** portions of the FIG. 20 rotor **2c** differ from the exterior shell **3a** shown in FIG. 7 and the shell **3b** shown in FIG. 8A. The FIGS. 7 and 8A shells **3a** and **3b** do not directly touch the blood in the processing chamber. The circumferential **110** and bottom **112** portions of wall **10** in FIG. 20 do touch the blood in the processing chamber **30**.

The top portion **108**, circumferential portion **110** and bottom portion **112** of the boundary wall **10** may be curved, so that the rotor is generally ovoid and the borders between the various wall portions are not distinct. Shaping the boundary wall **10** in this way may reduce the amount of stress on the diaphragm **31** (in much the same way that the shaping of the interior of chuck **4a** shown in FIG. 3 reduces stresses in the diaphragm, as discussed above).

The FIG. 20 rotor **2c** also includes central core **116**. The boundary wall **10** and the core **116** are preferably made of rigid plastic pieces joined together. At the top of the rotor **2c**, there is a collector assembly **46** attached to a tube **13** connected to the rest of the disposable blood processing set (e.g., a cassette and additional tubing). The collector assembly **46** also interfaces with a rotary seal **48**, like the rotary seals discussed in connection with the FIG. 2 and FIG. 11 rotors **2a**, **2b**. The rigid core **116** of rotor **2c** is covered by an elastic balloon-shaped diaphragm **31**, which is held in place with an air-tight seal by a clamp **122**. (In alternative embodiments, the diaphragm may be attached to any point on the bottom wall **112**, or even to the circumferential wall **110**. If the membrane is attached near the top of the circumferential wall, the rotor becomes very similar to the rotor **2a** and shell **3b** combination of FIG. 8A. In such a rotor, the circumferential and bottom walls would not be considered boundary walls, since they would no longer

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come into contact with the blood being processed.) Between the diaphragm **31** and the collector assembly **46** is a plate **40**. As in the previously discussed rotors **2a**, **2b**, the plate **40** prevents the diaphragm **31** from touching the collector assembly **46**. The plate **40** is held away from the upper part **108** of the boundary wall **10**, so as to form a passage **44** between the boundary wall **108** and the plate **40**. The plate **40** preferably contains many, preferably small, holes to permit fluid to flow into the passage **44** from almost any point along the plate **40**. In a wall within the core **116** separating the core into interior and exterior portions is a pressure-supply port **120**, which is blocked by a frangible diaphragm during storage.

FIG. 21 shows the rotor **2c** being held in a chuck **4c**, which is turned by a motor **50**. As noted above in relation to the rotor/exterior-shell arrangement shown in FIG. 8A, the chuck and motor may be made small enough to fit inside core **116**, below pressure-supply port **120**; thus the chuck would hold the rotor **2c** from inside the core **116** instead of from outside the circumferential wall **110** as shown in FIG. 21. The collector assembly **46** is held stationary and in the proper alignment by brace **11**. The shaft **51** projects up past the chuck **4c** and narrows into a thinner section **126** (a nozzle), which penetrates the frangible diaphragm on the pressure-supply port **120** and makes an airtight seal. The shaft **51** has an axial through hole and protrudes below the motor **50**. A rotary pneumatic seal **55** is attached to the shaft **51** and is held stationary by fixture **57**. The pneumatic rotary seal **55** is connected by tubing **59** to the compressor/vacuum-source **61** and to a controllable exhaust valve **63**.

FIG. 22 shows the rotor **2c** spinning and partially full. In operation, the motor **50** spins the rotor **2c**. The diaphragm **31** is inflated by the compressor **61** until it fully occupies the cavity **114** defined by the plate **40**, the core

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116 and the boundary wall's circumferential 110 and bottom 112 portions. The inflated diaphragm 31 thus expels all of the air previously in the cavity 114 into the passage 44 and collector assembly 46 and on through a filter in the disposable set out to the room atmosphere. This reduces to its minimum the volume of the processing chamber 30, which is defined by the boundary wall 10 and the diaphragm 31. Donor blood, shed blood or another type of biological fluid then is allowed to flow into the rotor from the rest of the disposable set through tube 13 and collector assembly 46. The blood is propelled by centrifugal force towards the perimeter of the rotor 2c. As more blood enters, it continues to be propelled to the perimeter eventually flowing through the holes in the plate into the cavity 114 defined by the boundary wall 10, the core 116 and the plate 40, thereby increasing the volume of the processing chamber 30. As blood enters the processing chamber 30, the diaphragm 31 slowly collapses around the core 116, and the air between the diaphragm 31 and the core 116 is allowed to escape through exhaust valve 63.

Blood flow into the rotor 2c is stopped when the desired or available amount of blood has entered the rotor 2c or when the cavity 114 is full. The blood is subjected to the centrifugal force as long as is appropriate to separate the various components. When the separation is complete, the compressor 61 begins to re-inflate the diaphragm 31.

The manner of processing blood in the FIG. 20 rotor 2c is very similar to that of the FIG. 2 rotor 2a. When the air pressure acting on the side of the diaphragm 31 opposite the blood exceeds the pressure from the radius of the diaphragm 31 to the skirt of the collector assembly 46, fluid begins to flow from the cavity 114 through the holes in the plate 40, into the passage 44 to the collector assembly 46 and out of the rotor 2c into the rest of the processing set. This fluid may be diverted to a specific container or returned to a donor depending on the intention

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of the process and the specifics of the processing set. The blood element with the lightest specific gravity first flows out of the cavity **114** through the holes in the plate at the smallest radius not yet covered by the diaphragm **31**. Each blood element in turn by specific gravity will flow out of the rotor **2c** and can be diverted as desired. The process of emptying the rotor **2c** can be stopped at any time by stopping the compressor **61** from increasing the air pressure on the diaphragm **31** (while keeping the chuck's rotational speed constant).

If the rotor **2c** is processing blood, one likely place to stop might be when the diaphragm **31** touches the RBC layer and another might be when the rotor **2c** is empty. As noted with the FIG. 2 rotor **2a**, this cycle can be repeated as desired or, if washing of the blood components left in the rotor **2c** is desired, other fluids can be allowed to flow into the rotor **2c** and back out again by inflating or deflating the diaphragm **31** and manipulating valves and/or tubes in the processing set. At the end of the last cycle, the diaphragm **31** can be inflated to the proper position to obtain the desired hematocrit in the final product. As noted above, it may be desirable to change the rotor speed at different times while the rotor **2c** is filling or emptying in order to achieve the most advantageous combination of centrifugal force for separation and air pressure inside the diaphragm **31** required to overcome the current fluid head.

The core **116** of the FIG. 20 rotor **2c** serves a similar purpose to the chuck core **64** of the chuck **4a** shown in FIGS. 3-4, 9 and 12-13. The core **116** helps shape the diaphragm **31** when the processing chamber **30** is at its largest volume (which in the FIG. 20 rotor **2c** is when the diaphragm **31** is its relaxed position, unlike the FIG. 2 rotor **2a**, in which the diaphragm is in its relaxed position when the processing chamber **30** is at its lowest volume). The core **116** ensures that, when the processing chamber **30** is at its largest volume, there are holes **39** located at the innermost radius

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of the processing chamber **30**. (It will be appreciated that by shaping the core **116** so that the top of the core **116** covers the plate's center **37**, and so that the diameter of the top of the core **116** is not greater than the diameter at any other point of the core **116**, one can ensure that all of the lighter fluid elements can be emptied out of the rotor **2c** first, even when the processing chamber **30** is at the greatest volume permitted by the boundary wall **10** and the core **116** of the FIG. 20 rotor **2c**.)

FIG. 23 shows an alternative rotor **2d**, which can be used in much the same way as the rotor **2b** shown in FIG. 11. Like the FIG. 11 rotor **2b**, the rotor **2d** shown in FIG. 23 permits fluids to flow in and out of the rotor at the same time. The rotor **2d**, like the FIG. 20 rotor **2c**, has a boundary wall **10** that surrounds the processing chamber **30** and that is preferably made of rigid plastic pieces joined together. At the top of the rotor **2d**, there is a collector assembly **46** attached to tubes **83**, **93** connected to the rest of the processing set. The collector assembly **46** interfaces with a rotary seal **48**. The passage between the skirts of the collector assembly **46** connect with tube **93**. The fixed portion of rotor **2d** has an extension tube **130**, which connects tube **83** with the bottom of the rotor **2d**. The rigid core **116** is covered by a sleeve-shaped elastic diaphragm **31**, which is held in place with a air-tight seal by the inner portion of a lower, imperforate interior wall **134** and the inner portion of the (upper) plate **40**. The lower interior wall **134** is shown in FIG. 23 as extending to the periphery of the cavity **114**, but in an alternative embodiment, a smaller-diameter lower interior wall **134** may be used, or the lower interior wall may be left out entirely except for the inner ring portion that is used to clamp the bottom of the diaphragm **31**, or a perforate plate, like item **134'** in FIG. 24, may be used.

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The rigid core **116** is attached to the air-introduction area **136** and has one or more generally vertical holes in it that act as air conduits from the air-introduction area **136** to the space between the diaphragm **31** and the rigid core **116**. There are gaps in the rigid core **116** below the lower interior wall **134** and above the air-introduction area **136** that allow blood to flow from the extension tube **130** towards the perimeter of the rotor **2d**. The outer wall of the air-introduction area **136** has a pressure-source port **120** covered with a frangible diaphragm.

FIG. 25 shows the rotor **2d** being held in a chuck **4d**. The collector assembly **46** is held stationary and in proper alignment by brace **11**. The shaft **51** projects up past the chuck **4d** and narrows into a thinner section **126**, which penetrates the frangible diaphragm covering the pressure-source port **120** and makes an airtight seal with the port **120**.

FIG. 26 shows the rotor **2d** spinning and partially filled with fluid and with the diaphragm **31** partially inflated. The motor **50** spins the rotor **2d** at the proper rate. The process may be started with the diaphragm **31** deflated. Blood or other fluid flows into the rotor **2d** from the rest of the processing set through tube **83** and extension tube **130**. When the blood touches the bottom of the rotor **2d** it is propelled by centrifugal force towards the perimeter of the rotor **2d** and into the processing area. As blood enters the rotor **2d**, the air in the processing chamber **30** exits through the collector assembly **46** and tube **93** to a holding container in the processing set.

If it is not desired to process a full rotor of blood, the diaphragm **31** can be inflated by compressor **61** when the desired volume of blood has entered the rotor **2d**. The diaphragm **31** is inflated until it fills the unwanted rotor volume **138**. Operation of the rotor **2d** can then continue as normal but with a smaller-volume processing chamber **30**.

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When the processing chamber **30** is full of blood (with or without the diaphragm **31** inflated), the flow of blood into the rotor can continue through tube **83** and extension tube **130**. This new blood simply displaces the elements of blood in the processing chamber **30** with the lowest specific gravity. The elements with the lower specific gravity flow out through the collector assembly **46** and tube **93** to be diverted as desired by the processing set.

The extension tube **130**, like the interior imperforate plate **87** of the FIG. 11 rotor **2b**, introduces the unprocessed whole blood into the processing chamber **30** at a point spaced away from where the separated blood components exit the chamber **30**. If the unprocessed whole blood was introduced into the chamber **30** at a point too close to the point where the separated blood components exit the chamber **30**, some unseparated whole blood may be drawn out of the chamber **30** with the separated blood components.

In order to wash RBCs, wash solution may be introduced through tube **83** and extension tube **130**. At the end of the process, the diaphragm **31** can be further inflated to push out remaining wash fluid thereby increasing the hematocrit of the final product.

At the end of the cycle, the air between the diaphragm **31** and the core **116** is vented to exhaust valve **63** and the rotor **2d** is stopped. As shown in FIG. 27, the blood remaining in the processing chamber **30** falls to the bottom of the rotor **2d** and is pumped out through the extension tube **130** and tube **83** and replaced by the previously collected air.

This cycle may be repeated as desired. As discussed above in connection with the other rotors, it may be desirable to change the rotor speed at different times in order to achieve the most advantageous combination of centrifugal force for separation and air pressure inside the elastic wall member required to overcome the current fluid head.

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In the modified version of the FIG. 23 rotor shown in FIG. 24, the imperforate interior plate **40"** may be substantially imperforate so that fluid can only exit the processing chamber **30**, **114** at the periphery of the chamber. The lower interior wall may be perforate. Whole blood may be introduced into the processing chamber through an extension tube, so that the whole blood emerges into the processing chamber near the rotor's axis of rotation. Concentrated RBCs may be collected from the periphery of the processing chamber. The plate **40"** of the FIG. 24 rotor may be modified so that intermediate-density blood components, e.g., platelets, may be collected. (See the discussion above regarding FIGS. 19A-19D.)

FIG. 28 shows a rotor **2e** having a central port **163** that rotates with the body of the rotor during centrifugation. The rotor **2e** can serve both as the reservoir for collecting the blood collected by vacuum (e.g., from a wound drain, i.e., post-operative salvage) and as the centrifugal processing chamber. The rotor **2e** consists of a rigid boundary wall **10** and central core **116** made of rigid plastic pieces joined together. In the center at the top of the rotor **2e**, there is a port **163** attached to a tube **165** which terminates in a luer-type connector **167**. The rigid core **116** is covered by an elastic balloon-shaped diaphragm **31**, which is held in place with an air-tight seal by a clamp **122**. Between the diaphragm **31** and the central port **163** is a plate **40**. In the wall separating the inner and outer portions of the core **116** is a pressure-source port **120** covered with a frangible member. The pressure-source port **120** may be used to connect the rotor to a vacuum source, so that a vacuum may be applied to the diaphragm during the collection of blood. Pressurized gas may also be applied to the diaphragm through the pressure-source port **120** so as to force blood components out of the rotor.

Once the desired amount of blood has been collected in rotor **2e**, the vacuum pulling the blood into the rotor **2e** is

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discontinued, and the collected blood may then be processed. The rest of a disposable processing set, such as that shown in FIG. 28, may be connected to the rotor's connector **167**. For washing or concentrating the collected blood, the rotor **2e** is placed in a chuck as shown in FIG. 28. As with the chuck **4c** shown in FIG. 21, a thin section **126** of the shaft **51** penetrates the frangible member on the rotor's pressure-source port **120** and makes an airtight seal with the port **120**.

In a variation of the systems discussed above (such as the systems shown in FIGS. 5 and 14), the tubing **170** leading from the rotor **2e** may contain the rotary seal **148**, instead of a rotary seal being incorporated into the rotor. Alternatively, a skip-rope system, such as those described in U.S. Patent Nos. 4,151,844 to Cullis et al., 4,283,004 to Lamadrid, 4,734,089 to Cullis, and 4,900,298 to Langley, may be used. (A skip-rope system has the effect of untwisting the tubing connected to the rotor as the tubing is being twisted by the spinning rotor. The skip-rope system results in the tubing having net zero twist, and thus the tubing can be directly attached to both the spinning rotor and the stationary portion of the processing set.)

The tubing **170** in the disposable processing set shown in FIG. 28 branches into three tubes, one of which leads to a bag of saline (which is the wash solution), while another tube leads to the waste bag and the third tube leads to the product bag (where the processed cells are stored). The rotary seal **148** is held stationary and in proper alignment by fixture **11b**. (Since the rotary seal **148** is separated from the body of the rotor **2e** by tube **165**, the outlet-control plate **40** in this rotor **2e** does not serve the purpose of protecting the diaphragm **31** from being abraded by a non-rotating portion of the rotor. The plate **40** still serves the purpose of ensuring the proper flow of the separated fluid elements out of the rotor **2e** when the rotor is being emptied.)

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To process the blood in the rotor **2e**, the motor **50** spins the chuck and rotor **2e**. When separation of the blood components is complete, the compressor **61** begins to inflate the diaphragm **31**, so as to cause the fluid to flow through the holes in the plate **40**, through the passage **44** and out of the rotor **2e** into the rest of the disposable processing set. The blood element with the lightest specific gravity (the plasma, irrigation fluid, anticoagulant, etc.) is forced out of the rotor first and may be diverted to the waste bag by a valve **174**. Typically, the process of emptying will be stopped when the diaphragm **31** touches the RBC layer.

At this time, if the user wants to wash the RBCs before concentrating them, the speed of rotation of motor **50** and rotor **2e** is reduced to a slow speed. Saline from the saline bag is directed by valve **174** into the rotor **2e**. When the rotor **2e** is sufficiently full of the saline wash solution, the motor **50** alternately goes forward and backwards to mix the wash solution and the cells. After sufficient mixing, the motor **50** goes forward and gains speed up to its processing speed. In a manner similar to that described above, once the blood is fully separated, the diaphragm **31** is inflated, pushing the used wash solution out into the waste bag. When the diaphragm **31** touches the RBC layer or when sufficient wash solution has been removed to reach the desired final hematocrit, the final emptying process begins. As RBCs emerge from the rotor **2e**, they are diverted by valve **174** to the product bag. This process continues until the rotor **2e** is empty.

If the user does not want to wash the blood collected in the rotor, the steps of introducing saline into the rotor **2e**, washing the cells, centrifuging and forcing out the used saline may be omitted. As with the processes previously discussed, it may be desirable to change the rotational speed at different times while the rotor is emptying in order to achieve the most advantageous combination of

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centrifugal force for separation and air pressure on the diaphragm **31** to overcome the current fluid head.

In order to draw fluid into the rotor **2e**, the elastic diaphragm may be used to create the vacuum. Prior to attaching the port **163** to the tubing leading to the patient, the diaphragm is inflated by a source of compressed air, such as pump **61**. (FIG. 29 shows the diaphragm in its relaxed position **31e** and in its inflated position **31f**.) A compressor may be used to inflate the diaphragm to position **31f**, and the air in the interior of the rotor **2e** is vented to atmosphere through port **163**. After the diaphragm **31** is inflated to its maximum diameter, port **163** is attached by means of a tube to a patient, and the compressor **61** is turned off. The air on the core **116** side of the diaphragm **31** is vented to atmosphere--through vent **63**, if the rotor is mounted in a chuck as shown in FIG. 28. The vacuum caused by the stretched, resilient diaphragm (shown by line **31f** in FIG. 29) trying to resume its natural shape (shown by line **31e** in FIG. 29) causes blood to flow from the patient into the rotor **2e**.

After a vacuum has been pulled on the diaphragm, the vacuum source can be turned off or even disconnected until sufficient blood has flowed into the rotor to reduce the vacuum below an acceptable level. This would allow the patient to be transported (for example between the operating room and the recovery room) without being attached to a vacuum source.

FIG. 29 shows an inexpensive and simple means of providing compressed air to inflate the diaphragm and a vacuum to assist deflating it. The rotor **2e** is attached to spring bellows **180** which incorporates a calibrated spring **182**. The bellows **180** and the rotor **2e** are supported by legs **184**. To inflate the diaphragm **31e**, the operator squeezes the spring bellows **180**. After the patient is connected to port **163** of rotor **2e**, the operator allows the spring bellows **180** to re-expand under the force of the spring **182** thereby

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creating the vacuum assist for the inflated diaphragm **31f** for pulling blood into the rotor **2e** from the patient.

The rotor **2c** shown in FIG. 20 can also be used to collect blood from a wound drain, in much the same way as the rotor **2e** of FIGS. 28 and 29. A spring bellows similar to the one shown in FIG. 29 can also be adapted for providing a vacuum to the diaphragm of the rotors **2a** of FIG. 2, or for supplementing the vacuum in the rotor/shell combinations shown in FIGS. 7 and 8A.

FIG. 30 shows an alternative rotor according to the present invention using a set of tubes **190** extending from the top wall **191** of the rotor. This rotor, unlike all of the previously discussed rotors, does not have an interior wall--i.e., a wall (plate) both sides of which come into contact with the blood or other biological fluid being processed. The set of tubes **190** all join together into a common tube **165**, through which fluid both enters and exits the rotor. When this rotor is emptied, fluid first exits the innermost tube or tubes not covered by the diaphragm. Thus, if the processing chamber is at its maximum volume, the innermost tube or tubes **188** provide the first pathway for the exiting fluid. The common tube **165** may be attached to the rest of the processing set (which of course does not rotate) by means of a rotary seal, such as the rotary seal **148** shown in FIG. 28, or a skip-rope system.

FIG. 31 shows a rotor similar to the FIG. 30 rotor except that the various tubes connected to the rotor remain separate and attach through a skip-rope system or rotary seal to various parts of the stationary portion of the processing set. These tubes permit the addition of various fluids to the rotor at chosen radii and/or the removal of fluids from chosen points by controls such as pumps or clamps acting on the stationary portion of the processing set.

In an alternative rotor shown in FIGS. 32 and 33, the set of tubes **190** are located within the processing chamber--

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between the boundary wall **10** and the diaphragm **31**. The common outlet tube **165** exits the rotor's top wall **10** at only one location, instead of several locations as shown in FIG. 30. The tubes of the FIG. 32 rotor are oriented radially and may be located adjacent the top wall **10**. The tubes may be formed by spot welding a sheet of material that is at least semi-rigid to the bottom of the boundary wall **10**. The tubes must be rigid enough to maintain open channels from one end of the tube to the other even when air pressure in the chuck is pressing the diaphragm **31** towards the boundary wall **10**. A set of tubes **190** having varying lengths, such as the tubes shown in phantom in FIG. 32, may be used to permit fluid communication between the outlet port **165** and points at various radii in the processing chamber. The set of tubes **190** includes tubes **196** extending substantially to the periphery of the rotor, tubes **198** not extending very far from the rotor's axis of rotation, and tubes **192** of varying intermediate lengths. Of course, more or fewer tubes may be used. In addition, the tubes may include holes to provide the separated fluid elements additional points of exit from the rotor's processing chamber.

In one alternative arrangement, all the tubes extend substantially to the rotor's periphery, and all the tubes have holes in order to provide fluid communication with different points in the rotor's processing chamber. In another alternative embodiment, a single tube having a plurality of holes along its length may be arranged in a spiral extending from the rotor's axis of rotation to its periphery. In all of these embodiments using tubes, the tubes perform the function of the outlet-control plates: they keep open passageways for fluid to flow to and from various points at various radii in the processing chamber. Thus, only tubes **192** of intermediate length may be used to draw fluid components of intermediate density from the rotor's processing chamber (like the plate **40** shown in FIG. 19A), and tubes **196** that extend to the rotor's periphery may

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be used as an inlet-control structure to introduce unseparated fluid to the periphery of the rotor (like the imperforate plate **87** shown in FIG. 11).

FIG. 34 shows a rotor having tubes arranged in a manner similar to the rotor shown in FIGS. 32 and 33. The FIG. 34 rotor has a fixed portion with a collector assembly **46**, which is separated from the diaphragm **31** by a small-diameter wall **137**, to which all the tubes are attached and which spins with the tubes, the boundary wall **10** and the diaphragm **31**. A rotary seal **48** provides the seal between the collector assembly **46** and the collector/rotary-seal area **28** of the boundary wall **10**. The rotor's cross-section shown in FIG. 34 shows tubes **192** extending an intermediate distance between the rotor's axis of rotation and the rotor's perimeter. The rotor may also have additional tubes of different lengths. One of the tubes **192** shown in FIG. 34 has a hole **139** to permit flow into the tube **192** from a point closer to the rotor's axis of rotation. Instead of tubes (or an interior plate), grooves may be formed on the bottom of the top wall **10** in order to provide an outlet control means, as shown below in FIGS. 41 and 42.

The FIG. 34 rotor may also be adapted to function like the two-conduit, edge-loading rotor **2b** shown in FIG. 11, by adding an imperforate interior wall between the boundary wall **10** and the tubes, and adding a second conduit to the fixed portion. Instead of tubes, radial grooves (like those shown in FIGS. 41 and 42) may be formed on the bottom of the imperforate interior wall. In another alternative embodiment, imperforate tubes extending all the way to the periphery of the processing chamber may be used to introduce unseparated fluid to the edge of the processing chamber, instead of an imperforate interior wall.

FIGS. 35 and 36 show another alternative rotor. This rotor has a plurality of tubes **196** which extend from a small-diameter wall **137** all the way to the rotor's periphery. The tubes **196** have holes **139** in order to permit

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flow from the chamber **30** to the collector assembly **46**. Instead of having a top wall, this rotor's diaphragm **31** bends around the tubes **196** so as to cover most of the top of the rotor. The rigid rotating portion **28** of the rotor covers the collector assembly **46** and the rotary seal **48**. The diaphragm **31** is attached to the circumference of the rigid rotating portion **28**. The rigid rotating portion **28** is capable of being held and turned by a chuck so as to cause the diaphragm **31**, the tubes **196** and any fluids in the chamber **30** to spin as well. The chuck should also have a lid to cover the top portion of the diaphragm **31** so as to limit how far the diaphragm **31** can expand upwards. The FIG. 35 rotor may also be adapted to function like the two-conduit, edge-loading rotor **2b** shown in FIG. 11, by adding a second conduit to the fixed portion, and adding an imperforate interior wall above the tubes **196** or imperforate tubes extending to the periphery of the processing chamber.

It will be appreciated that, during centrifugation in the systems shown in FIGS. 3, 9, 12 and 21, rigid portions of the chuck and/or rotor limit how far the diaphragm **31** can expand outwardly in a radial direction or in an axial direction. For instance, in the system shown in FIG. 3, the chuck **4a** limits how far the diaphragm can expand in a radial outward direction and in a downward axial direction. The rotor's rigid boundary wall **10** prevents fluid from flowing upwardly out of the chamber. In the system shown in FIG. 20, the top **108**, bottom **112** and circumferential **110** portions of the rotor's boundary wall **10** respectively limit the diaphragm's expansion in the upward and downward axial directions and in the outward radial direction. By limiting the expansion of the diaphragm **31**, stresses on the diaphragm during centrifugation may be limited, and better control of the volume of the processing chamber **30** may be maintained.

The rotors having a fixed portion and a rotatable portion (e.g., the rotors shown in FIGS. 2, 11, 16-18, 19A-19D, 19E, 20, 23, 34 and 35) all have a rotary seal **48**.

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FIG. 37 shows a rotary seal **48** typical of the prior-art rotary seals made by Haemonetics and others. The fixed portion **204** is held in place by a rotor brace (such as item **11** shown in FIGS. 5, 21 and 25) and is thus restrained from vertical, horizontal and rotational movement. While the fixed portion **204** is held in place, the body of the rotor **10**, only part of which is shown in FIG. 37, may be spun by a chuck, which restrains the body of the rotor from vertical and horizontal movement while spinning the rotor body. The rotating body **10** of the rotor has rigidly attached and sealed to it an annular rotating seal face **209**, which is typically made of ceramic or carbon and is lapped to a very flat surface. The rotating seal face **209** interfaces with an annular non-rotating seal face **208**, which is also typically made of ceramic or carbon and lapped to a very flat surface. The non-rotating seal face **208** is held against the rotating seal face **209** by resilient seal member **206**. The resilient sealing member **206** is attached and sealed to the fixed portion **204**.

This rotary seal **48** is less effective when the pressure inside the rotor becomes greater than the ambient pressure, because the greater inside pressure tends to push up the resilient seal member **206** and thus reduces the force the non-rotating seal face **208** exerts against the rotating seal face **206**. The rotors shown hereinabove are subjected to greater internal pressures, especially during the emptying phase, when air pressure in the chuck pushes against the diaphragm in order to force fluid out of the rotor. If the pressure differential becomes large enough, the seal faces **208**, **209** will separate momentarily until the internal and external pressures equalize. This momentary separation permits gas to escape from the rotor. Alternately, when a vacuum is created in the interior of the rotor, greater force pushes the seal faces **208**, **209** together, thereby creating more heat from friction.

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Although the rotary seal shown in FIG. 37, or another type of rotary seal, may be used in the rotors of the present invention, the improved rotary seal **48** shown in FIG. 38 is preferred. As in the prior-art rotary seal, the fixed portion **204** is held by a brace, preventing vertical, horizontal and rotational movement by the fixed portion **204**. The boundary wall **10** of the rotor body is spun by a chuck, which restrains the rotor body from horizontal and vertical movement. The annular rotating seal face **209**, preferably made from ceramic or carbon and lapped to a very flat surface is rigidly attached and sealed to the boundary wall **10**.

An annular non-rotating seal face **212** is pressed against the rotating seal face **209** by a spring **214**, one end of which is attached to the fixed portion **204** and the other end of which is attached to the non-rotating seal face **212**. The force applied by this spring **214** is not affected by changes in air pressure within the rotor. The non-rotating seal face **212** can move up and down with respect to the fixed portion **204**. The non-rotating seal face **212** is also preferably made of ceramic or carbon and lapped to a very flat surface. A seal is provided between the non-rotating seal face **212** and the fixed portion **204** by flexible seal member **216**. The flexible seal member **216** and the spring member **214** are separate members (unlike the prior-art rotary seals). Both seal faces **209**, **212**, the spring **214** and the flexible seal member **216** surround the rotor's axis of rotation.

It is important that the fixed portion and the rotor body be located an acceptable distance apart, otherwise the spring **214** may not exert the desired amount of force. If the spring is compressed too much (because the fixed portion and the rotor body are too close to each other), the rotary seal may generate excessive heat when the rotor is spun. If the spring is not compressed enough (because the fixed portion and the rotor body are too far from each other), the

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rotary seal may not exert enough force to keep contaminants from entering the processing chamber between the seal faces **209**, **212**.

The flexible seal member **216** and the non-rotating seal face **212** may be designed so that any pressure differential between the inside and the outside of the rotor does not affect the force holding the non-rotating seal face **212** against the rotating seal face **209**. This may be accomplished by creating opposing surfaces of equal surface area on the flexible seal member **216** and the non-rotating seal face **212**, so any effect caused by pressure on one surface is canceled by the effect on the other equal and opposing surface. One way of accomplishing this is to use a flexible seal member **216** with a circular cross-section (as shown in FIG. 38) and to place a small step **218** in the non-rotating seal face **212** (as also shown in FIG. 38) to make up for the small gap in the circular cross-section of the flexible seal member **216**. In this design, increases or decreases in pressure act uniformly in all directions and therefore exert no net force. With this design, the seal strength is independent of any pressure differential between the inside and outside of the rotor and is determined solely by the spring constant and the amount of compression of the spring **214**.

The rotary seal may be configured so that the spring **214** is connected to and extends from the rotating body of the rotor to the rotating seal face, the flexible seal member **216** connects the rotating body and the rotating seal face, and the non-rotating seal face is rigidly attached to the rotor's fixed portion. Alternatively, two springs and two flexible seal members may be used, so that both seal faces are mounted on springs--one spring being attached to the rotor's fixed portion and the other spring being attached to the rotor's rotating body--and so that a flexible seal member forms a seal between each seal face and

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its respective portion of the rotor (i.e., the rotating portion or the fixed portion).

The rotary seal shown in FIG. 38 may be modified in a number of ways. For instance, as shown in the detail view represented in FIG. 39, the spring **314** and the flexible seal member **316** of the rotary seal may be made out of the same piece of material **310**. In addition to manufacturing advantages, such a design has the advantage of providing a spring **314** that applies an even vertical force around the axis of rotation (whereas a coil spring may apply a greater force on some areas of the seal face **212** than on others). One end **303** of the integral spring/seal member **310** is attached to the fixed portion **204** of the rotor. Of course, as noted above with respect to the FIG. 38 rotary seal, the non-rotating seal face **212** can move up and down with respect to the fixed portion **204**. The middle **305** of the member **310** is attached and sealed to the seal face **212**. The spring portion **314** of the member **310** stretches between these two points of attachment **303**, **305**. The other end **307** of the member **310** is also attached and sealed to the rotor's fixed portion **204**. The flexible-seal-member portion **316** of the member **310** connects the two points of attachment **307** and **305**. FIG. 39 also shows the step **218** in the seal face **212** for negating the effects of internal rotor pressure on the force applied to the seal faces.

FIGS. 38 and 39 show the springs **214**, **314** located outside of the flexible seal **216**, **316**, so that the spring is in contact with ambient pressure but is not in direct contact with the rotor air, which air undergoes the rapid pressure variations. The spring may also be located inside the flexible seal. Thus, the spring may be mounted in the region of the step **218**, spanning the space between the fixed portion **204** and the non-rotating seal face **212**. If the spring is perforated, the changes in internal rotor pressure may pass through the spring to the flexible seal member, so that changes in internal pressure exert no net changes in

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force between the rotating and non-rotating seal faces **209**, **212**.

If the flexible seal member **216**, **316** is resilient and rigid enough to maintain an adequate seal, it may function as the spring member as well, so that a separate spring member is not required. As long as the components of the rotary seal are shaped properly, changes in internal rotor pressure will exert no net changes in force between the rotating and non-rotating seal faces **209**, **212**. For example, since the seal portion **316** and the rotating seal face **212** in the rotary seal shown in FIG. 39 have opposing surfaces of equal surface area--so that any effect caused by pressure on one surface is canceled by the effect on the other equal and opposing surface--the separate spring portion **314** may be eliminated without causing the changes in internal rotor pressure to effect the effectiveness of the rotary seal as long as the seal portion **316** is resilient and rigid enough.

It will be appreciated that the rotors of the present invention can have shapes other than those described hereinabove. For example, FIG. 40 shows a rotor similar in function to the rotor of FIG. 11, but having a generally hemispherical shape.

Different types of outlet-control means may be used. For example, FIGS. 41 and 42 show top and cross sectional views of a preferred embodiment of the rotor. This rotor uses grooves **244**--preferably radially aligned--formed on the bottom of the top wall **10** as the outlet control means, instead of tubes or an interior perforate wall. The grooves **244** are defined by vertical channel walls **240**; if the vertical channel walls **240** are placed close enough to each other, they can keep channels--the grooves **244**--open from the holes **239**, which connect the processing chamber and the collector assembly **46**, to the periphery of the rotor, or to whatever radius it is desired to maintain a channel. The FIG. 42 rotor has a fixed portion (which includes the collector assembly **46** and which interfaces the rotating

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portion of the rotor at a rotary seal **48**), and thus a small-diameter internal wall **237** is necessary to keep the spinning diaphragm **31** from coming into contact with the fixed portion and possibly being abraded.

Although the invention has been described with reference to several preferred embodiments, it will be understood by one of ordinary skill in the art that various modifications can be made without departing from the spirit and the scope of the invention, as set forth in the claims hereinbelow.

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What is claimed is:

1. A rotor for use in a centrifuge system having means for holding and spinning the rotor, the rotor comprising:

a rigid mounting member for being held and spun by the spinning means; and

an elastic diaphragm mounted on the rigid mounting member so as to spin with the rigid mounting member, the diaphragm defining a chamber of varying volume, wherein the rigid mounting member defines a conduit in fluid communication with the chamber.

2. A rotor according to claim 1 further including a fixed portion, through which the conduit passes; and

a rotary seal located around the rotor's axis of rotation, the rotary seal providing a seal between the rigid mounting member and the fixed portion; wherein the rigid mounting member is rotatably mounted around the fixed portion and the rotor's axis of rotation, the mounting member capable of being held and spun by the spinning means.

3. A rotor according to one of claims 1 and 2, further including outlet-control means for controlling the flow of liquid out of the chamber into the conduit.

4. A rotor according to claim 3, wherein the outlet-control means includes channel walls, defining a channel from a point in the processing chamber to a point in fluid communication with the conduit, the channel walls being spaced close enough to each other so as to prevent the diaphragm from blocking the channel.

5. A rotor according to claim 3, wherein the rigid mounting member includes an imperforate boundary wall, and wherein the outlet control means includes channel walls on the interior side of the boundary wall, the channel walls defining channels on the interior of the imperforate boundary wall.

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6. A rotor according to claim 3, wherein the outlet-control means includes a perforate, substantially rigid interior wall located within the chamber.

7. A rotor according to claim 6, wherein the rigid mounting member includes a boundary wall, the boundary wall being substantially rigid and substantially imperforate, and wherein the perforate interior wall is mounted adjacent to the boundary wall.

8. A rotor according to one of claims 5 and 7, wherein the outlet control means extends substantially to the periphery of the chamber.

9. A rotor according to claim 8, wherein the outlet control means provides fluid communication between a variety of points within the chamber and the conduit.

10. A rotor according to one of claims 5 and 7-9, wherein the boundary wall extends substantially to the chamber's periphery.

11. A rotor according to claim 10, wherein the boundary wall includes a circumferential portion, and wherein the chamber and the diaphragm are located inside of the circumferential portion.

12. A rotor according to one of claims 5 and 7, wherein the boundary wall defines the top of the chamber and the diaphragm is mounted near the perimeter of the boundary wall.

13. A rotor according to one of claims 10 and 12, further including an exterior shell mounted around the circumference of the boundary wall, such that the exterior shell and the boundary wall define a cavity and the diaphragm is located within the cavity.

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14. A rotor according to claim 13, wherein the exterior shell includes a core.

15. A rotor according to claim 3, wherein the outlet-control means includes at least one tube, wherein the tube provides fluid communication between the chamber and the conduit.

16. A rotor according to claim 3, wherein the outlet-control means includes a set of tubes.

17. A rotor according to one of claims 3-16, further including a second conduit, so that uncentrifuged fluid may enter the chamber through the second conduit, while centrifuged fluid may exit the chamber through the first conduit.

18. A rotor according to claim 17, wherein the rotor further includes an imperforate interior wall mounted adjacent the outlet control means, so as to direct fluid entering the chamber from the second conduit towards the periphery of the chamber, the imperforate interior wall also defining the first conduit so that fluid may flow from the outlet-control means to the first conduit.

19. A rotor according to claim 18, wherein the imperforate interior wall extends substantially to the chamber's periphery.

20. A rotor according to claim 17, wherein the rotor further includes

a rigid core member fixedly mounted to the rigid mounting member and about the rotor's axis of rotation, the diaphragm being located around the core member, and

wherein one of the first and second conduits includes a tube extending through the core member to the bottom of the chamber.

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21. A rotor according to claim 2, wherein the rotary seal includes

a base,

a spring member surrounding the rotor's axis of rotation and mounted on the base,

first and second seal faces, which surround the rotor's axis of rotation and which spin in relation to each other, the first seal face being mounted on the spring member so that the spring member applies a force pressing the first seal face against the second seal face, and

a flexible seal member surrounding the rotor's axis of rotation, and preventing flow between the first seal face and the base.

22. A rotor according to claim 21, wherein the spring member and the flexible seal member are different portions of a single piece of material.

23. A rotor according to one of claims 21 and 22, wherein the flexible seal member and the first seal face are disposed so that the force with which the spring member presses the first seal face against the second seal face is not substantially affected by pressure within the rotor.

24. A rotor according to one of claims 21-23, wherein the rotary seal's base is part of the rotor's fixed portion and the rotary seal's second seal face is attached to the rigid mounting member.

25. A rotor according to claim 21, wherein the spring member has an interior side and an exterior side, and the pressures on the interior and exterior sides is the same.

26. A rotor according to claim 2, wherein the rotary seal includes

a base,

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first and second seal faces, which surround the rotor's axis of rotation and which spin in relation to each other, wherein a force presses the first seal face against the second seal face, and

a flexible seal member surrounding the rotor's axis of rotation, and preventing flow between the first seal face and the base, wherein the flexible seal member and the first seal face are disposed so that the force pressing the first seal face against the second seal face is not substantially affected by pressure within the rotor.

27. A rotor according to claim 2, wherein the rotor includes an interior wall fixedly attached to the rigid mounting member, wherein the interior wall separates the diaphragm from the fixed portion of the rotor.

28. A rotor according to claim 27, further including channel walls, defining a channel from a point in the processing chamber to a point in fluid communication with the conduit, the channel walls being spaced close enough to each other so as to prevent the diaphragm from blocking the channel.

29. A rotor according to claim 28, further including

a second conduit, so that uncentrifuged fluid may enter the chamber through the second conduit, while centrifuged fluid may exit the chamber through the first conduit; and

an imperforate interior wall attached to the rigid mounting member so as to spin with the rigid mounting member, and mounted with respect to the second conduit so as to direct fluid entering the chamber through the second conduit towards the periphery of the chamber, wherein the imperforate interior wall having the channel walls disposed thereon so as to permit flow from the chamber to the first conduit.

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30. A system for separating a fluid having heavier and lighter components, the system comprising:

a rotor according to one of claims 1-29; and

means for holding the rigid mounting member of the rotor and for spinning the rotor around an axis; and

means, in fluid communication with the spinning means, for changing the pressure of a control fluid adjacent the rotor's diaphragm.

31. A system according to claim 30, wherein the pressure-changing means includes means for applying pressurized gas against the diaphragm, so as to force fluid out of the rotor.

32. A system according to one of claims 30 and 31, wherein the pressure-changing means includes means for applying a vacuum against the diaphragm, so as to draw fluid into the rotor.

33. A system for processing blood from a wound drain according to claim 32, further including

a wound drain placed in a patient, the wound drain being attached the rotor, wherein a vacuum is applied to the diaphragm so as to draw blood from the wound drain into the chamber; and

means for directing, after the rotor is spun, lighter blood components to a separate reservoir and returning concentrated red blood cells remaining in the rotor to the patient.

34. A system according to claim 33, wherein the directing means directs the concentrated red blood cells to a second separate reservoir, which may be connected to the patient.

35. A system for processing blood from a wound drain according to claim 31, further including

a wound drain placed in a patient;

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canister means, in fluid communication with the wound drain and the rotor, for holding blood from the wound drain, wherein a vacuum is applied to the canister means so as to draw blood from the wound drain into the canister means;

means for moving blood from the canister means to the rotor; and

means for directing, after the rotor is spun, lighter blood components to a separate reservoir and returning concentrated red blood cells remaining in the rotor to the patient.

36. A system for processing blood from a patient's surgery site according to claim 31, further including

a suction tube leading from the surgery site, the suction tube being attached to the rotor, wherein blood drawn from the surgery site through the suction tube may be provided to the rotor; and

means for directing, after the rotor is spun, lighter blood components to a separate reservoir and returning concentrated red blood cells remaining in the rotor to the patient.

37. A system for processing blood from a patient's surgery site according to claim 36, further including

canister means, in fluid communication with the suction tube and the rotor, for holding blood from the suction tube, wherein a vacuum is applied to the canister means so as to draw blood from the wound drain into the canister means; and

means for moving blood from the canister means to the rotor.

38. A system for separating a fluid having heavier and lighter components, the system comprising:

a rotor according to one of claims15-17, 21 and 22; and

means for holding the rigid mounting member of the rotor and for spinning the rotor around an axis; and

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means, in fluid communication with the spinning means, for changing the pressure of a control fluid adjacent the rotor's diaphragm;

wherein the first conduit permits into flow of unseparated fluid into the chamber, while the second conduit flow of separated fluid components out of the chamber.

39. A system for performing red-blood-cell apheresis on a donor according to claim 38, further including

means for drawing whole blood from the donor and introducing the whole blood into the chamber through the second conduit; and

control means for controlling the speed of rotation of the spinning means and the rotor, and for controlling the pressure-changing means so that the pressure being applied to the diaphragm allows the chamber to increase in volume at a rate substantially equal to the volume of the red-blood-cell component of the whole blood entering the chamber, so that the volume of lighter fluid components in the chamber is kept relatively low.

40. A system according to claim 39, wherein the means for drawing blood includes means for adding replacement fluid to the whole blood as the whole blood is drawn from the donor.

41. A system according to claim 39, further including means for adding replacement fluid to blood components being returned to the patient.

42. A system according to claim 30-41, further including control means for controlling the speed of rotation of the spinning means and the rotor, and for controlling the pressure-changing means.

43. A system according to claim 42, wherein the control means includes means for determining the chamber's volume

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based on the speed of the spinning means and the pressure created by the pressure changing means.

44. A system according to claim 43, wherein the control means further includes means for controlling the volume of the chamber.

45. A system for processing biological fluids of different densities, the system comprising:

a rotor according to one of claims 3-22;

means for holding and spinning the rotor around the axis of rotation so as to separate the fluid into a denser component, a lighter component, and an intermediate-density component;

means for determining when the intermediate density component is located at the given radius; and

means for applying pressure radially outward from the axis of rotation, so as to force the intermediate-density component through the outlet-control means and the conduit.

46. A centrifuge system for accepting a rotor having a rigid mounting member and an elastic diaphragm attached to the mounting member, the system comprising:

means for holding the rigid mounting member of the rotor and for spinning the rotor around an axis; and

means for changing the pressure of a control fluid adjacent the rotor's diaphragm.

47. A system according to claim 46, wherein the spinning means includes a chuck and the pressure-changing means is in fluid communication with the chuck.

48. A system according to one of claims 46 and 47, wherein the pressure-changing means includes means for applying a vacuum against the diaphragm, so as to draw fluid into the rotor.

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49. A system according to one of claims 46-48, wherein the pressure-changing means includes means for applying pressurized gas against the diaphragm, so as to force fluid out of the rotor.

50. A system according to one of claims 46-49, further including control means for controlling the speed of rotation of the spinning means, and for controlling the pressure-changing means.

51. A system according to claim 50, wherein the control means includes means for determining the volume of fluid in the rotor based on the speed of the spinning means and the pressure created by the pressure-changing means.

52. A system according to claim 51, wherein the control means includes means for controlling the volume of fluid in the rotor by controlling the speed of the spinning means and the pressure created by the pressure-changing means.

53. A system according to claim 52, wherein the control means causes the volume of the processing chamber to remain constant.

54. A centrifuge system for accepting a rotor, the system comprising:

means for spinning the rotor around an axis; and

control means for controlling the spinning means so as to cause the spinning means to continually cycle through a range of rotational speeds around a desired rotational speed, so as to prevent the system from vibrating excessively.

55. A method for processing biological fluids of different densities, the method comprising the steps of:

providing a rotor according to one of claims 1-29;

introducing an unseparated fluid into the chamber; and

holding the rotor by the rigid mounting member and spinning the rotor around an axis so as to separate the fluid into denser and lighter components, the denser component congregating away from the axis while the lighter component congregates closer to the axis.

56. A method according to claims 55 further including the step of applying pressure to the diaphragm so as to force a fluid component out of the chamber.

57. A method according to claim 56, wherein a lighter component is forced out of the chamber first.

58. A method according to claim 56, wherein a denser component is forced out of the chamber first.

59. A method of processing blood from a donor according to claim 56, wherein the step of introducing unseparated fluid into the chamber includes the step of introducing blood into the chamber; and

wherein the method further includes the steps of

storing lighter blood components, and

directing concentrated red blood cells remaining in the rotor to the donor.

60. A method of processing blood according to claim 56, wherein the step of introducing unseparated fluid into the chamber includes the step of introducing blood into the chamber; and

wherein the method further includes the steps of

directing lighter blood components to the donor, and

storing concentrated red blood cells.

61. A method of processing blood from a wound drain according to claim 56, wherein the step of introducing unseparated fluid into the chamber includes the step of

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placing a wound drain in a patient,
attaching the wound drain to the rotor, and
drawing blood from the wound drain into the chamber; and

wherein the method further includes the steps of
directing lighter blood components to a separate reservoir, and
returning concentrated red blood cells remaining in the rotor to the patient.

62. A method of processing blood from a wound drain according to claim 56, wherein the step of introducing unseparated fluid into the chamber includes the steps of
placing a wound drain in a patient,
attaching the wound drain to a canister,
attaching the canister to the rotor, and
drawing blood from the canister into the chamber; and

wherein the method further includes the steps of
directing lighter blood components to a separate reservoir, and
returning concentrated red blood cells remaining in the rotor to the patient.

63. A method of processing blood from a patient's surgery site according to claim 56, wherein the step of introducing unseparated fluid into the chamber includes the steps of
drawing blood from the surgery site into the chamber; and

wherein the method further includes the steps of
directing lighter blood components to a separate reservoir, and
returning concentrated red blood cells remaining in the rotor to the patient.

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64. A method according to claim 56, wherein the speed that the rotor is spun is reduced so as to force a fluid component out of the chamber.

65. A method according to claim 56, wherein the rotor is spun at a constant speed, while the pressure applied against the diaphragm is increased, until a predetermined pressure is reached, then while the pressure against the diaphragm is held constant, the speed of the rotor is reduced.

66. A system according to claim 56, wherein the pressure-changing means maintains a constant pressure against the diaphragm, while the speed of the rotor's spinning is decreased until a predetermined speed is reached, then the pressure against the diaphragm is increased.

67. A method according to claim 56, wherein the rotor is emptied by reducing the speed that the rotor is spun and increasing the pressure against the diaphragm.

68. A method according to claim 56, wherein the volume of the chamber is controlled by changing the pressure applied to the diaphragm and by controlling the speed of rotation of the rotor.

69. A method according to claim 56, wherein the rotor is stopped and pressure applied to the diaphragm so as to force the remaining fluid out of the rotor.

70. A method for processing biological fluids of different densities, the method comprising the steps of:

providing a rotor according to one of claims 15-17, 21 and 22;

introducing an unseparated fluid into the chamber;

holding the rotor by the rigid mounting member and spinning the rotor around an axis so as to separate the fluid into denser and lighter components, the denser

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component congregating away from the axis while the lighter component congregates closer to the axis; and

applying pressure to the diaphragm,

wherein the first and second conduits permit the separated lighter components to be forced out of the rotor through the first conduit while unseparated fluid is introduced into the chamber through the second conduit.

71. A method according to claim 70, wherein the pressure being applied to the diaphragm is held constant so as to maintain the chamber at a constant volume, so that the volume of lighter components being forced out of the chamber is substantially equal to the volume of unseparated fluid entering the chamber.

72. A method of performing red-blood-cell apheresis on a donor according to claim 70, wherein the step of introducing unseparated fluid into the chamber includes the steps of

drawing whole blood from the donor, and

introducing the whole blood into the chamber through the second conduit while the rotor is being spun; and

wherein the step of applying pressure to the diaphragm includes the step of

forcing lighter blood components out of the chamber through the first conduit to the donor, while the rotor is being spun and while whole blood is being introduced into the chamber.

73. A method according to claim 72, further including the step of adding anticoagulant to the whole blood as the whole blood is drawn from the donor.

74. A method according to one of claims 72 and 73, further including the step of adding replacement fluid to the blood components being returned to the donor.

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75. A method according to one of claims 72-74, wherein the pressure being applied to the diaphragm allows the chamber to increase in volume at a rate substantially equal to the volume of the red-blood-cell component of the whole blood entering the chamber, so that the volume of lighter fluid components in the chamber is kept relatively low.

76. A method of separating fluid into lighter and heavier components, the method comprising the steps of:

providing a rotor having an elastic diaphragm defining a variable-volume processing chamber, and having first and second conduits providing fluid communication to the processing chamber;

spinning the rotor; and

introducing the unseparated fluid into the processing chamber through the second conduit while the rotor is being spun and while separated fluid components are forced out of the processing chamber through the first conduit.

77. A method of performing red-blood-cell apheresis on a donor according to claim 76, the method further including the steps of

drawing whole blood from the donor;

adding replacement fluid to the whole blood before the whole blood is separated;

introducing the whole blood into the rotor through the second conduit while the rotor is being spun, so that the whole blood is separated into red blood cells and lighter fluids, including plasma and replacement fluid; and

returning the plasma and the replacement fluid to the donor while whole blood is still being drawn from the donor.

78. A method of collecting red blood cells from a donor, the method comprising the steps of:

providing a rotor having first and second conduits providing fluid communication to the processing chamber;

drawing whole blood from the donor;

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adding replacement fluid to the whole blood;

after adding the replacement fluid to the whole blood, introducing the whole blood into the rotor through the second conduit;

spinning the rotor, so that the whole blood is separated into red blood cells and lighter fluids, the lighter fluids including plasma and replacement fluid; and

drawing plasma and replacement fluid out of the rotor through the first conduit.

79. A method according to claim 78, further including the step of:

returning the plasma and the replacement fluid to the donor.

80. A method according to claim 78, further including the step of:

returning the plasma and the replacement fluid to the donor, while whole blood is still being drawn from the donor.

81. A method according to 78, wherein the step of adding replacement fluid to the whole blood includes adding anticoagulant to the whole blood.

82. A method for processing biological fluids of different densities, the method comprising the steps of:

providing a rotor comprising:

an elastic diaphragm defining a chamber for holding the biological fluids,

a conduit leading from the chamber, and

outlet-control means for maintaining an open channel to the conduit for fluid at a given radius in the chamber;

spinning the rotor around an axis so as to separate the fluid into a denser component, a lighter component, and an intermediate-density component;

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determining when the intermediate density component is located at the given radius; and

applying pressure radially outward from the axis of rotation, so as to force the intermediate-density component through the outlet-control means and the conduit.

83. A rotary seal comprising:

a base;

a spring member surrounding the rotary seal's axis of rotation and mounted on the base;

first and second seal faces, which surround the axis of rotation and which spin in relation to each other, the first seal face being mounted on the spring member so that the spring member applies a force pressing the first seal face against the second seal face; and

a flexible seal member, separate from the spring member, the flexible seal member surrounding the axis of rotation and preventing flow between the first seal face and the base.

84. A rotary seal according to claim 83, wherein the flexible seal member and the first seal face are disposed so that the force with which the spring member presses the first seal face against the second seal face is not substantially affected by pressure within the rotor.

85. A rotary seal according to one of claims 83 and 84, wherein the spring member and the flexible seal member are different portions of a single piece of material.

86. A rotary seal comprising:

a base;

first and second seal faces, which surround the axis of rotation and which spin in relation to each other;

means, surrounding the rotary seal's axis of rotation and mounted on the base, for applying a force pressing the first seal face against the second seal face and for

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preventing flow between the first seal face and the base, wherein the means and the first seal face are disposed so that the force with which the spring member presses the first seal face against the second seal face is not substantially affected by pressure within the rotor.

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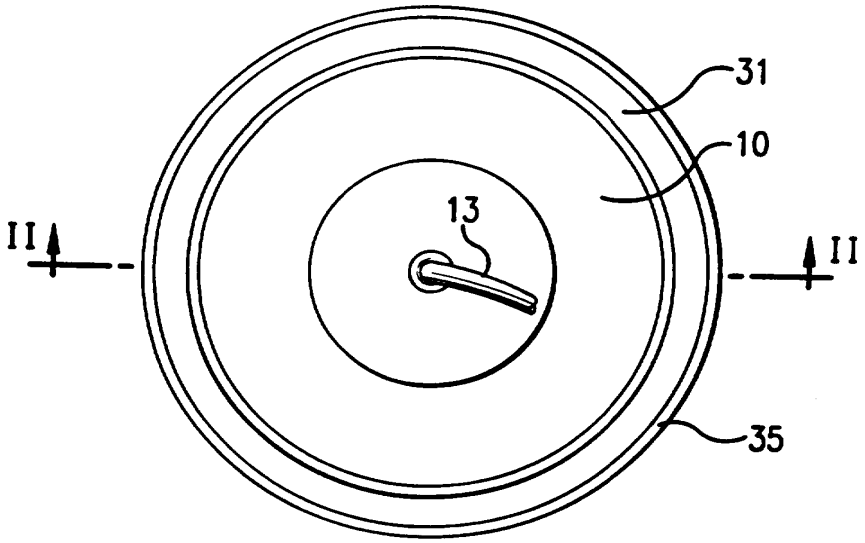


FIG. 1

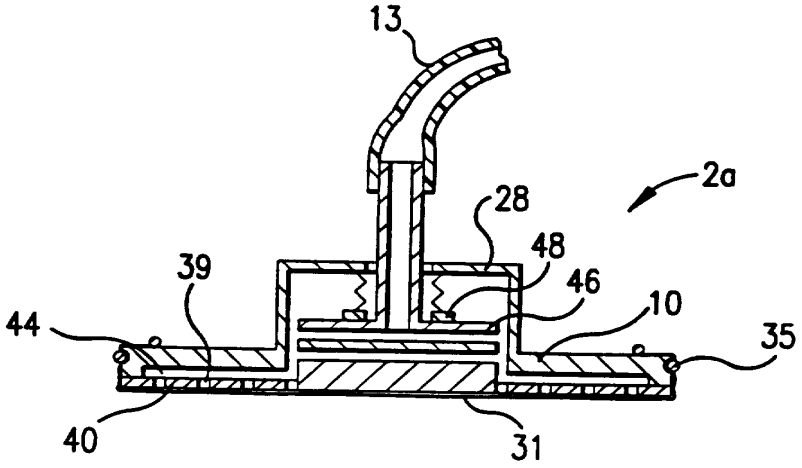


FIG. 2

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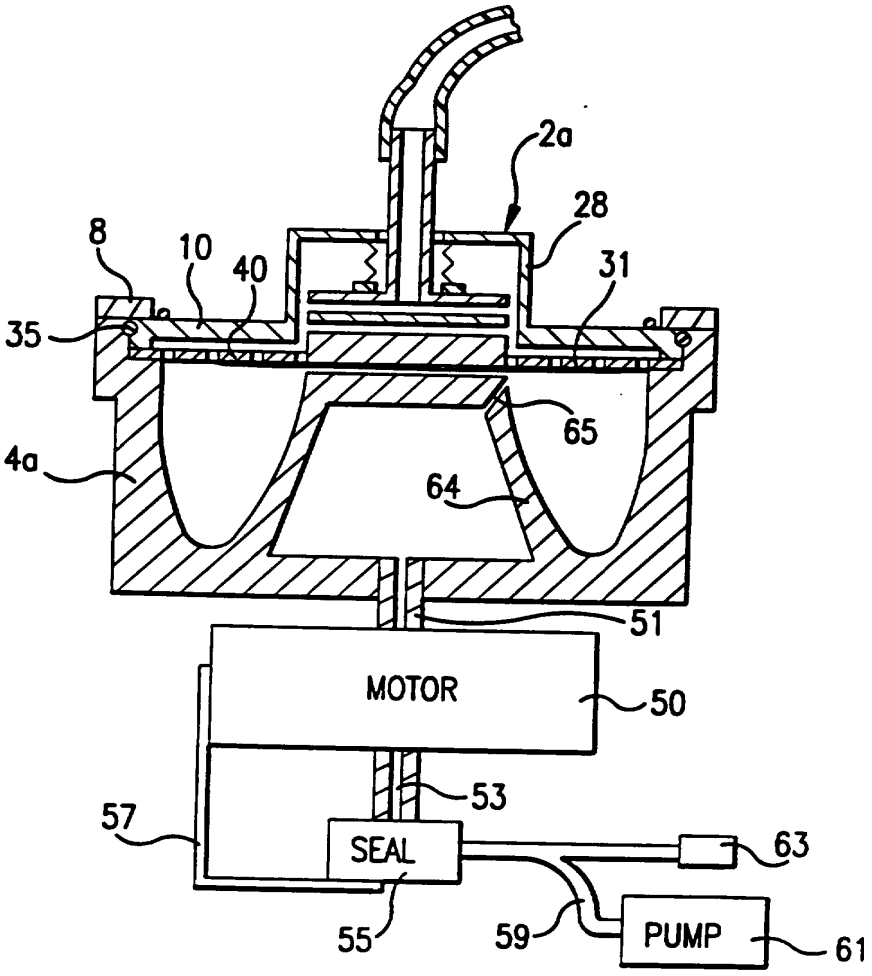


FIG.3

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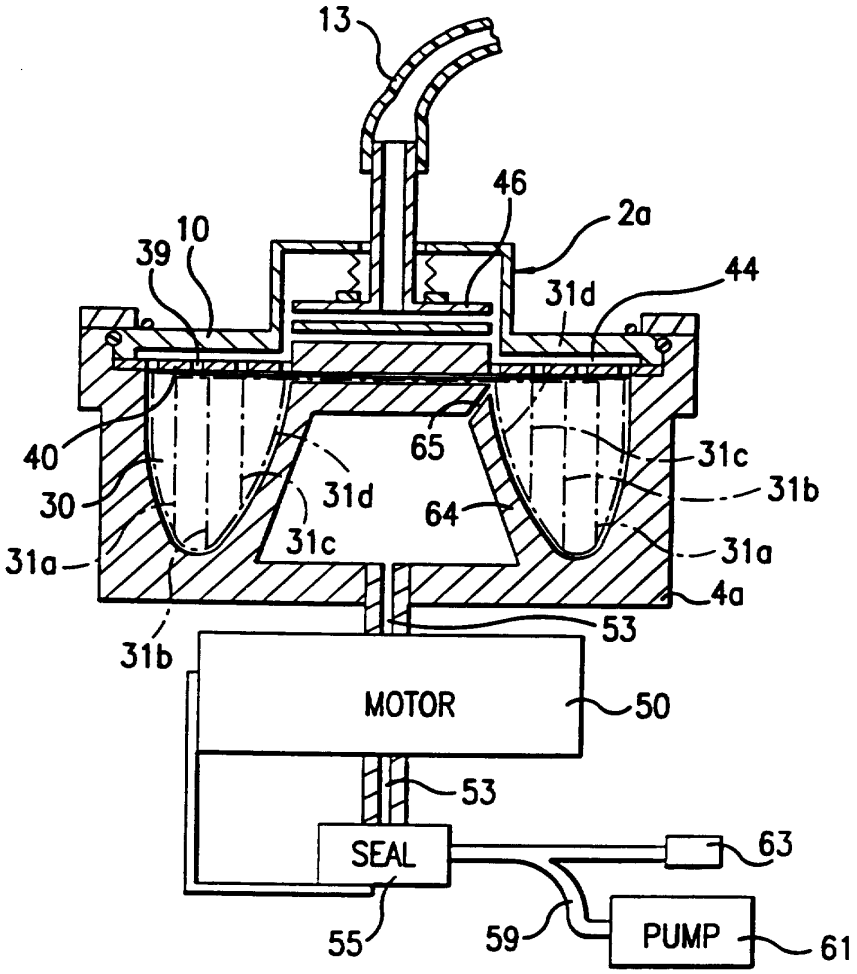


FIG.4

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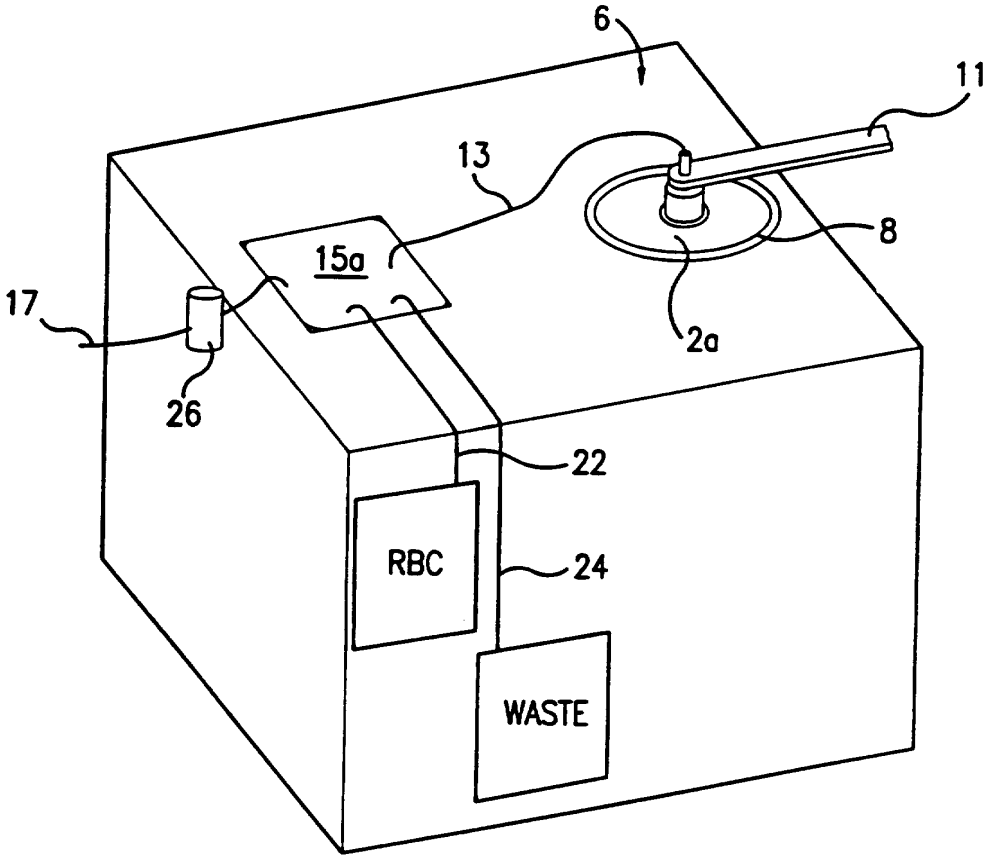


FIG.5

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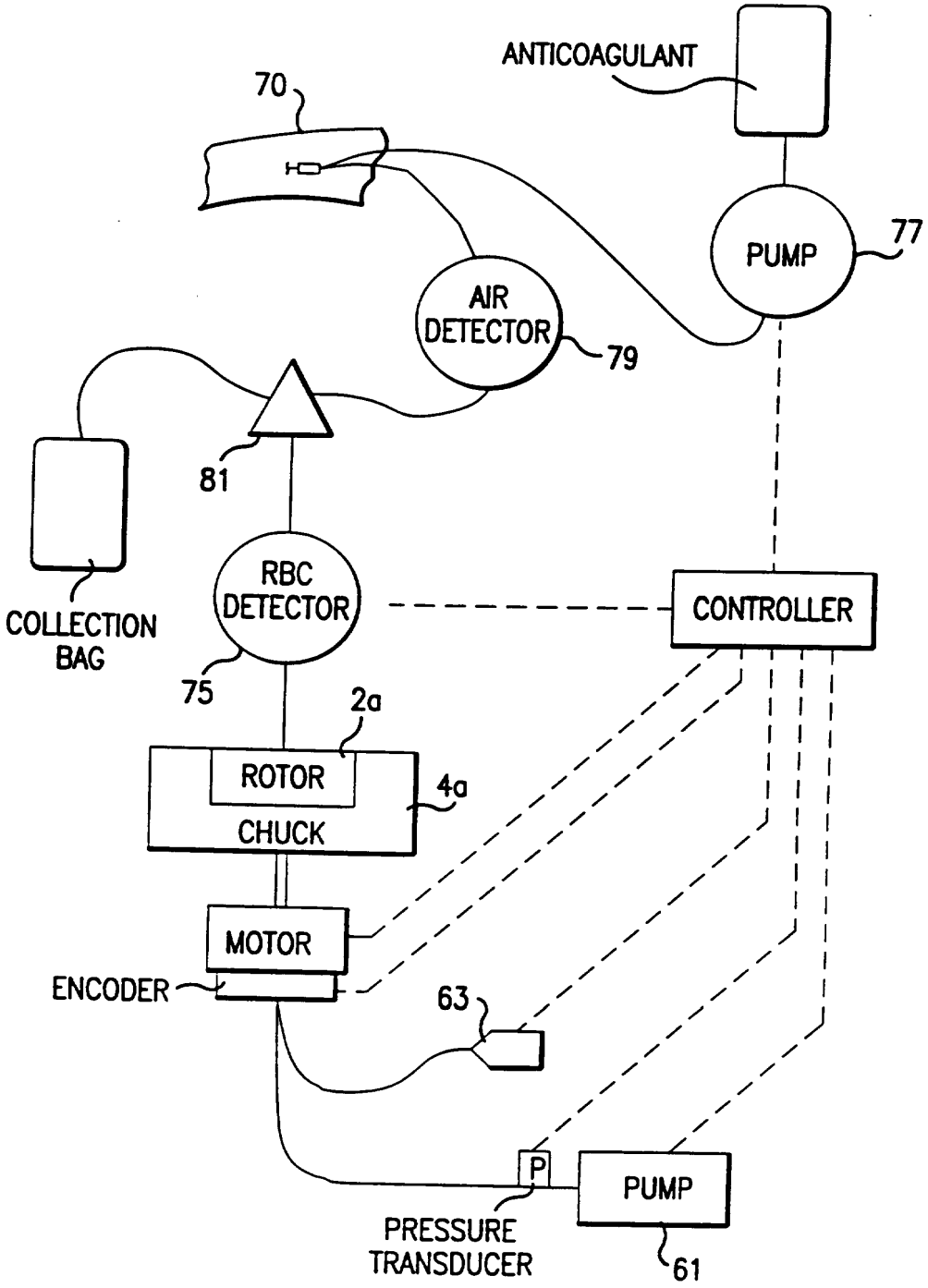


FIG.6

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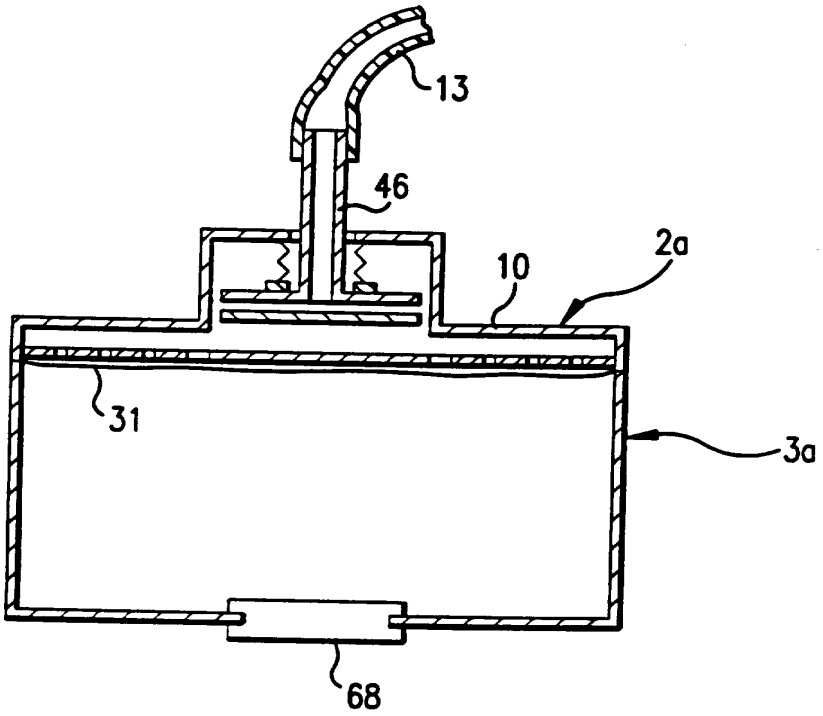


FIG.7

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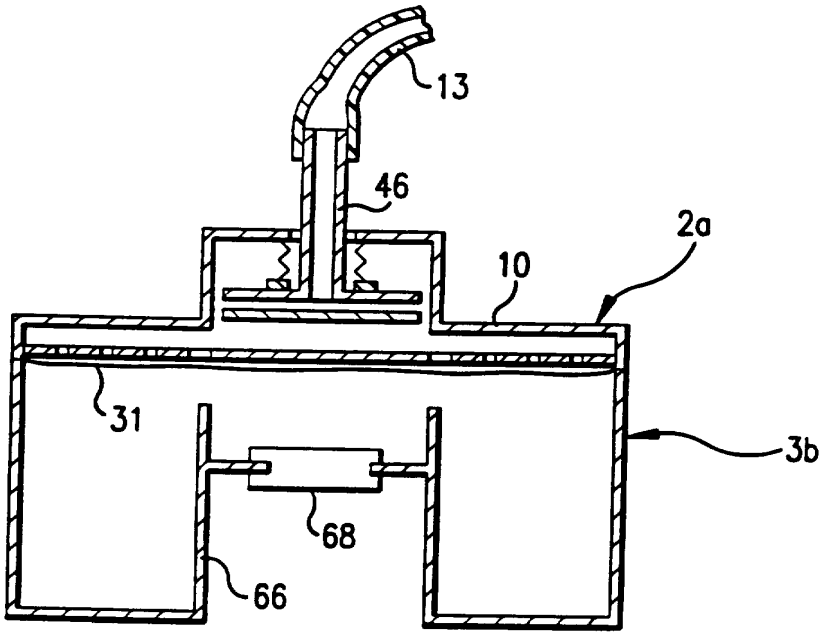


FIG.8A

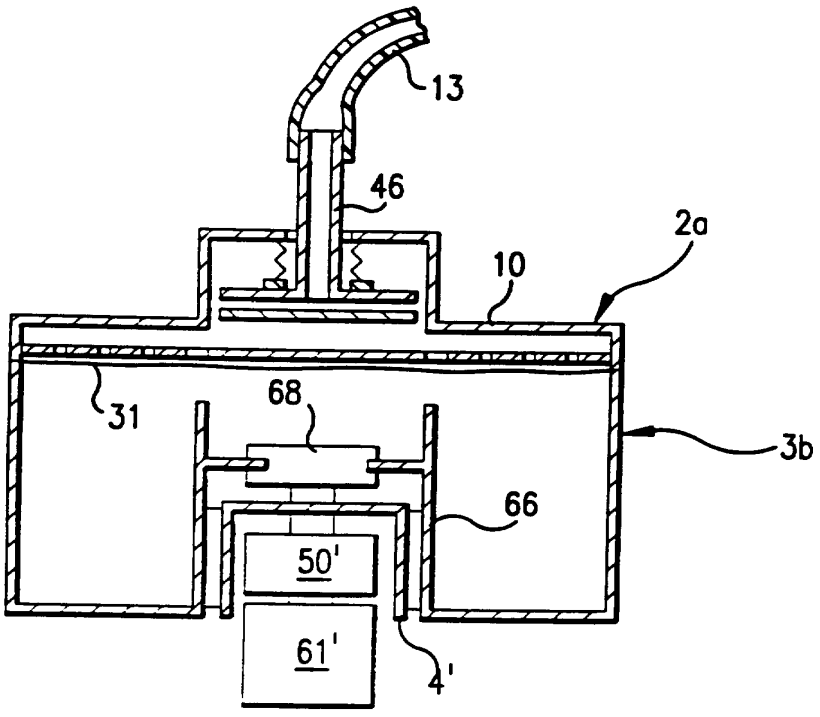


FIG.8B

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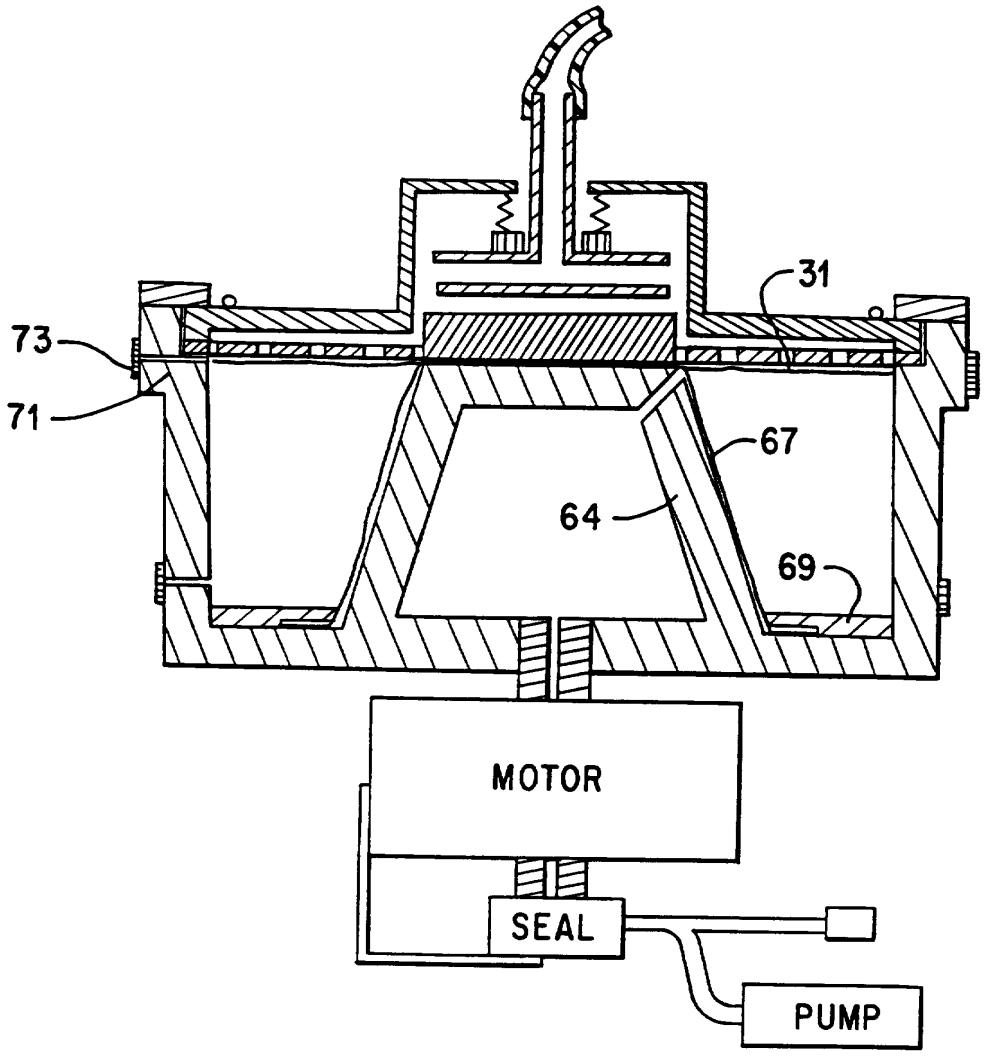


FIG. 9

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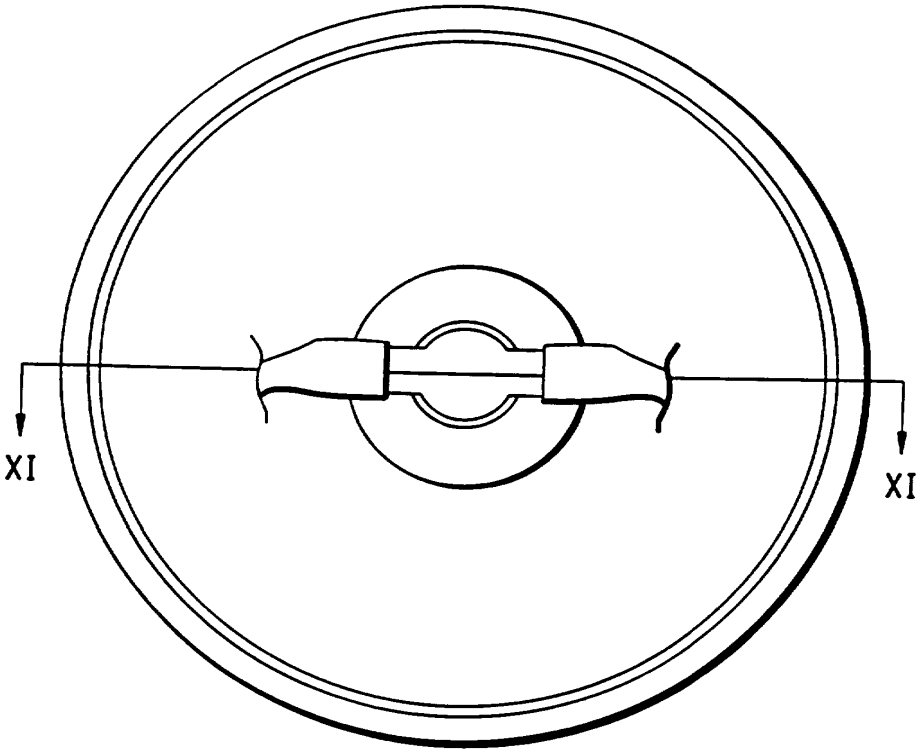


FIG.10

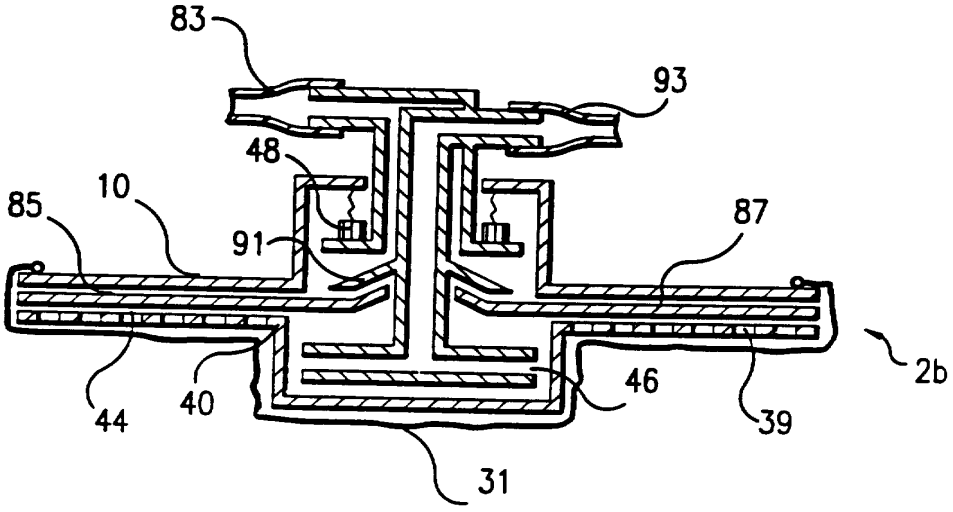


FIG.11

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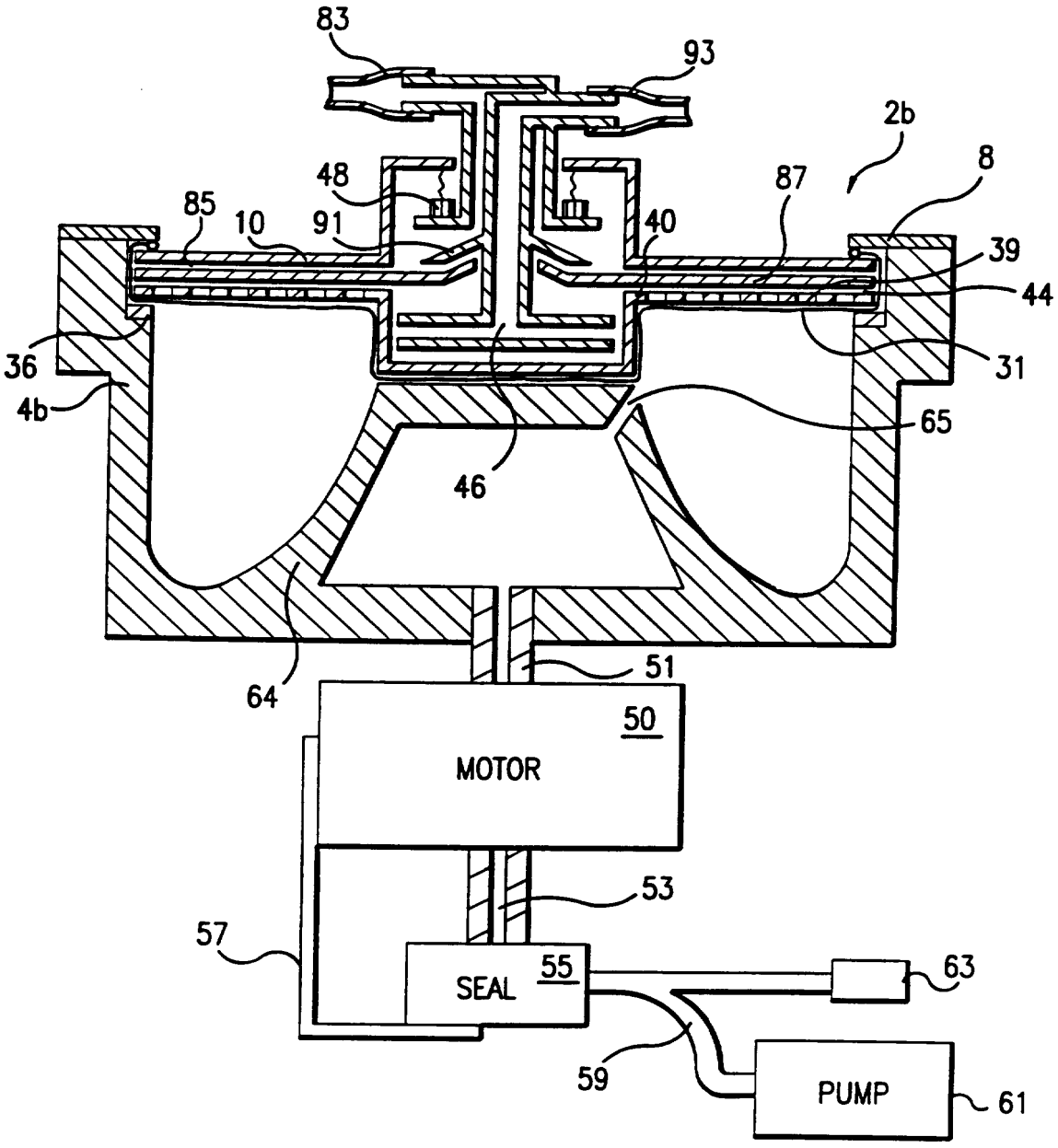

83
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MOTOR
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SEAL
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PUMP
61

FIG.12

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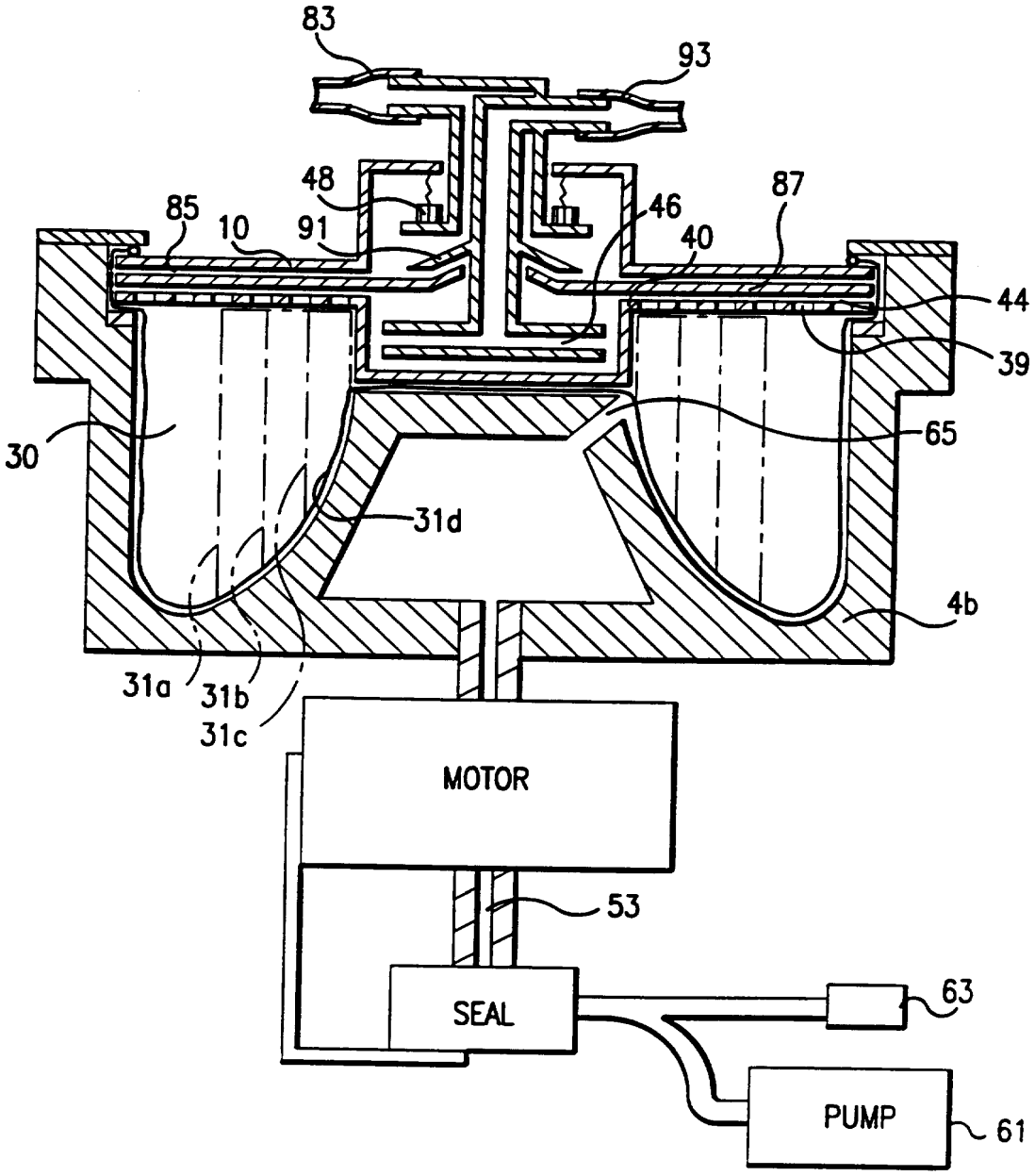

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FIG.13

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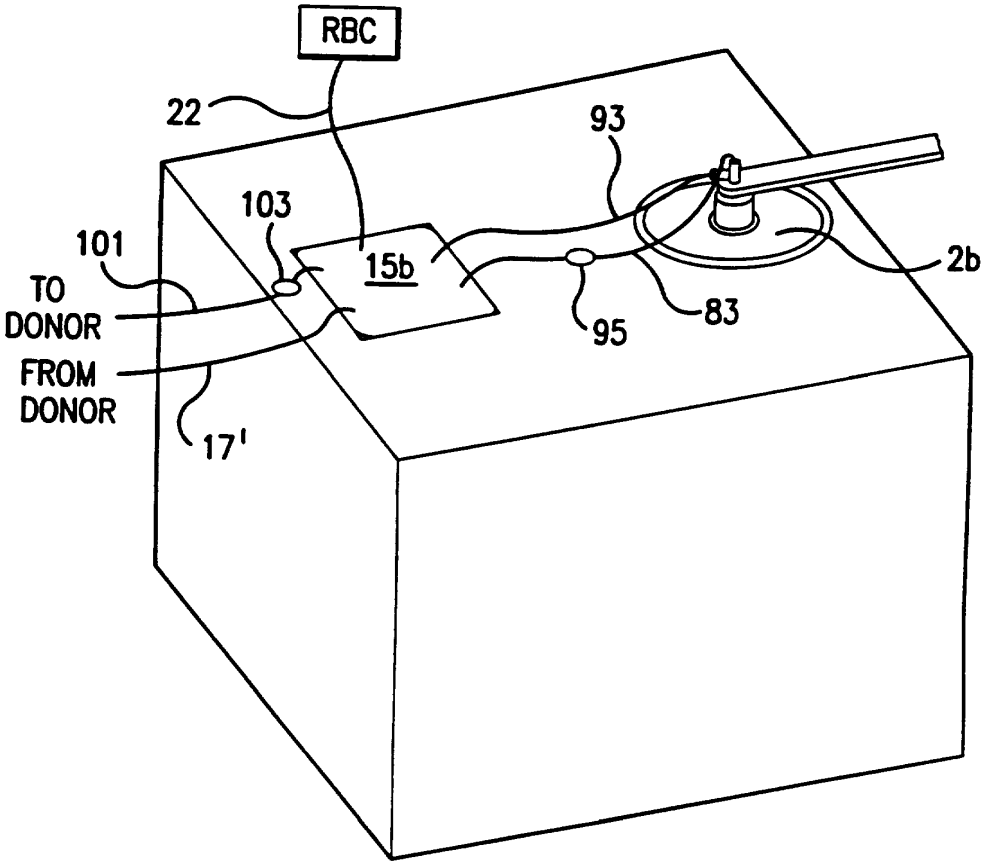


FIG. 14

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0890

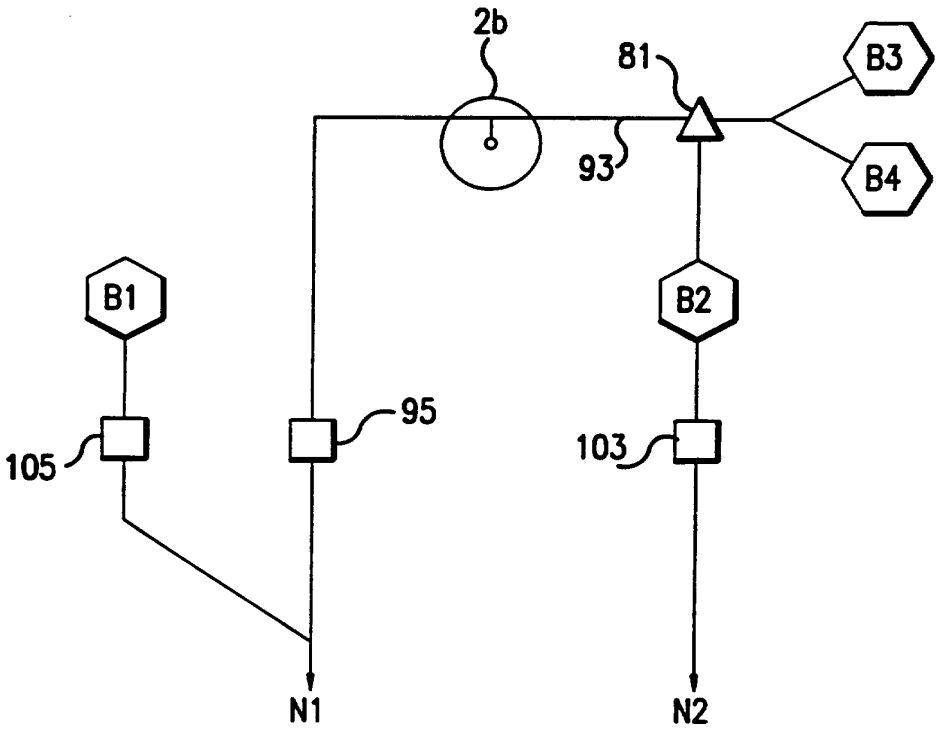


FIG.15

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0891

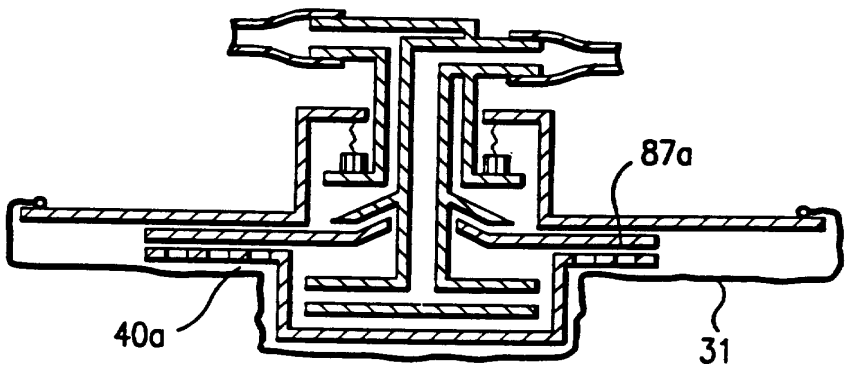


FIG.16

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0892

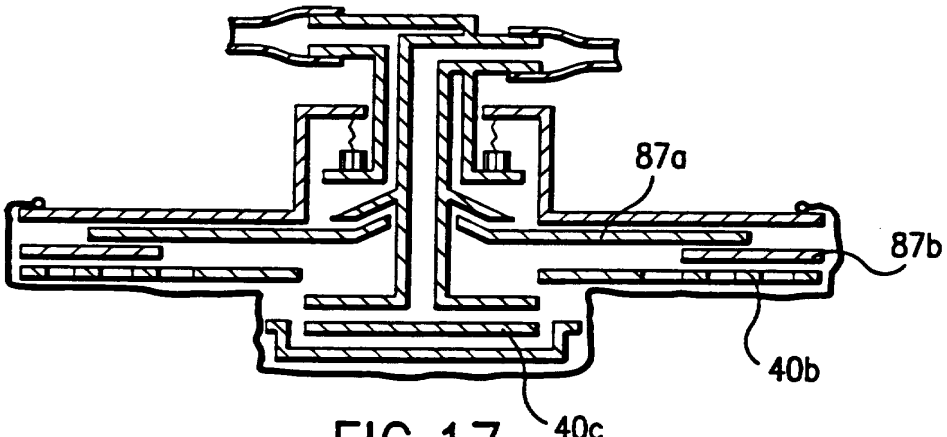


FIG.17

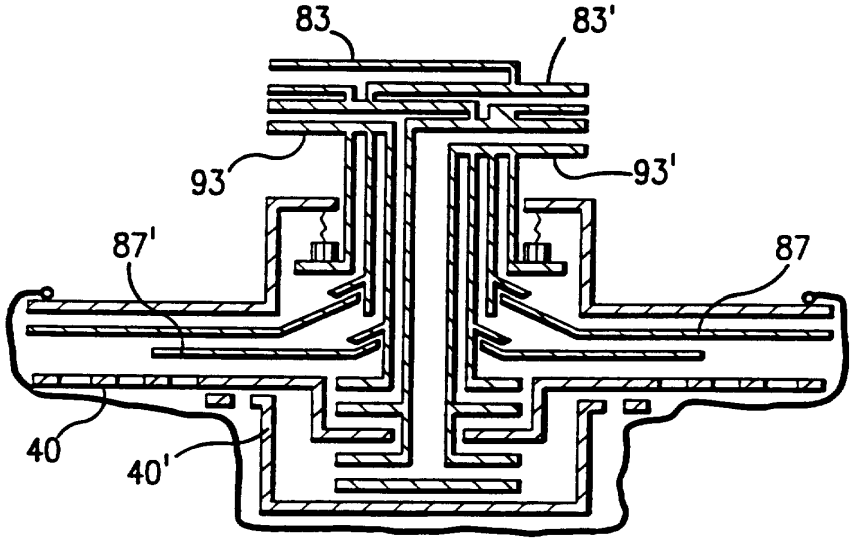


FIG.18

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0893

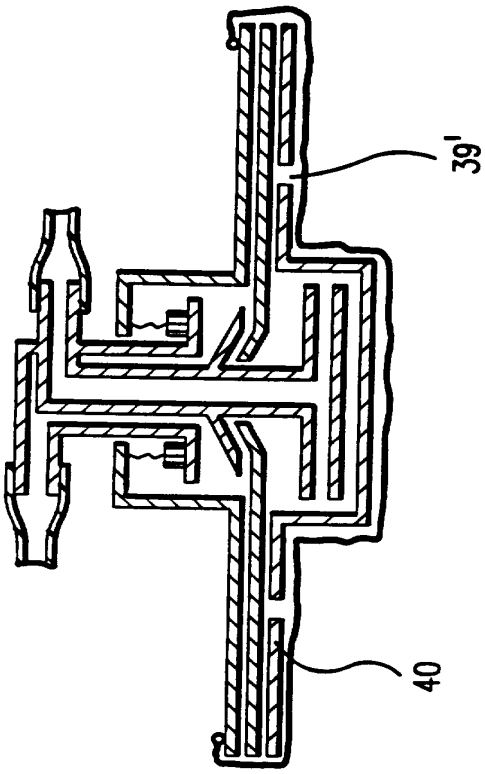


FIG.19A

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0894

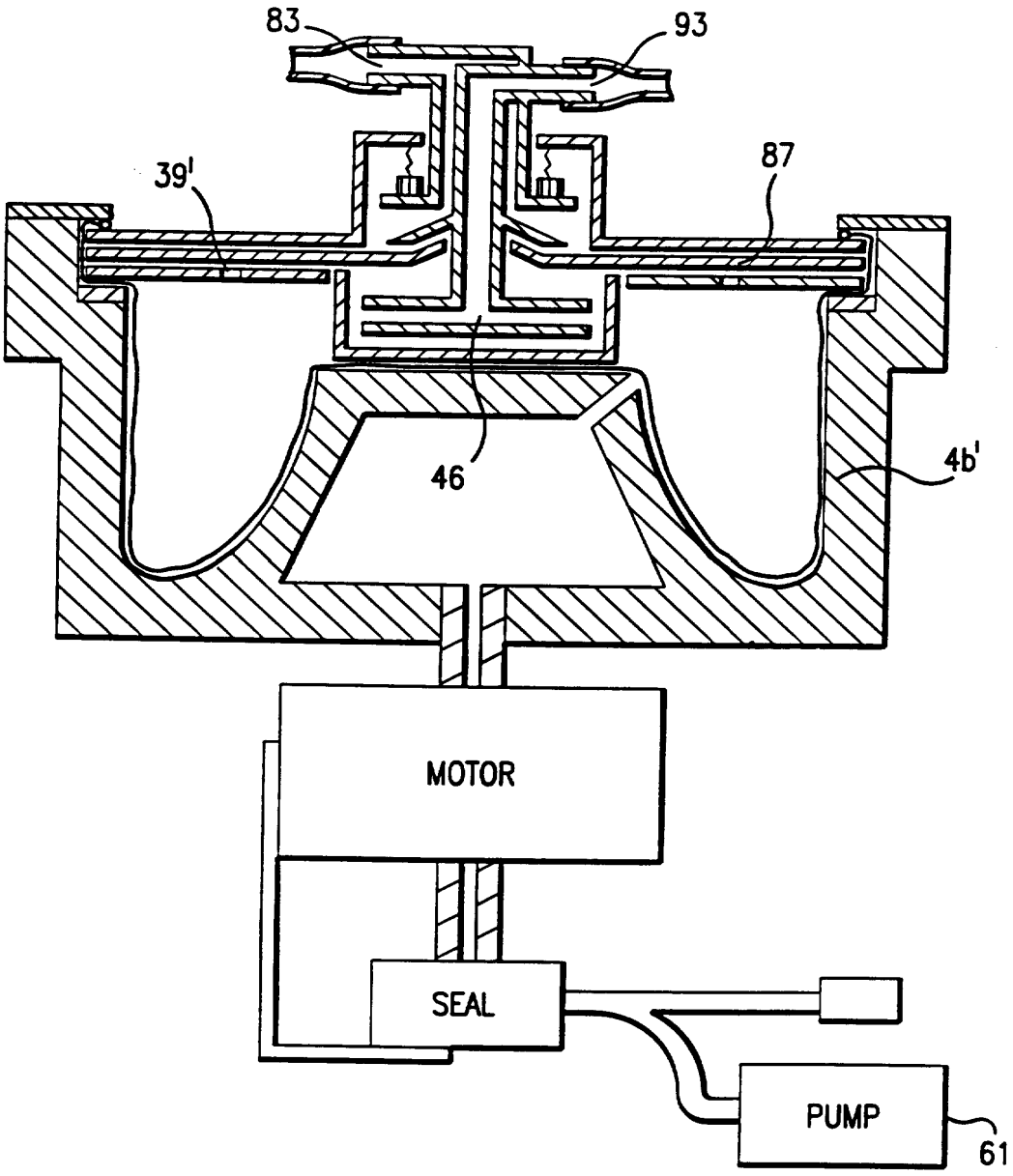


FIG.19B

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Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0895

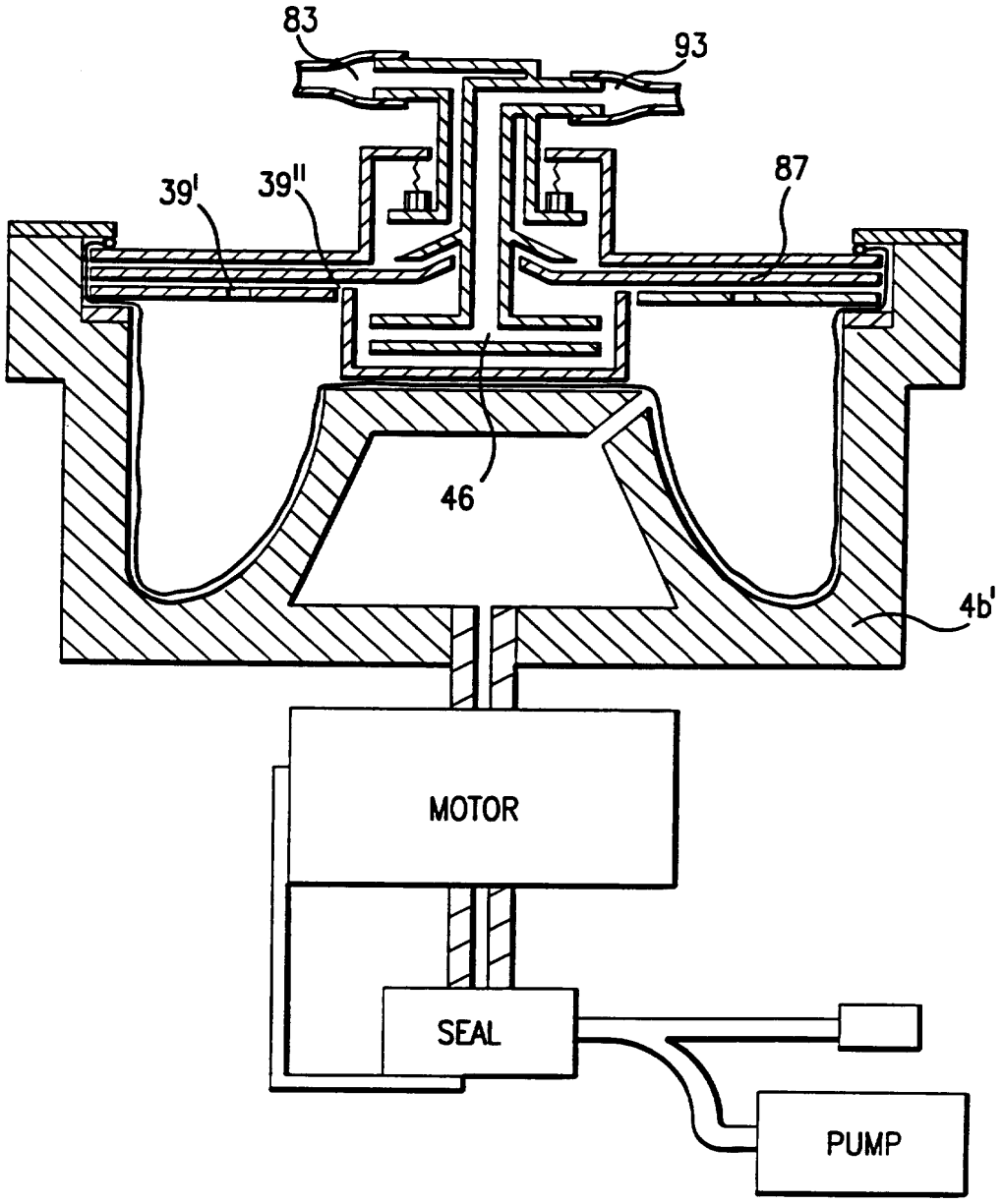


FIG.19C

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0896

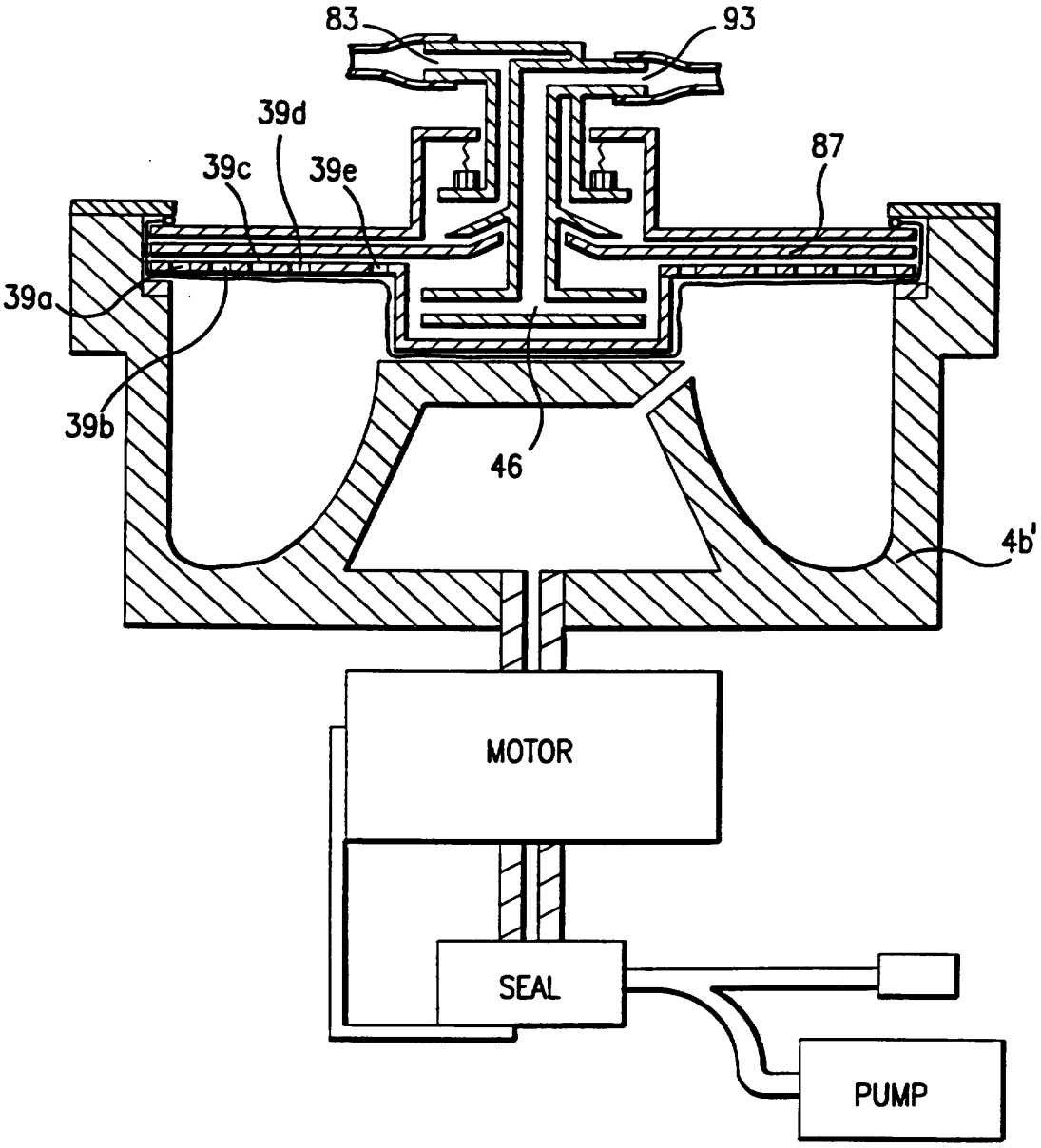


FIG.19D

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0897

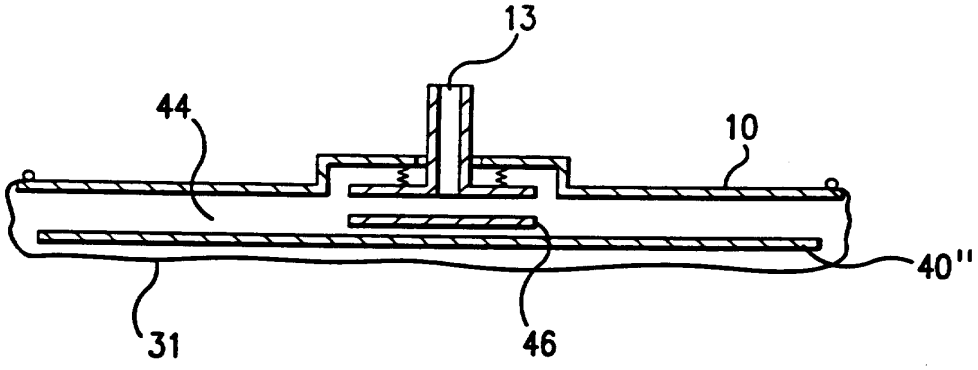


FIG.19E

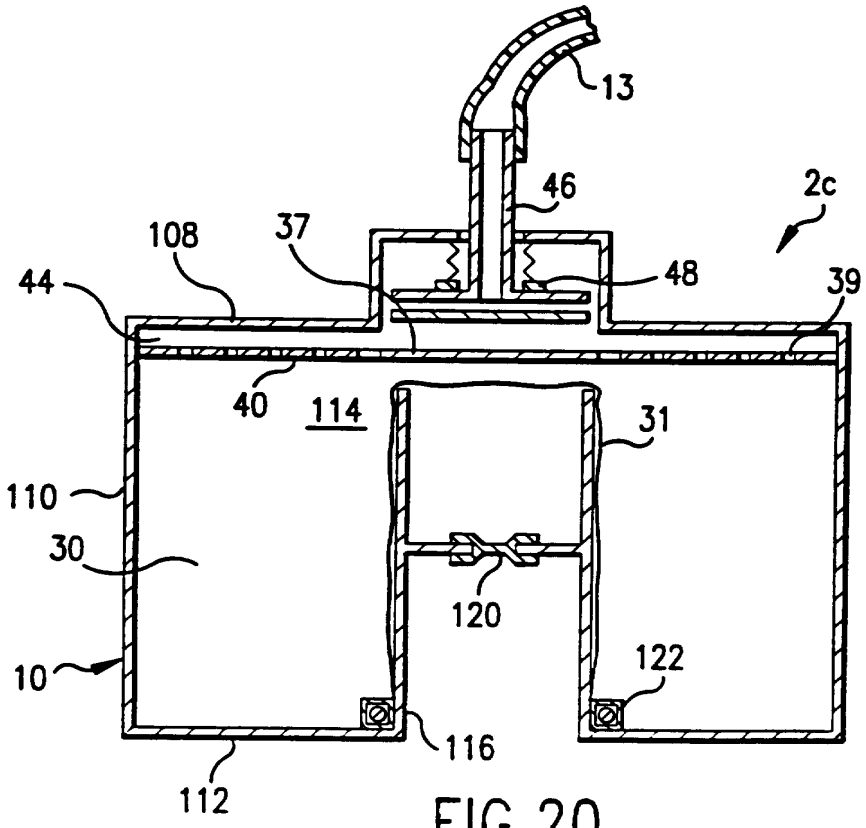


FIG.20

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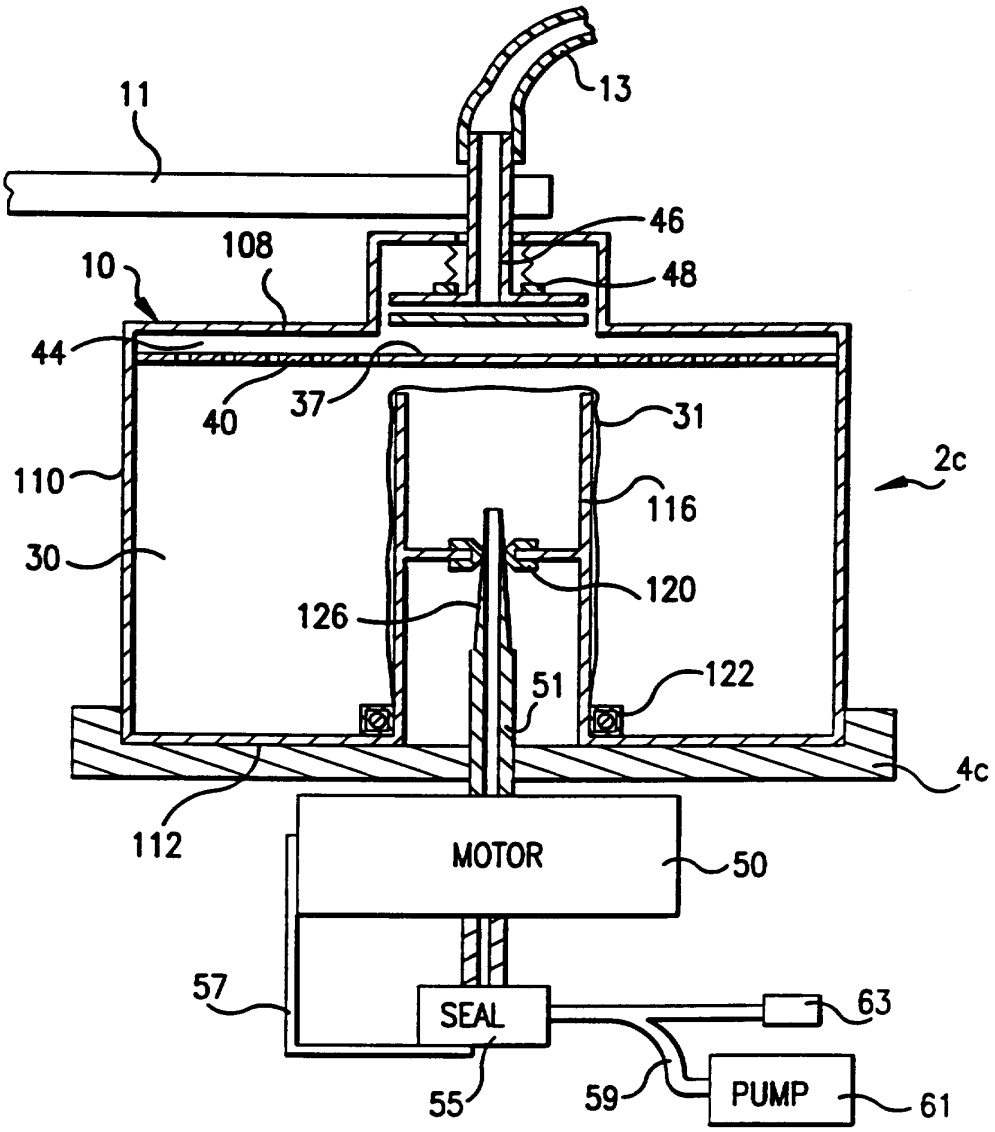


FIG.21

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Petitioner Terumo Exhibit 1021-0899

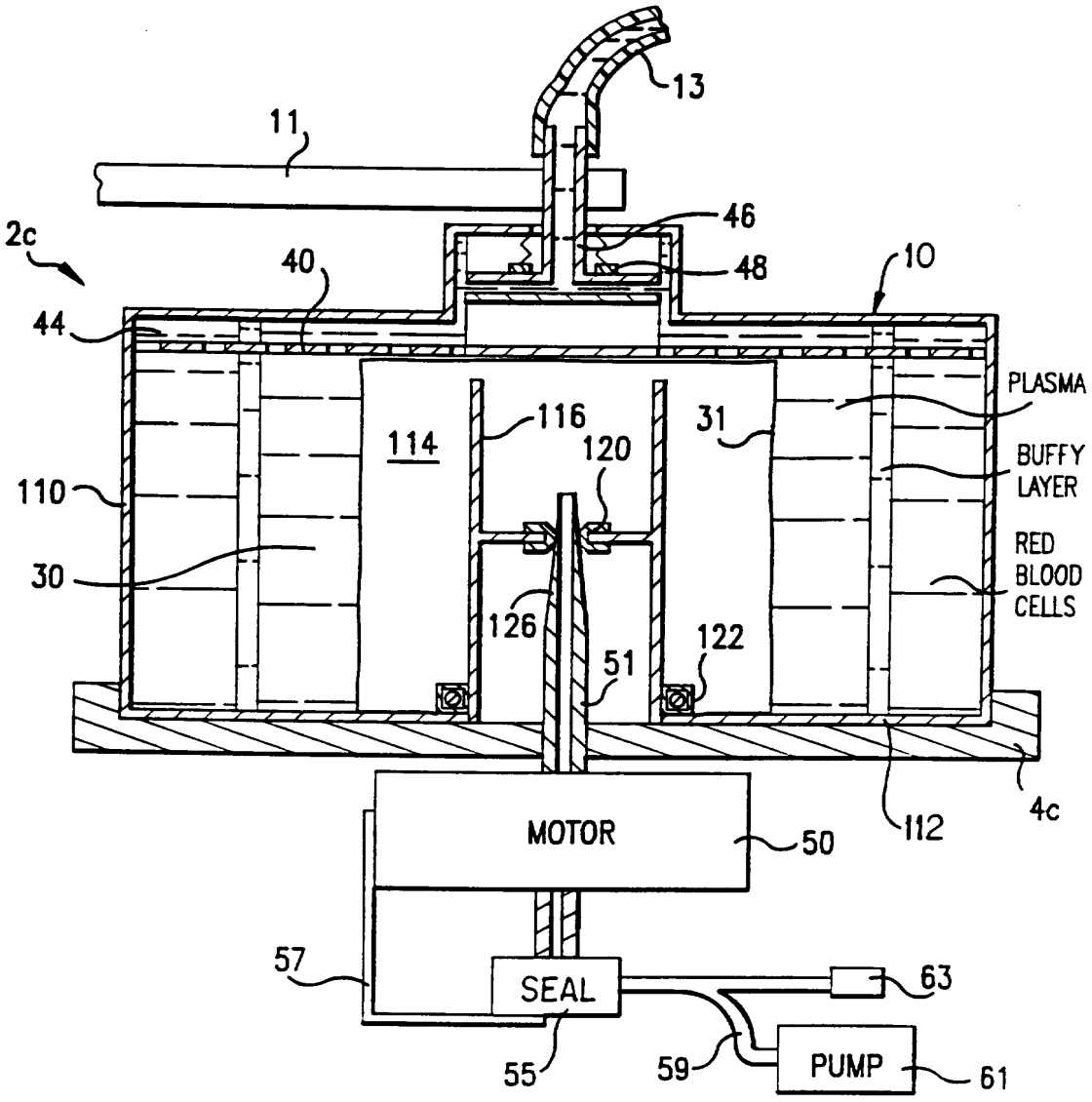


FIG.22

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Petitioner Terumo Exhibit 1021-0900

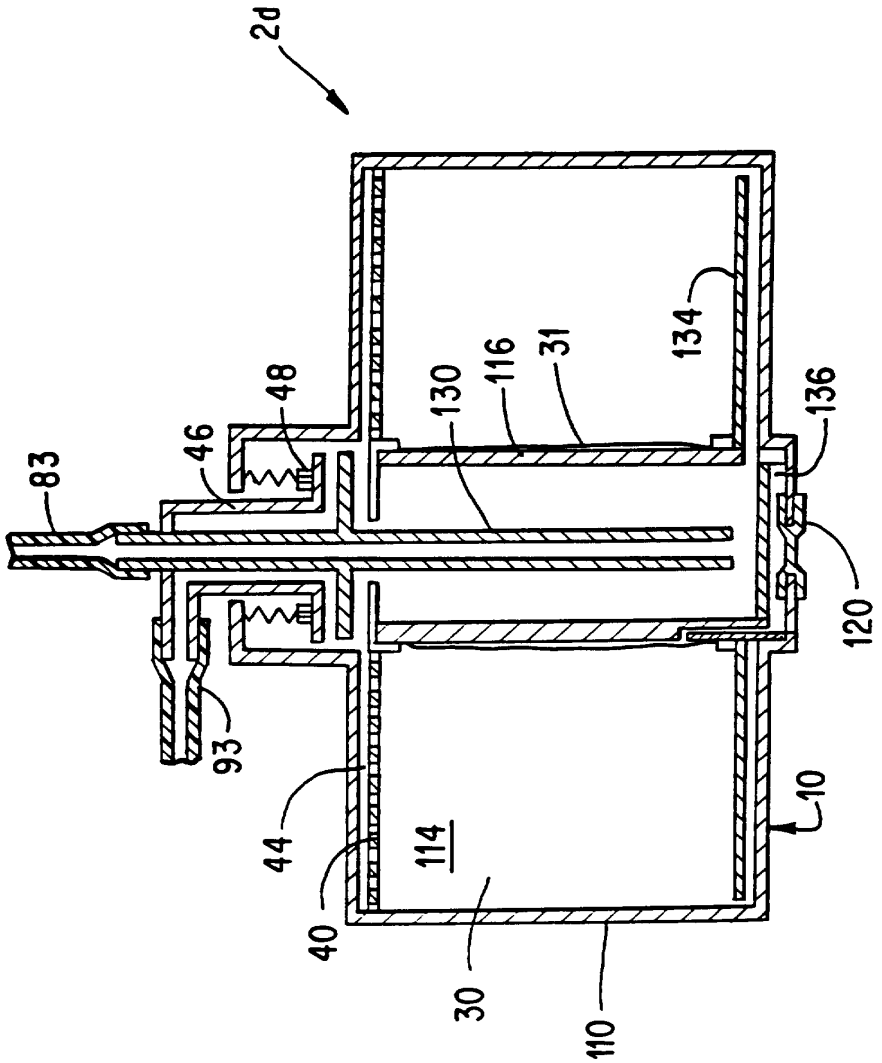


FIG.23

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Petitioner Terumo Exhibit 1021-0901

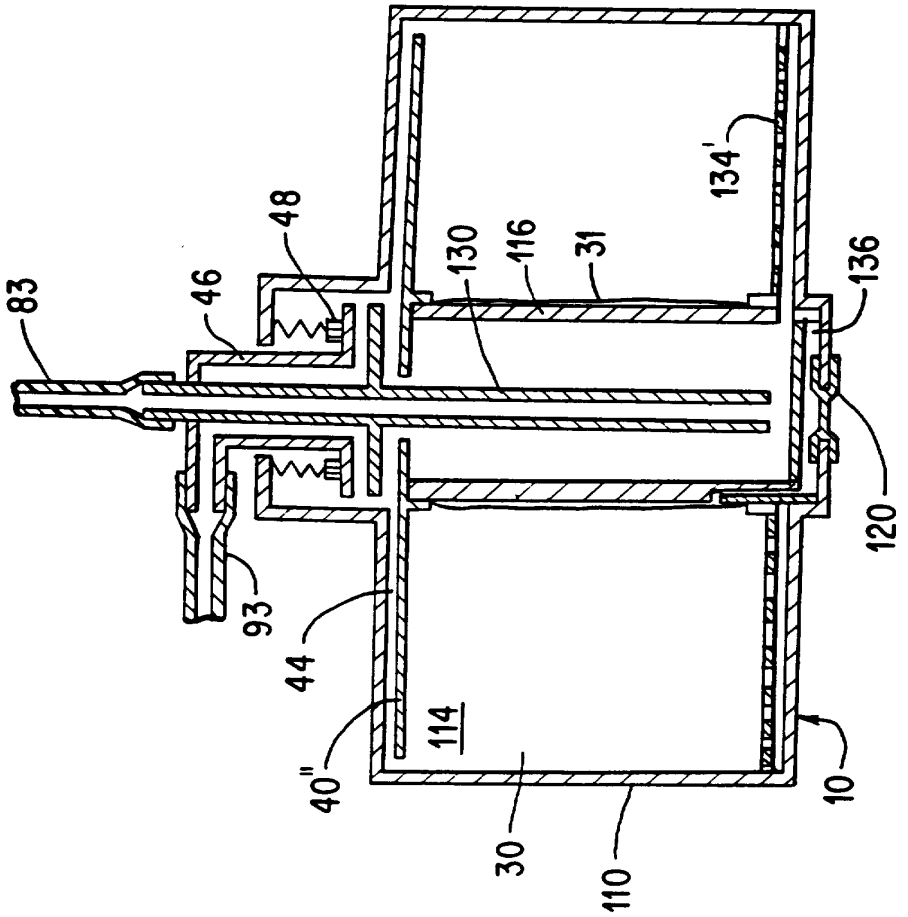


FIG.24

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Petitioner Terumo Exhibit 1021-0902

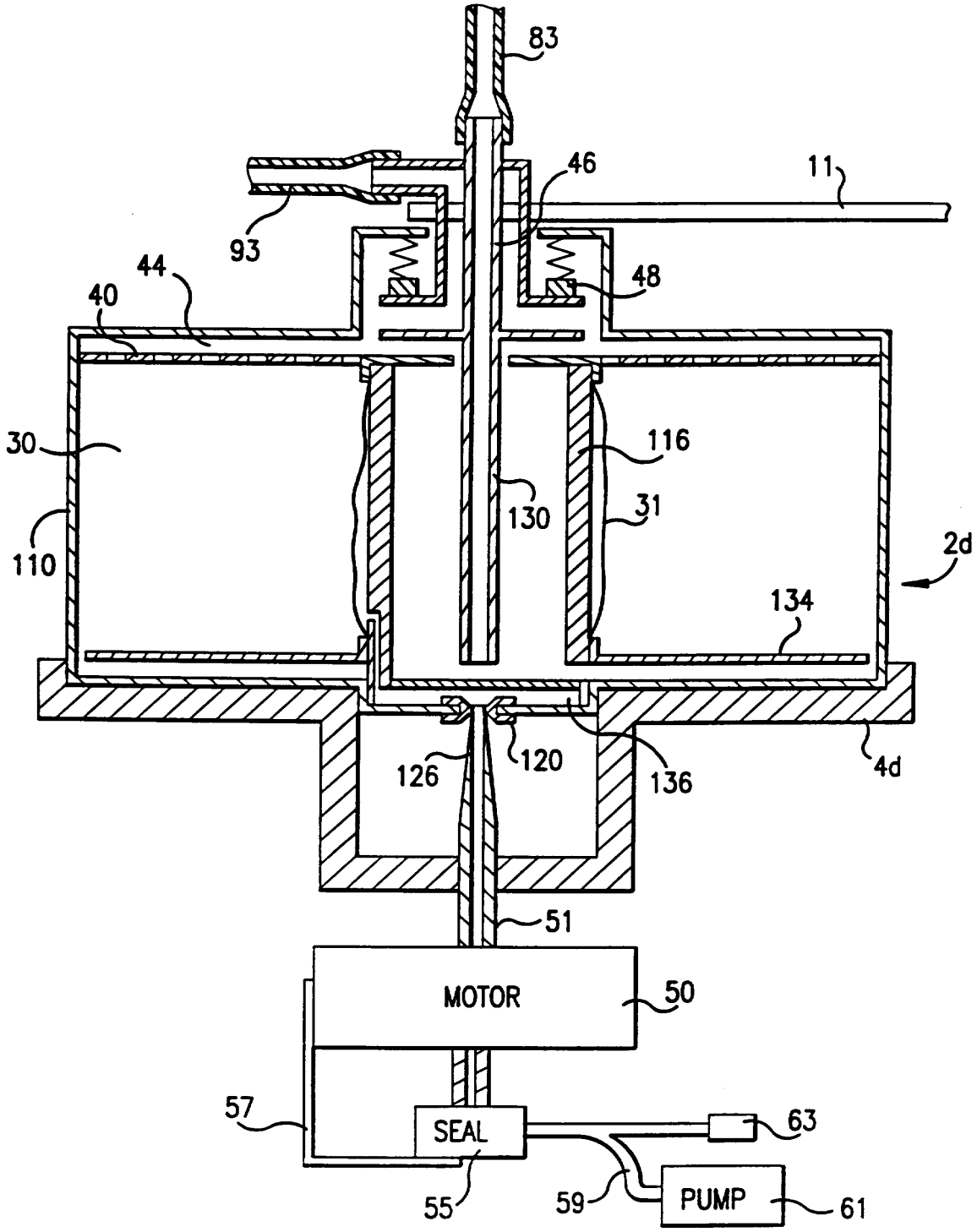

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FIG.25

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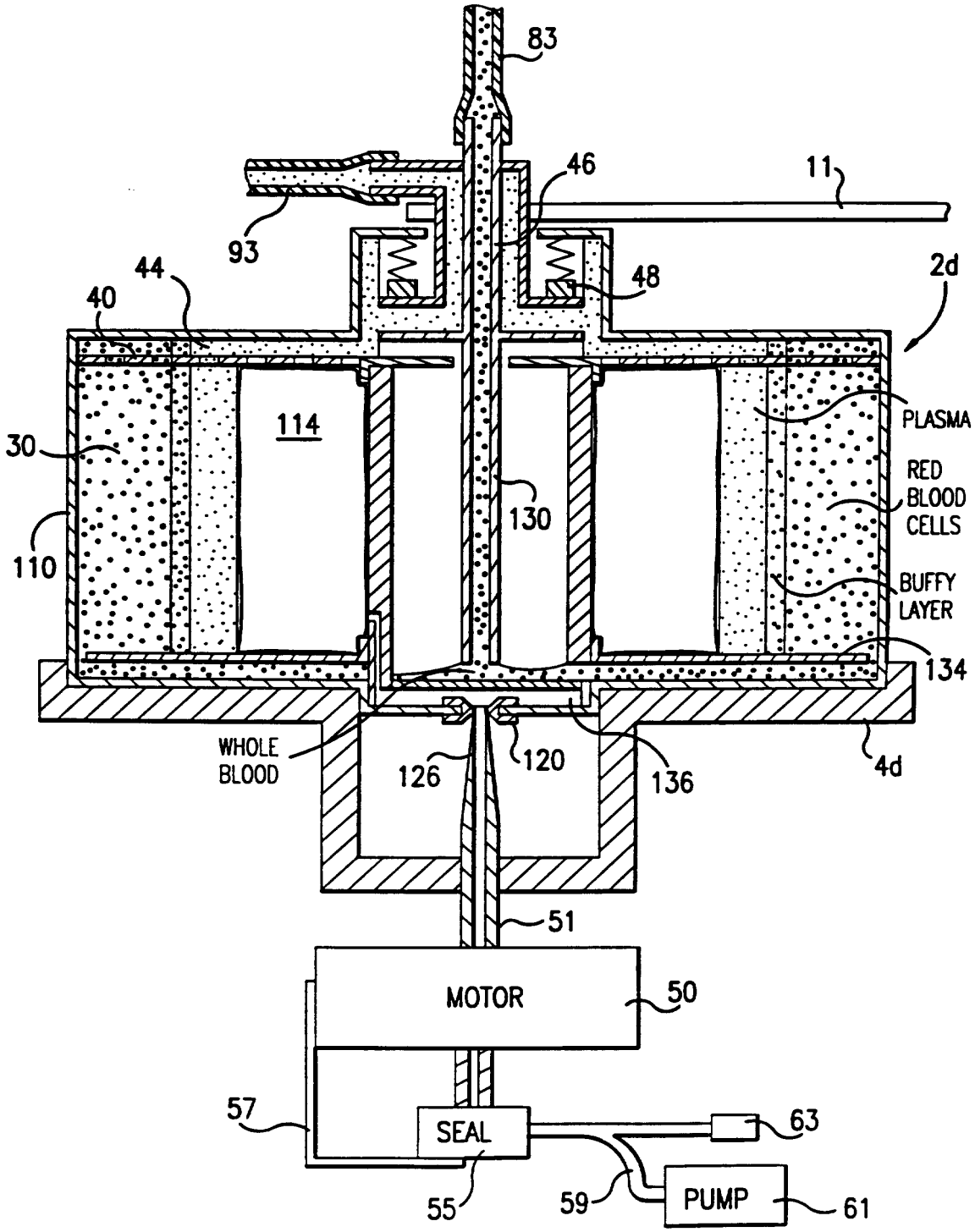


FIG.26

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Petitioner Terumo Exhibit 1021-0904

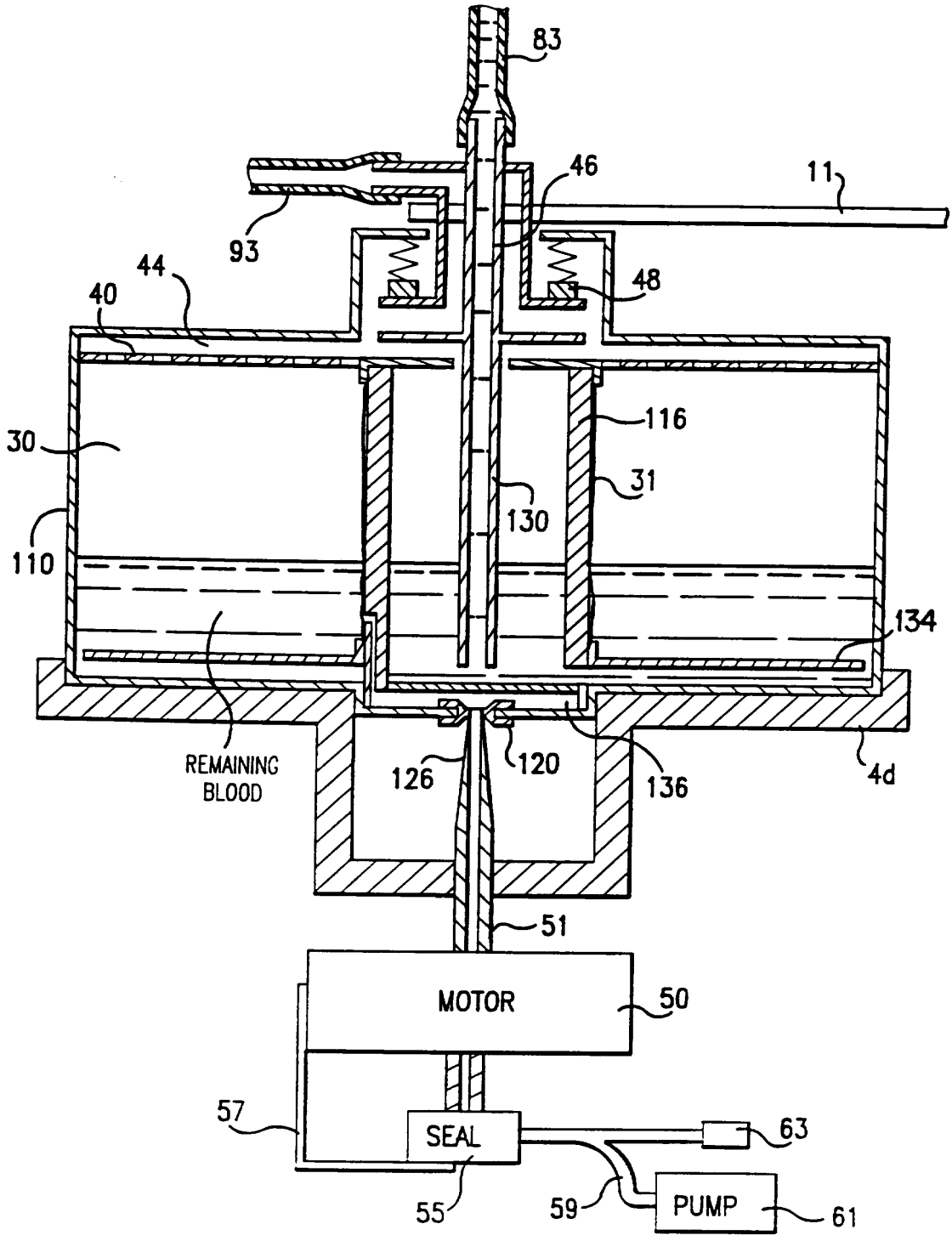


FIG.27

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Petitioner Terumo Exhibit 1021-0905

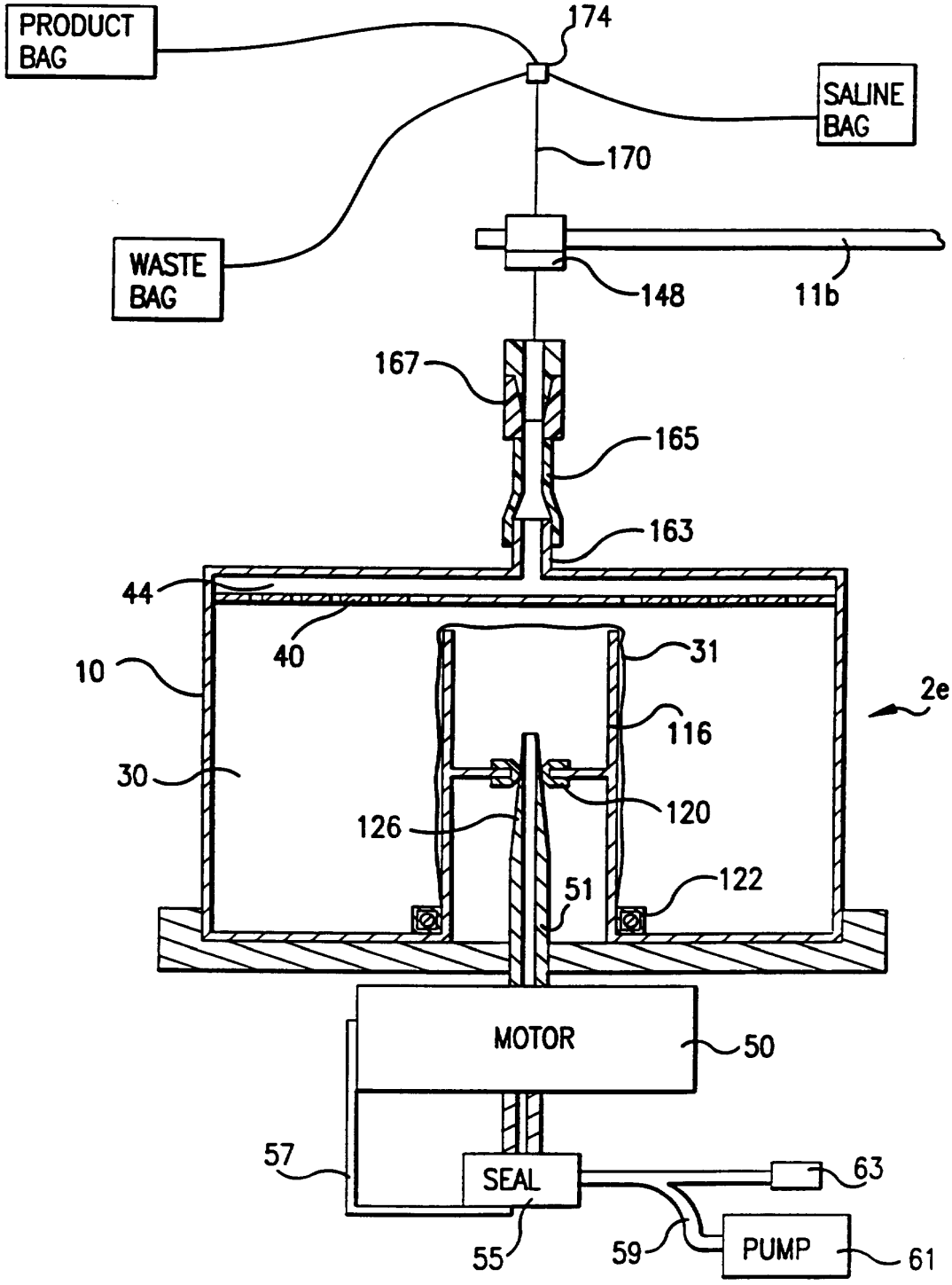

PRODUCT BAG
174
SALINE BAG
170
WASTE BAG
148
11b
167
165
163
44
40
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31
2e
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MOTOR
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FIG.28

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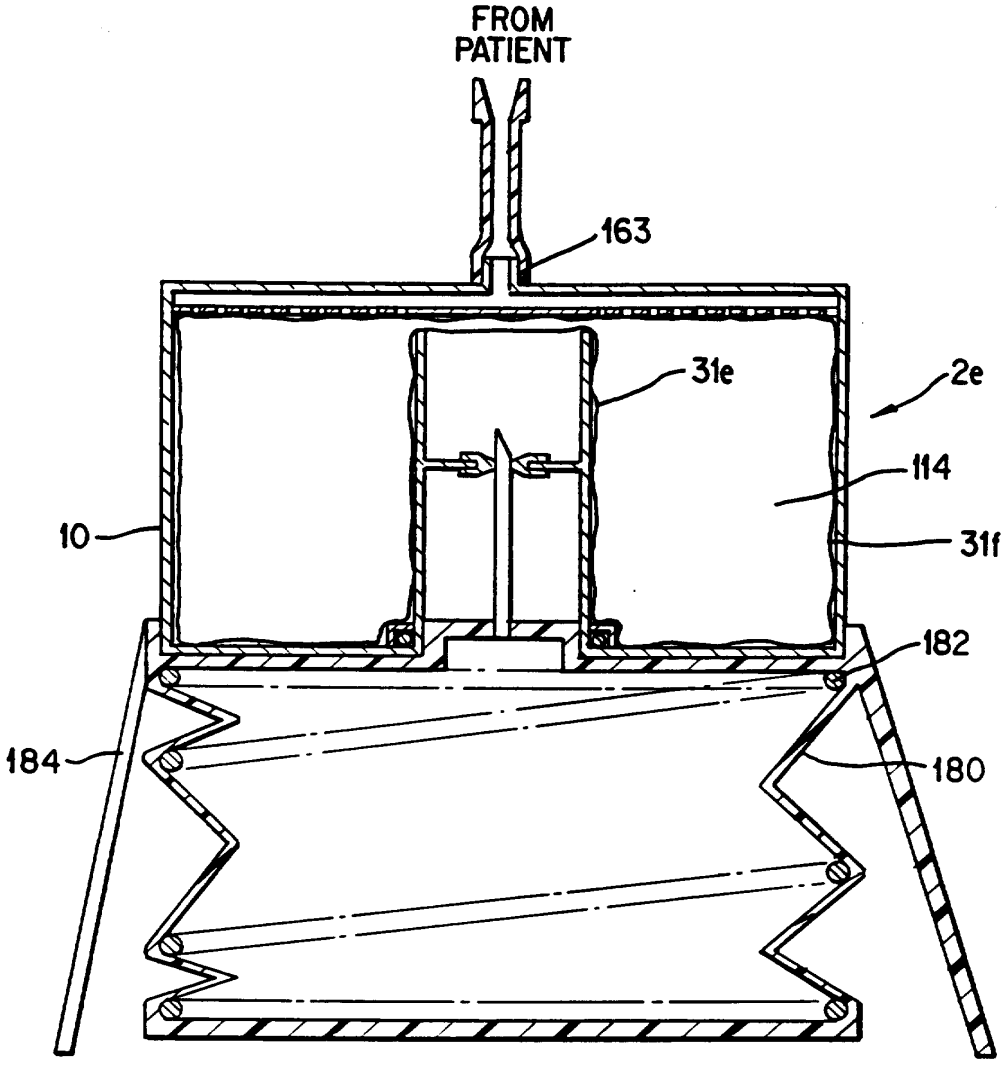


FIG. 29

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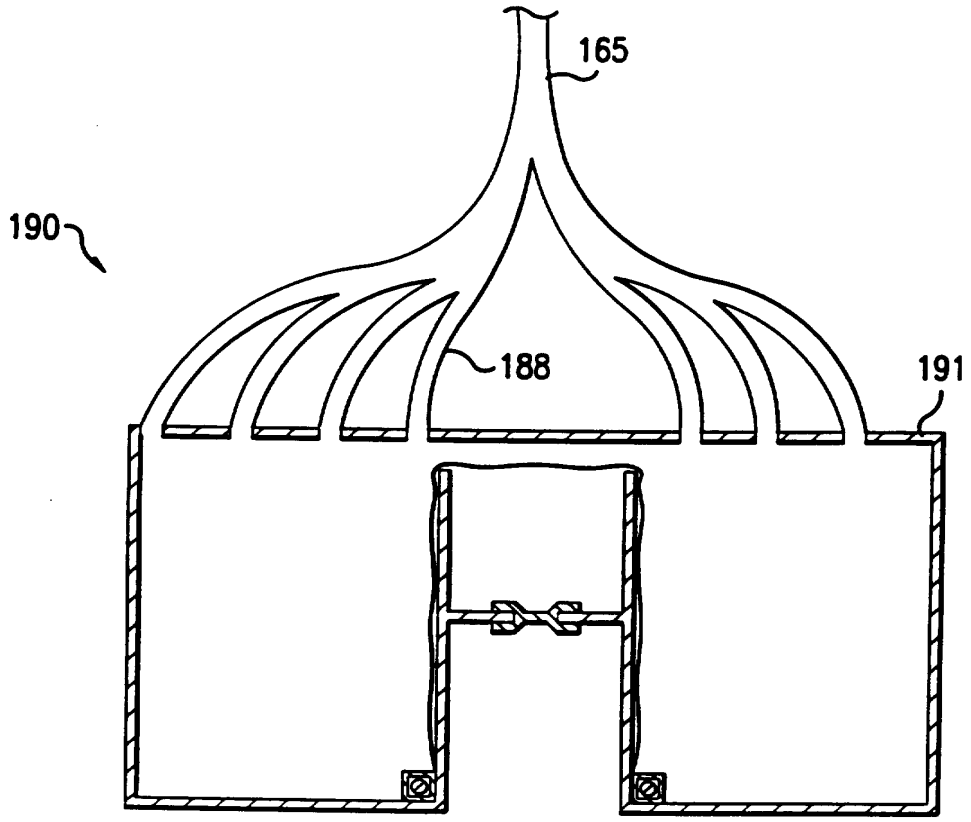


FIG.30

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Petitioner Terumo Exhibit 1021-0908

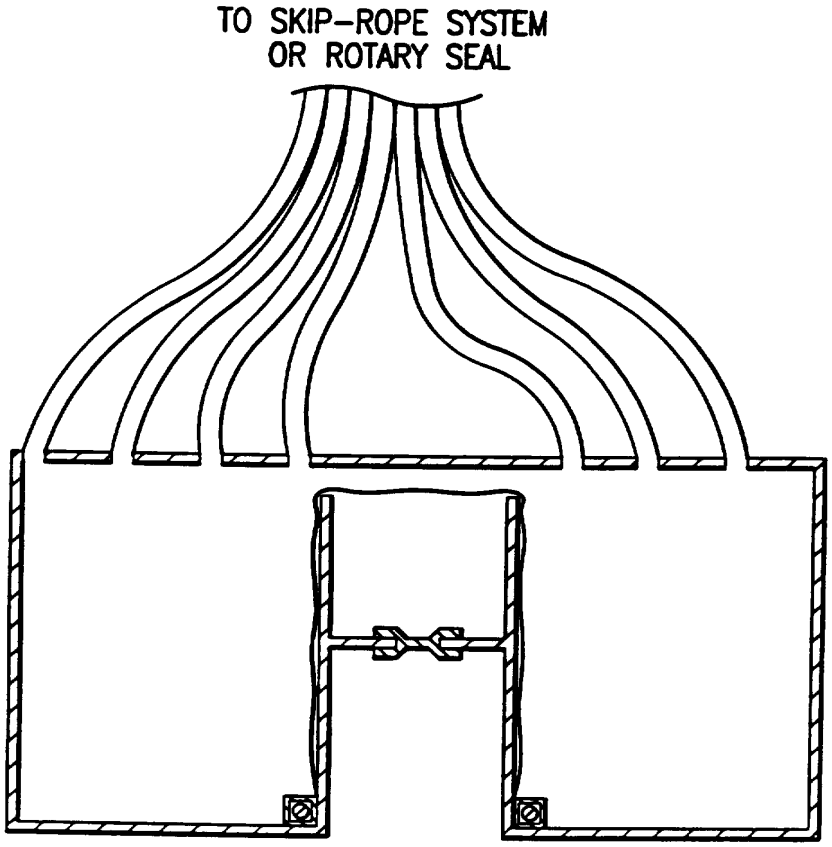


FIG.31

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Petitioner Terumo Exhibit 1021-0909

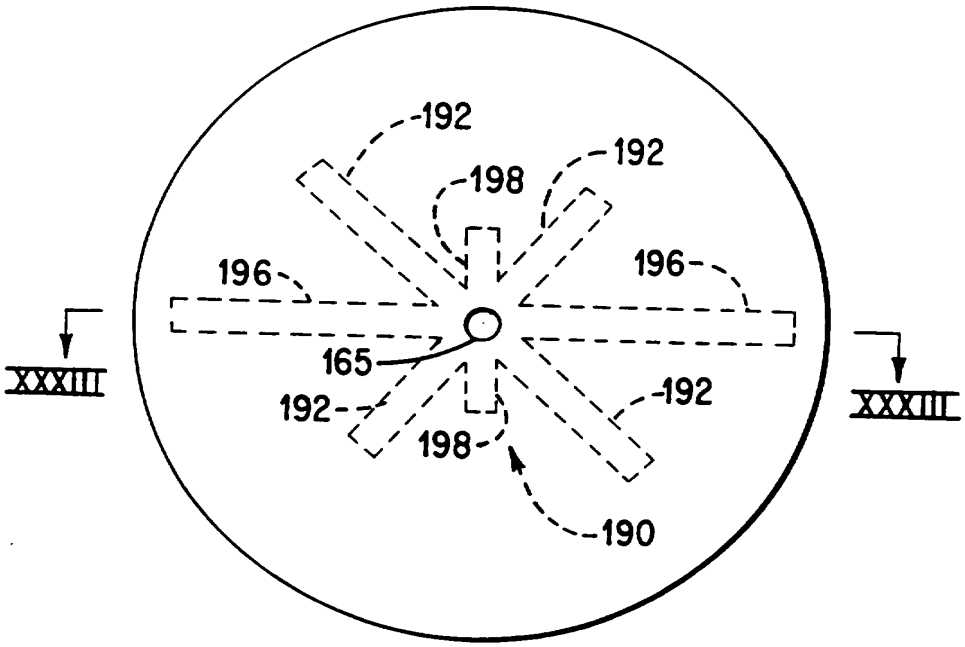


FIG.32

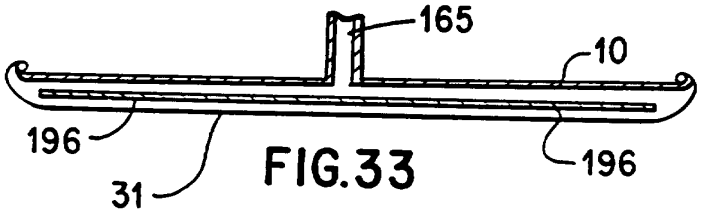


FIG.33

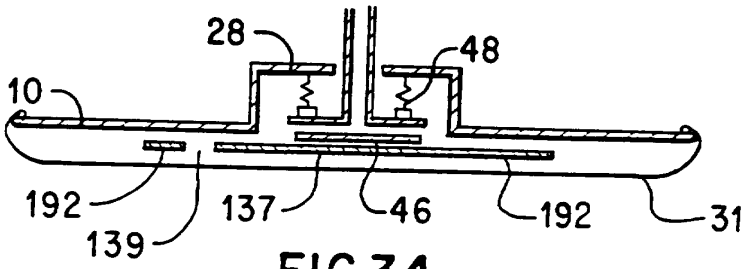


FIG.34

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Petitioner Terumo Exhibit 1021-0910

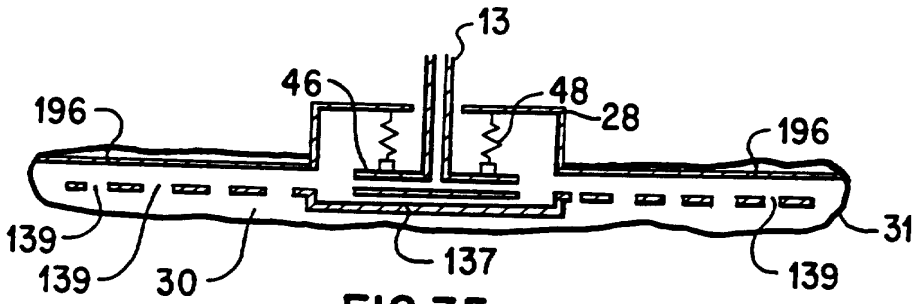


FIG.35

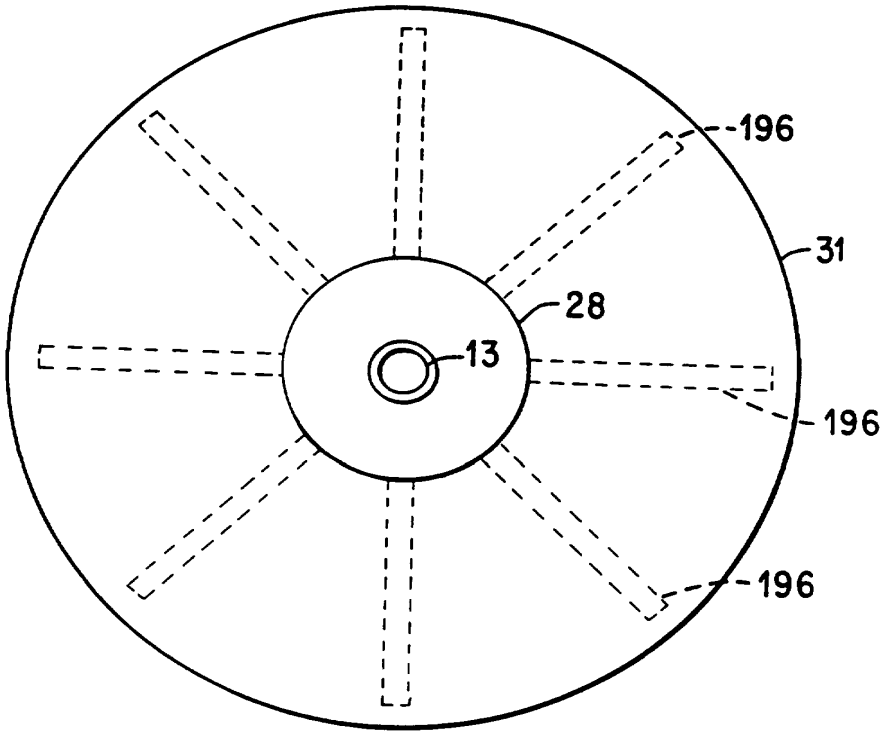


FIG.36

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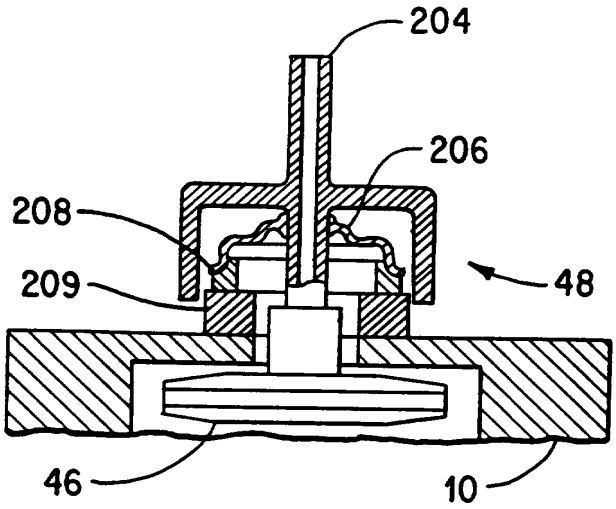


FIG.37

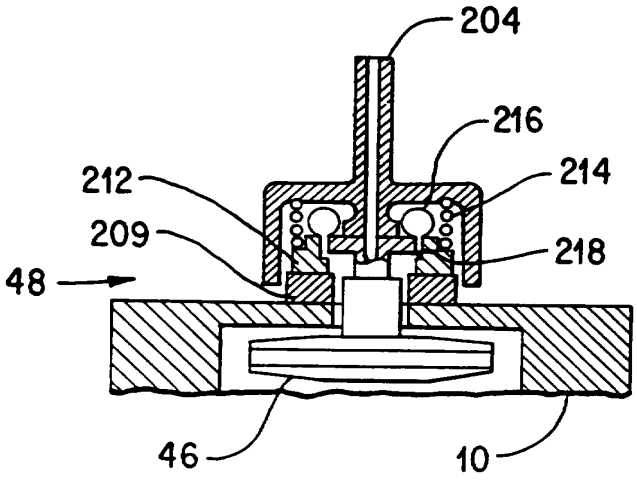


FIG.38

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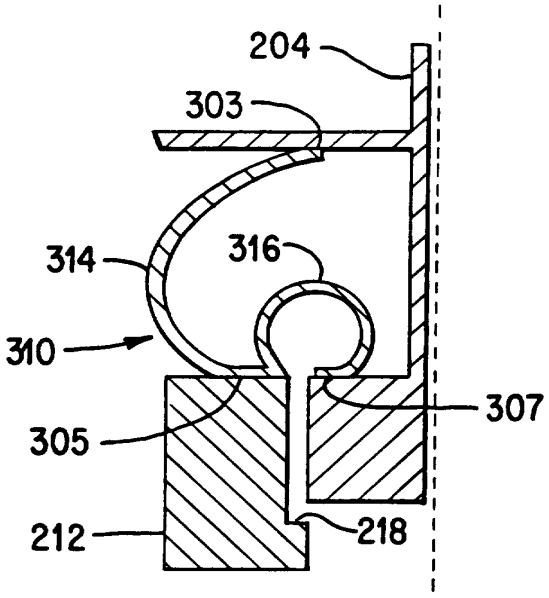


FIG. 39

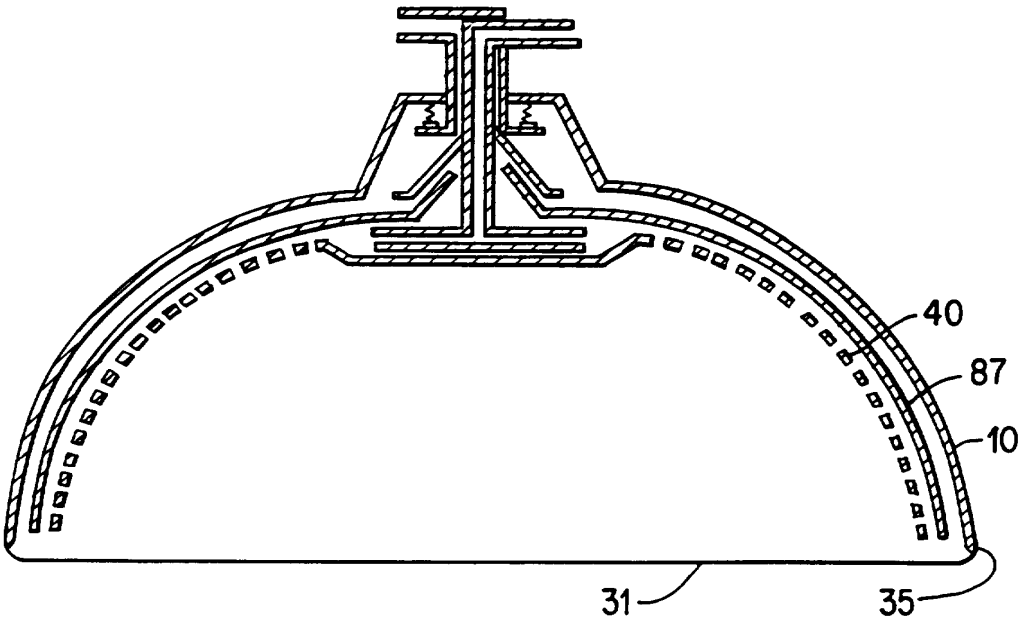


FIG. 40

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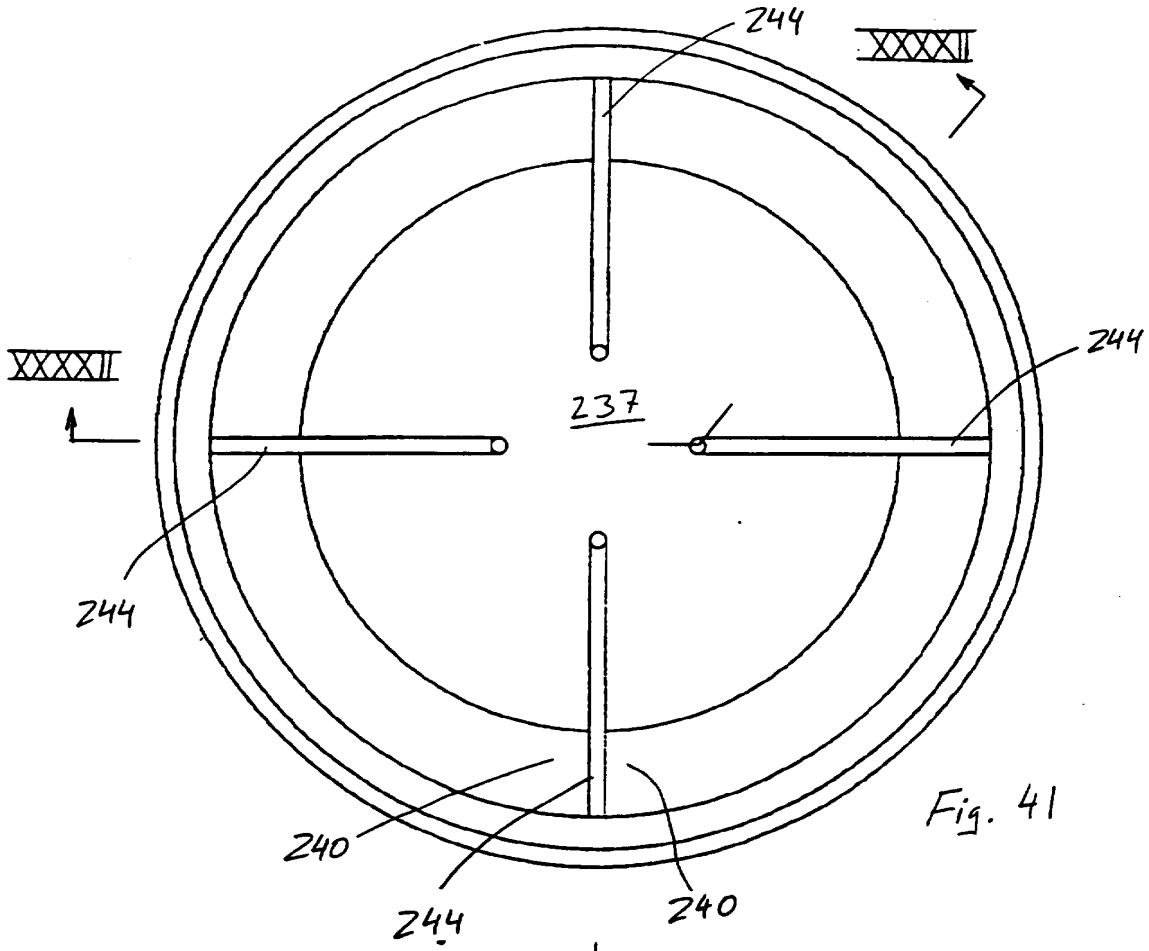


Fig. 41

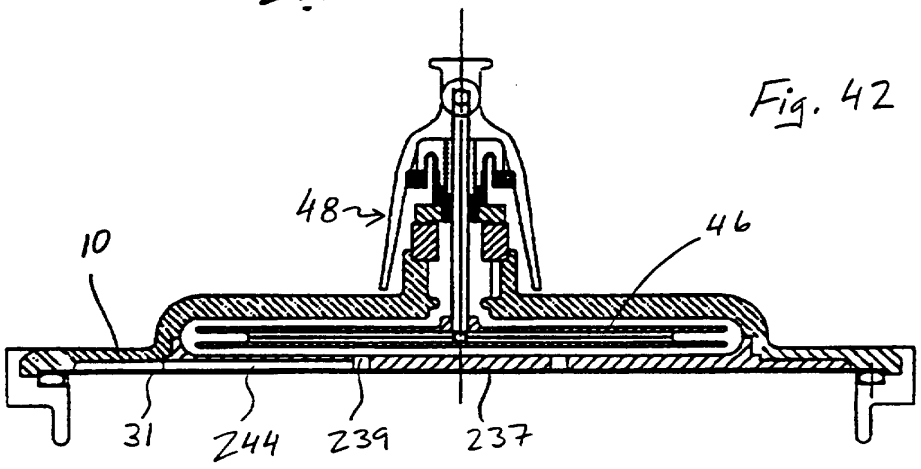


Fig. 42

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Espacenet

Bibliographic data: WO9633023 (A1) — 1996-10-24

PARTICLE SEPARATION APPARATUS AND METHOD

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Applicant(s): COBE LAB [US] ± (COBE LABORATORIES, INC)

Classification: **- international:** ***A61M1/02; A61M1/36; B04B11/04; B04B5/04;*** (IPC1-7): A61M1/36; B04B5/04
- cooperative: **A61M1/0227**; **A61M1/0236**; **A61M1/3618**; **A61M1/362**; **A61M1/3693**; **A61M1/3696**; **B04B5/0428**; **B04B5/0442**; B04B2005/0471

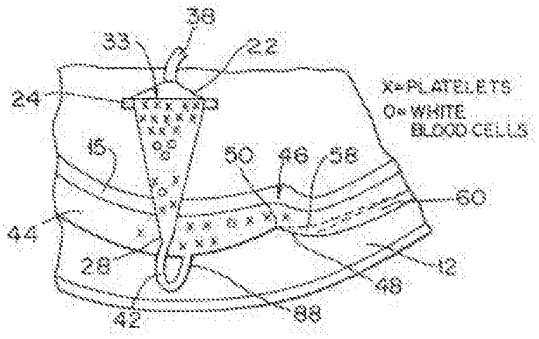
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Abstract of WO9633023 (A1)

An apparatus and method are disclosed for filtering or separating particles. The apparatus has a centrifuge rotor (12) rotatable about an axis of rotation. A fluid chamber (22) rotates with the rotor. A substance is supplied to the inlet (28) of the chamber. A saturated fluidized bed of first particles forms within the fluid chamber and obstructs flow of second particles through the chamber. In an embodiment of the invention, additives substances alter sedimentation velocity of the first particles to modify the filtration characteristics of the saturated fluidized bed. The fluid chamber includes a wall extending between an inlet (28) and outlet (32) to form a fluid chamber interior. The



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interior converges from a position of maximum cross-sectional area toward the inlet. A groove or a step may be formed on an inner surface of the fluid chamber wall to improve particle separation within the fluid chamber.

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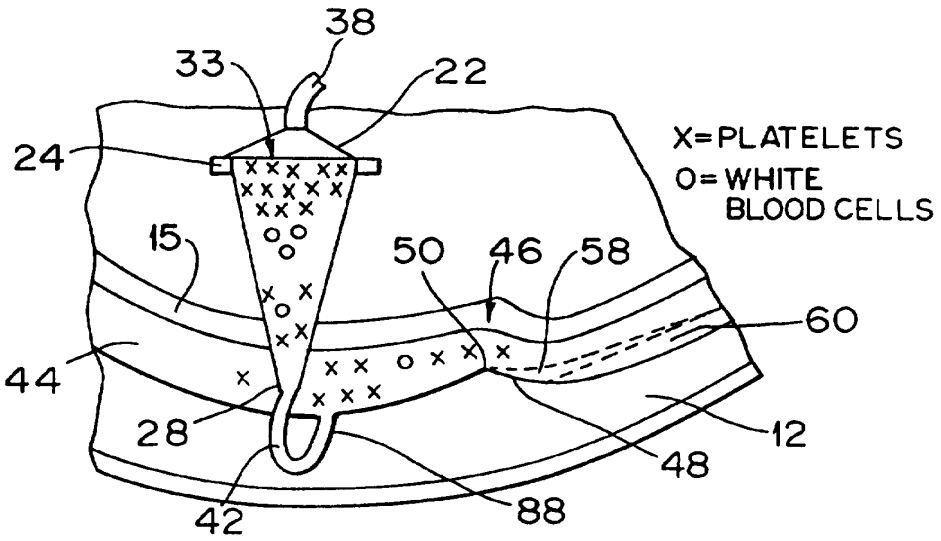
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(72) Inventors: HLAVINKA, Dennis; 7365 N. Salvia Court, Golden, CO 80419 (US). CORBIN, Frank; 9703 West Arlington Avenue, Littleton, CO 80123 (US). LANGLEY, Robert; 10160 Xavier Court, Westminster, CO 80030 (US). TAYLOR, Linda, A.; 6159 S. Sheridan Boulevard, Littleton, CO 80123 (US). WALKER, John, C.; 405 S. 42nd Street, Boulder, CO 80303 (US).

(74) Agents: GARRETT, Arthur, S. et al.; Finnegan, Henderson, Farabow, Garrett & Dunner, L.P.P., 1300 I Street, N.W., Washington, DC 20005-3315 (US).

(54) Title: PARTICLE SEPARATION APPARATUS AND METHOD



(57) Abstract

An apparatus and method are disclosed for filtering or separating particles. The apparatus has a centrifuge rotor (12) rotatable about an axis of rotation. A fluid chamber (22) rotates with the rotor. A substance is supplied to the inlet (28) of the chamber. A saturated fluidized bed of first particles forms within the fluid chamber and obstructs flow of second particles through the chamber. In an embodiment of the invention, additives substances alter sedimentation velocity of the first particles to modify the filtration characteristics of the saturated fluidized bed. The fluid chamber includes a wall extending between an inlet (28) and outlet (32) to form a fluid chamber interior. The interior converges from a position of maximum cross-sectional area toward the inlet. A groove or a step may be formed on an inner surface of the fluid chamber wall to improve particle separation within the fluid chamber.

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Description

Particle Separation Apparatus and Method

The entire disclosures of U.S. patent application Serial Nos. 08/423,578 and 08/423,583 are incorporated herein by reference.

Background of the Invention

Field of the Invention

The present invention relates to a method and apparatus for separating first particles from second particles and for separating particles and liquid. The invention has particular advantages in connection with separating blood components.

Description of the Related Art

In many different fields, liquids carrying particle substances must be filtered or processed to obtain either a purified liquid or purified particle end product. In its broadest sense, a filter is any device capable of removing or separating particles from a substance. Thus, the term "filter" as used herein is not limited to a porous media material but includes many different types of processes where particles are either separated from one another or from liquid.

In the medical field, it is often necessary to filter blood. Whole blood consists of various liquid constituents and particle constituents. Sometimes, the particle constituents are referred to as "formed elements". The liquid portion of blood is largely made up of plasma, and the particle constituents include red blood cells (erythrocytes), white blood cells (including leukocytes), and platelets (thrombocytes). While these constituents have similar densities, their average density relationship, in order of decreasing density, is as follows: red blood cells, white blood cells, platelets, and plasma. In addition, the particle constituents are related according to size, in order of decreasing size, as follows: white blood cells, red blood cells, and platelets. The size of red blood cells, however, may vary because red blood cells osmotically change size depending on the hypotonicity or hypertonicity of a liquid,

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such as plasma, in which the red blood cells are disbursed. When hypotonicity of plasma increases, the red blood cells osmotically become larger. Conversely, when hypertonicity of plasma increases, the red blood cells osmotically become smaller. Most current purification devices rely on density and size differences or surface chemistry characteristics to separate and/or filter the blood components.

Numerous therapeutic treatments require groups of particles to be removed from whole blood before either liquid or particle components can be infused into a patient. For example, cancer patients often require platelet transfusions after undergoing ablative, chemical, or radiation therapy. In this procedure, donated whole blood is processed to remove platelets and these platelets are then infused into the patient. However, if a patient receives an excessive number of foreign white blood cells as contamination in a platelet transfusion, the patient's body may reject the platelet transfusion, leading to a host of serious health risks.

Typically, donated platelets are separated or harvested from other blood components using a centrifuge. The centrifuge rotates a blood reservoir to separate components within the reservoir using centrifugal force. In use, blood enters the reservoir while it is rotating at a very rapid speed and centrifugal force stratifies the blood components, so that particular components may be separately removed. Centrifuges are effective at separating platelets from whole blood, however they typically are unable to separate all of the white blood cells from the platelets. Historically, blood separation and centrifugation devices are typically unable to consistently (99% of the time) produce platelet product that meets the "leukopoor" standard of less than 5×10^6 white blood cells for at least 3×10^{11} platelets collected.

Because typical centrifuge platelet collection processes are unable to consistently and satisfactorily separate white blood cells from platelets, other processes have been added to improve results. In one procedure, after centrifuging, platelets are passed through a porous woven or non-woven media

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filter, which may have a modified surface, to remove white blood cells. However, use of the porous filter introduces its own set of problems. Conventional porous filters may be inefficient because they may permanently remove or trap approximately 5-20% of the platelets. These conventional filters may also reduce "platelet viability," meaning that once passed through a filter a percentage of the platelets cease to function properly and may be partially or fully activated. In addition, porous filters may cause the release of brandykinin, which may lead to hypotensive episodes in a patient. Porous filters are also expensive and often require additional time consuming manual labor to perform a filtration process.

Although porous filters are effective in removing a substantial number of white blood cells, they have drawbacks. For example, after centrifuging and before porous filtering, a period of time must pass to give activated platelets time to transform to a deactivated state. Otherwise, the activated platelets are likely to clog the filter. Therefore, the use of porous filters is not feasible in on-line processes.

Another separation process is one known as centrifugal elutriation. This process separates cells suspended in a liquid medium without the use of a membrane filter. In one common form of elutriation, a cell batch is introduced into a flow of liquid elutriation buffer. This liquid which carries the cell batch in suspension, is then introduced into a funnel-shaped chamber located in a spinning centrifuge. As additional liquid buffer solution flows through the chamber, the liquid sweeps smaller sized, slower-sedimenting cells toward an elutriation boundary within the chamber, while larger, faster-sedimenting cells migrate to an area of the chamber having the greatest centrifugal force.

When the centrifugal force and force generated by the fluid flow are balanced, the fluid flow is increased to force slower-sedimenting cells from an exit port in the chamber, while faster-sedimenting cells are retained in the chamber.

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If fluid flow through the chamber is increased, progressively larger, faster-sedimenting cells may be removed from the chamber.

Thus, centrifugal elutriation separates particles having different sedimentation velocities. Stoke's law describes sedimentation velocity (SV) of a spherical particle as follows:

$$SV = \frac{2}{9} \frac{r^2 (\rho_p - \rho_m) g}{\eta}$$

where, r is the radius of the particle, ρ_p is the density of the particle, ρ_m is the density of the liquid medium, η is the viscosity of the medium, and g is the gravitational or centrifugal acceleration. Because the radius of a particle is raised to the second power in the Stoke's equation and the density of the particle is not, the size of a cell, rather than its density, greatly influences its sedimentation rate. This explains why larger particles generally remain in a chamber during centrifugal elutriation, while smaller particles are released, if the particles have similar densities.

As described in U.S. Patent No. 3,825,175 to Sartory, centrifugal elutriation has a number of limitations. In most of these processes, particles must be introduced within a flow of fluid medium in separate discontinuous batches to allow for sufficient particle separation. Thus, some elutriation processes only permit separation in particle batches and require an additional fluid medium to transport particles. In addition, flow forces must be precisely balanced against centrifugal force to allow for proper particle segregation.

Further, a Coriolis jetting effect takes place when particles flow into an elutriation chamber from a high centrifugal field toward a lower centrifugal field. The fluid and particles turbulently collide with an inner wall of the chamber facing the rotational direction of the centrifuge. This phenomenon mixes particles within the chamber and reduces

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the effectiveness of the separation process. Further, Coriolis jetting shunts flow along the inner wall from the inlet directly to the outlet. Thus, particles pass around the elutriative field to contaminate the end product.

Particle mixing by particle density inversion is an additional problem encountered in some prior elutriation processes. Fluid flowing within the elutriation chamber has a decreasing velocity as it flows in the centripetal direction from an entrance port toward an increased cross sectional portion of the chamber. Because particles tend to concentrate within a flowing liquid in areas of lower flow velocity, rather than in areas of high flow velocity, the particles concentrate near the increased cross-sectional area of the chamber. Correspondingly, since flow velocity is greatest adjacent the entrance port, the particle concentration is reduced in this area. Density inversion of particles takes place when the centrifugal force urges the particles from the high particle concentration at the portion of increased cross-section toward the entrance port. This particle turnover reduces the effectiveness of particle separation by elutriation.

In addition to red and white blood cells, plasma, and platelets, human blood also includes other particle components, such as T cells, stem cells, and, in some cases, tumor cells. These cells have substantially similar densities, but different sedimentation velocities and sizes. Generally, stem cells are larger than T cells and smaller than tumor cells. Some tumor cells (approximately 30%), however, are smaller than stem cells.

Existing purification devices are capable of purifying peripheral blood to isolate what is known as a peripheral cell collection for transfusion or reinfusion purposes. The peripheral cell collection typically includes primarily plasma, red blood cells, stem cells, and T cells, and may also include tumor cells if the donor's blood included such cells. Although transfusion of a peripheral cell collection is a common medical treatment, transfusion of a large number of T

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cells or tumor cells into a patient may have adverse consequences. Removal of T cells and tumor cells from a peripheral cell collection or whole blood before transfusion, however, is extremely difficult.

After undergoing a therapeutic treatment, such as chemotherapy or radiation therapy to eliminate cancerous tumor cells, cancer patients often receive a peripheral cell or bone marrow transfusion to replace stem cells destroyed as a side effect of the treatment. To reduce risks associated with infusing blood components from a foreign donor, some of these transfusions are autologous, where blood components collected from the patient are later reinfused back to the patient.

Blood components initially collected from cancer patients may include cancerous tumor cells, which are then infused back into the cancer patient during reinfusion. This reinfusion of tumor cells may diminish the effectiveness of therapeutic treatments aimed at reducing cancerous tumors in a patient's body.

Another type of transfusion, known as allogenic transfusion, involves collecting blood components from a donor and then infusing the collected blood components into a recipient who is different from the donor. Sometimes, however, the recipient of an allogenic transfusion experiences a disease commonly known as graft versus host disease. In graft versus host disease, T cells, which may accompany the blood components, are infused into the recipient and "recognize" that the recipient's body is "foreign" from that of the donor's. These T cells "attack" healthy cells in the recipient's body, rather than performing a normal immunological protective function.

Prior attempts to separate stem cells from tumor cells or separate stem cells from T cells prior to reinfusion have had limited success. In one separation method, a selective antibody is introduced into a collected blood component sample. The selective antibody chemically attaches to stem cells in the collection to "mark" them. To separate the marked stem cells from the remaining blood components, the

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collected blood components are passed between stationary beads coated with a material which chemically bonds with the selective antibody. These chemical bonds retain the marked stem cells on the beads to filter them from the remaining blood components. To remove the marked stem cells from the beads, a chemical solution is flushed through the beads to break the chemical bonds between the material and selective antibody. This separation process, however, is extremely expensive, tedious, and time consuming.

Centrifugal elutriation has been used to separate tumor cells from stem cells or to separate T cells from stem cells. With existing elutriation devices, however, this is time consuming, difficult, and of limited effectiveness.

For these and other reasons, there is a need to improve particle separation.

Summary of the Invention

The present invention is directed to an apparatus and method that substantially obviate one or more of the limitations and disadvantages of the related art. To achieve these and other advantages and in accordance with the purpose of the invention, as embodied and broadly described herein, the invention comprises an apparatus for filtering first particles from a liquid. The apparatus includes a motor, and a centrifuge rotor coupled to the motor for rotation about an axis of rotation. A holder is provided for holding a fluid chamber on the rotor with an outlet of the fluid chamber positioned closer to the axis of rotation than an inlet of the fluid chamber. Means are provided for supplying a substance to the inlet of the fluid chamber, and means are also provided for controlling at least one of the motor and the supplying means to maintain a saturated fluidized bed of second particles within the fluid chamber and to cause first particles to be retained within the fluid chamber.

In another aspect, the invention includes a method of separating first particles from second particles. The method comprises the steps of rotating a centrifuge rotor about an axis of rotation, the rotor having a fluid chamber. With the

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method of the invention, rotation of the rotor is controlled and second particles are passed into an inlet of the fluid chamber. A saturated fluidized bed is formed within the chamber with the second particles. Liquid having at least first particles is flowed into the chamber inlet while maintaining the bed in the fluid chamber so that the bed substantially prevents flow of first particles from the inlet to the outlet while substantially permitting flow of liquid to the outlet.

When the method of the invention is used in connection with blood filtering, the liquid may include plasma and the first particles may be white blood cells, while the second particles may be platelets or red cells. Thus, the bed may filter and obstruct the passage of white blood cells.

Further, the invention may include an apparatus for separating constituent components of a fluid. This apparatus comprises a conduit configured to be received by a centrifuge rotor. The conduit has an inlet connected to an inlet line and an outlet fluidly coupled to a fluid chamber.

In another aspect, the invention includes a tubing set having a generally annularly configured channel, a plurality of lines, and a fluid chamber.

In another aspect the invention includes a fluid chamber for separating particle constituents from a liquid. The fluid chamber has at least one groove formed on an inner surface of a wall.

In another aspect, a fluid chamber includes at least one step formed on an inner surface of a wall.

In another aspect, the invention includes an apparatus having a holder for holding a fluid chamber on a rotor. Means are provided on the rotor for receiving a separation chamber capable of separating particles in response to centrifugal force.

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In another aspect, the invention includes a method of separating white blood cells from a liquid by forming a substantial barrier to white blood cell flow through the fluid chamber, where the barrier includes a saturated fluidized bed of particles.

In an additional aspect, the invention includes a method of separating first particles from second particles by forming a saturated fluidized bed of third particles.

In another aspect of the invention, a method is provided for separating smaller first particles from larger second particles. This method includes the steps of adding third particles to a liquid having the first particles and second particles, the third particles being larger than the first particles and smaller than the second particles, and forming a saturated fluidized bed of at least one of the first and third particles.

In another aspect, the invention includes a fluid chamber connected to centrifugal generating means, means for establishing a saturated fluidized bed of particles within the fluid chamber and means for maintaining the saturated fluidized bed in the chamber.

In another aspect, the invention includes an apparatus having a fluid chamber, a separation chamber configured to be received by a centrifuge rotor to centrifugally separate particles within the separation chamber, and means for fluid coupling the fluid chamber to the separation chamber.

In another aspect, the invention includes a method of separating blood components. The method comprises the steps of applying a centrifugal force to blood to separate the blood into components including at least plasma, platelets, and white blood cells, whereby at least a portion of the platelets become activated during the applying step, and filtering the components to remove white blood cells, while a substantial number of platelets remain activated.

In another aspect the invention includes an apparatus and method for separating particles from a liquid by initially separating particles in a liquid according to different

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densities and/or different sedimentation velocities, flowing at least a portion of the particles separated in the initial separating step into a fluid chamber, and further separating the particles within the fluid chamber according to different sedimentation velocities.

In another aspect, the invention includes an apparatus and method for separating blood components by directing separated blood components from a separation chamber into a fluid chamber to filter the separated components.

In another aspect, the invention includes a method and apparatus for reducing Coriolis jetting and/or density inversion.

In another aspect, the invention includes a method of separating particles without adding a substantial amount of a diluting fluid.

In another aspect, the invention includes an apparatus and method for separating and/or filtering blood components.

In particular the invention includes a method for continuously separating particles.

In another aspect of the invention, the sedimentation velocity of the bed forming particles is altered.

In an aspect of the invention, the bed forming particles include red blood cells and the obstructed particles include cells chosen from a group consisting of stem cells and tumor cells.

In another aspect, the invention includes a method of separating first particles from second particles having a sedimentation velocity different from that of the first particles. The method comprises the steps of altering sedimentation velocity of third particles, forming within a fluid chamber a saturated fluidized bed of third particles, and obstructing with the saturated fluidized third particle bed movement of the second particles through the fluid chamber while permitting liquid and the first particles to pass through the fluid chamber.

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In another aspect, the method of the invention comprises the steps flowing liquid having first, second, and third particles into a fluid chamber and forming a saturated fluidized bed of the third particles within the fluid chamber. The saturated fluidized third particle bed obstructs flow of the second particles through the fluid chamber. The method also includes the step of permitting the liquid, the first particles, and a portion of the third particles to pass through the fluid chamber.

In another aspect, the method includes an additional step of separating particles flowing from the outlet of the fluid chamber from the liquid flowing from the outlet of the fluid chamber.

The invention also includes an apparatus for separating first particles from second particles. The apparatus comprises a motor and a centrifuge rotor coupled to the motor for rotation about an axis of rotation. A holder is provided for holding a fluid chamber on the rotor with an outlet of the fluid chamber positioned closer to the axis of rotation than an inlet of the fluid chamber. First and second particles are supplied to the inlet of the fluid chamber, as are substances that alter sedimentation velocity of the second particles. In addition, the apparatus includes structure for controlling at least one of the motor and substances supplied to the fluid chamber in order to maintain a saturated fluidized bed of first particles within the fluid chamber and to cause second particles to be retained in the fluid chamber.

In another variation of the apparatus, structure is provided for separating particles and liquid flowing from the outlet of the fluid chamber.

According to another aspect of the present invention, the bed forming particles may comprise particles osmotically responsive to the concentration of a solute dissolved in a liquid in which the second particles are dispersed. In accordance with this aspect of the invention, the size, and thus the settling velocity, of the bed forming particles are

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adjusted by adjusting the solute concentration thereby adjusting the separation characteristics of the particles in the fluid chamber.

It is to be understood that both the foregoing general description and the following detailed description are exemplary, and are intended to provide further explanation of the invention as claimed. The accompanying drawings are included to provide a further understanding of the invention and are incorporated in and constitute a part of this specification. The drawings illustrate embodiments of the invention and, together with the description, serve to explain the principles of the invention.

Brief Description of the Drawings

Fig. 1 is a perspective view of a centrifuge apparatus in accordance with a embodiment of the invention;

Fig. 2 is an exploded side view of a fluid chamber shown in Fig. 1;

Fig. 3 is a partial schematic view of the apparatus of Fig. 1 illustrating a detailed view of components of the apparatus;

Fig. 4 depicts a portion of a tubing set in accordance with the invention;

Fig. 5 schematically illustrates a saturated fluidized bed formed within a fluid chamber, where the fluid chamber is a component of the tubing set of Fig. 4 mounted to the centrifuge apparatus of Fig. 1;

Fig. 6 is a cross-sectional view of a first alternate embodiment of the fluid chamber of Fig. 2;

Fig. 7 is a cross-sectional view of a second alternative embodiment of the fluid chamber of Fig. 2;

Fig. 8 is a cross-sectional view of a third alternative embodiment of the fluid chamber of Fig. 2;

Fig. 9 is a cross-sectional view of a fourth alternative embodiment of the fluid chamber of Fig. 2;

Fig. 10 is a perspective view of an alternate embodiment of a centrifuge apparatus of the invention;

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Fig. 11 is a cross-sectional schematic view of another embodiment of the centrifuge apparatus of the invention;

Fig. 12 is a partial perspective view of the centrifuge apparatus of Fig. 11;

Fig. 13 illustrates a separation chamber and fluid chamber in another embodiment of the invention;

Fig. 14 is a partial view of a centrifuge apparatus including a separation chamber and multiple fluid chambers in a further embodiment of the invention;

Fig. 15 is a schematic diagram illustrating a tubing set in accordance with the present invention, including the portion depicted in Fig. 4;

Fig. 16 is a cross-sectional view of a fifth alternative embodiment of the fluid chamber of Fig. 2;

Fig. 17 is a cross-sectional view of a sixth alternative embodiment of the fluid chamber of Fig. 16;

Fig. 18 is a schematic diagram of an embodiment of the invention including a fluid supply line coupled to a primary substance container and additive containers;

Fig. 19 is a partial schematic diagram of a centrifuge apparatus including a fluid chamber and supplemental fluid chamber in accordance with an embodiment of the invention; and

Fig. 20 is a partial schematic diagram of a centrifuge apparatus including a fluid chamber and separation channel in accordance with the invention.

Description of the Preferred Embodiments

Reference will now be made in detail to the present preferred embodiments of the invention illustrated in the accompanying drawings.

An embodiment of the present invention is described by referring to its use with a COBE® SPECTRA™ two stage sealless blood component centrifuge manufactured by the assignee of the invention. The COBE® SPECTRA™ centrifuge incorporates a one-omega/two-omega sealless tubing connection as disclosed in U.S. Patent No. 4,425,112 to Ito, the entire disclosure of which is incorporated herein by reference. The COBE® SPECTRA™ centrifuge also uses a two-stage blood component separation

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channel substantially as disclosed in U.S. Patent No. 4,708,712 to Mulzet, the entire disclosure of which is also incorporated herein by reference. Although the embodiment of the invention is described in combination with the COBE® SPECTRA™ centrifuge, this description is not intended to limit the invention in any sense.

As will be apparent to one having skill in the art, the present invention may be advantageously used in a variety of centrifuge devices commonly used to separate blood into its components. In particular, the present invention may be used with any centrifugal apparatus that employs a component collect line such as a platelet collect line or a platelet rich plasma line, whether or not the apparatus employs a two stage channel or a one-omega/two-omega sealless tubing connection.

In accordance with the invention there is provided an apparatus for filtering first particles from a liquid, comprising a centrifuge rotor coupled to a motor for rotating the centrifuge rotor about an axis of rotation. As embodied herein and illustrated in Fig. 1, centrifuge 10 includes a rotor 12. The rotor 12 has an annular groove or passageway 14 having an open upper surface adapted to receive a conduit or channel 44 of a tubing set 70 shown in Fig. 4. The passageway 14 completely surrounds the rotor's axis of rotation 13 and is bounded on an inner surface by wall 15 positioned on a top surface 17 of rotor 12. A motor 16 is coupled to rotor 12 to rotate the rotor 12 about the axis of rotation 13. This coupling is accomplished directly or indirectly through a shaft 18 connected to an arm 19 that mounts to the rotor 12. Alternately, the shaft 18 may be coupled to the motor 16 through a gearing transmission (not shown). A shroud 20 is positioned on the rotor 12 to protect the motor 16 and shaft 18.

In accordance with the present invention, a holder is provided for holding a fluid chamber on the rotor with an outlet of the fluid chamber positioned closer to the axis of rotation than an inlet of the fluid chamber. As embodied

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herein and as illustrated in Fig. 1, the holder may include a mounting bracket 24 for maintaining a fluid chamber 22 on rotor 12 with an outlet 32 generally positioned closer to the rotation axis 13 than an inlet 28. The fluid chamber 22 fits within the mounting bracket 24 as illustrated in Fig. 1. The fluid chamber 22 may also be secured to the rotor 12 at alternate locations, such as beneath passageway 14. The fluid chamber 22 may be constructed of a transparent or translucent copolyester plastic, such as PETG, to allow viewing of the contents within the chamber interior with the aid of an optional strobe (not shown) during a centrifuge procedure.

As illustrated in Fig. 2, the fluid chamber 22 is formed by joining a first chamber section 26 having the inlet 28 to a second chamber section 30 having the outlet 32. The inlet 28 and outlet 32 are arranged along a longitudinal axis A-A.

In an embodiment of the invention the fluid chamber 22 has an interior volume of about 14.5 ml., although this parameter may be increased or decreased depending on the particular application. The interior of the first chamber section 26 has a frustoconical shape with a conical angle 34a of approximately 30 degrees. The interior of the second chamber section 30 also has a frustoconical shape having a conical angle 34b of approximately 120 degrees. These angles may be varied. For example, the conical angle 34b may range from approximately 90 to 120 degrees and the conical angle 34a may range from approximately 30 to 90 degrees.

The volume of the fluid chamber 22 should be at least large enough to accommodate enough platelets to provide a saturated fluidized particle bed (described below) for a particular range of flow rates, particle sizes, and centrifuge rotor 12 speeds.

Preferably, the fluid chamber interior has a maximum cross- sectional area 33 located at a position intermediate the inlet 28 and outlet 32 where sections 26, 30 join. The cross sectional area of the fluid chamber interior decreases or tapers from the maximum cross-sectional area 33 in both directions along axis A-A. Although the fluid chamber 22 is

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depicted with two sections 26, 30 having frustoconical interior shapes, the interior shapes may be paraboloidal, or of any other shape having a major cross-sectional area greater than the inlet or outlet area. The fluid chamber 22 may be constructed from a unitary piece of plastic rather than from separate sections.

In accordance with the present invention, there is also provided means for supplying a substance to the inlet of the fluid chamber. As embodied herein and as schematically illustrated in Fig. 3, a pump 36 is fluidly connected to the fluid chamber 22 through outflow tubing 38. The pump 36 draws fluid and particles from the outlet 32 of the fluid chamber 22. The pump 36 is preferably a peristaltic pump or impeller pump configured to prevent significant damage to blood components, but any fluid pumping or drawing device may be provided. In an alternative embodiment (not shown), the pump 36 may be fluidly connected to the inlet of the fluid chamber 22 to directly move substances into and through the fluid chamber 22. The pump 22 may be mounted at any convenient location.

In accordance with the invention there is also provided means for controlling the motor and/or the supply means to maintain a saturated fluidized bed of second particles within the fluid chamber and to cause first particles to be retained in the chamber. As embodied herein and illustrated in Fig. 3, the controlling means may include a controller 40 connected to both the centrifuge motor 16 and the pump 36. As explained in detail below, during a centrifuge operation, controller 40 maintains a saturated fluidized particle bed within the fluid chamber 22 to separate particles. Controller 40 may include a computer having programmed instructions provided by a ROM or RAM as is commonly known in the art.

The controller 40 may vary the rotational speed of the centrifuge rotor 12 by regulating frequency, current, or voltage of the electricity applied to the motor 16. Alternatively, the rotor speed can be varied by shifting the arrangement of a transmission (not shown), such as by changing

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gearing to alter a rotational coupling between the motor 16 and rotor 12. The controller 40 may receive input from a rotational speed detector (not shown) to constantly monitor the rotor speed.

The controller 40 may also regulate the pump 36 to vary the flow rate of the substance supplied to the fluid chamber 22. For example, the controller 40 may vary the electricity provided to the pump 36. Alternatively the controller 40 may vary the flow rate to the chamber 22 by regulating a valving structure (not shown) positioned either within an inflow tubing 42 connected to the inlet 28 or within outflow tubing 38. The controller 40 may receive an input from a flow detector (not shown) positioned within the inflow tubing 42 to monitor the flow rate of substances entering the fluid chamber 22. Although a single controller 40 having multiple operations is schematically depicted in the embodiment shown in Fig. 3, the control means of the invention may include any number of individual controllers, each for performing a single function or a number of functions. The controller 40 may control flow rates in many other ways as is known in the art.

As described above, the rotor 12 is configured with an annular passageway 14 that is open along a top surface as illustrated in Fig. 1. This passageway 14 is provided to receive a channel 44 of tubing set 70, as partially shown in Fig. 5. As best illustrated in Fig. 4, tubing set 70 preferably includes a semi-rigid conduit formed into a channel 44 having a generally rectangular cross-section. A connector 71 joins ends of the channel 44 to form an annular or loop shape that fits within passageway 14. A supply line 78 provides whole blood to an inlet of the semi-rigid channel 44, while a tubing segment 42, outlet lines 72, 74, and a control line 76 allow for removal of blood components during a centrifuge operation and flow control within the channel 44. Further details of the general configuration and functioning of the channel 44, tubing segment 42, and lines 72, 74, 76 and 78 are described in U.S. Patent 4,708,712.

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A protective sheath 80 surrounds the lines 72, 74, 76, 78 and outflow tubing 38. When the channel 44 of the tubing set 70 is removably positioned within the passageway 14, the lines 72, 74, 76 and 78 extend through slots 82, 84, 86, respectively, formed in wall 15, while the inflow tubing 42 rests in a slot 88 formed by passageway 14 (See Figs. 1 and 5).

Fig. 15 is a more complete view of a second embodiment of the tubing set 70. The tubing set 70 may further include a plurality of additional elements for collecting blood components including, but not limited to one or more donor access lines 902, sample devices 904, spikes 906, filled solution bags (not shown) for the addition of fluids to the tubing set 70, wastes bags 908, accumulator bags 910, blood component bags 912, pump cartridges 914 for interfitting with various fluid pumps such as the pump 36, air chambers 916, monitoring device interfaces 918, inter-connecting tubing and fittings 920, and various miscellaneous elements and accessories.

As shown in Figs. 3 and 5, a separation chamber 46 is positioned within a flow passage of the channel 44. Particles initially separate within the separation chamber 46 according to density and/or sedimentation velocity in response to centrifugal force. The separation chamber 46 includes a ridge 48 positioned on an outer wall of the passageway 14 for deforming a portion of the channel 44 to create a dam 50 within the channel 44. Alternatively, the dam 50 may be a permanent structure mounted within the flow passage of the channel 44. Although only a single separation chamber 46 and dam 50 are depicted in the figures, the flow passage may have multiple separation chambers or dams depending upon desired use.

When channel 44 is positioned in passageway 14, a collect well 54 forms in channel 44 adjacent dam 50. A tubing segment 42 connecting an outlet 56 of the well 54 to the inlet 28 of the fluid chamber 22 allows for separated substances in the collect well 54 to be conveyed to the fluid chamber 22.

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Although the embodiment shown in Figs. 3-5 includes a tubing segment 42, any fluid coupling may be used between the separation chamber 46 and fluid chamber 22. For example, the inlet 28 of fluid chamber 22 may be directly connected to channel 44.

A method of separating particles of blood is discussed below with reference to Figs. 3 and 5. Although the invention is described in connection with a blood component separation process, it should be understood that the invention in its broadest sense is not so limited. The invention may be used to separate a number of different particles. In addition the invention is applicable to both double needle and single needle blood purification or filtration applications. For example, the invention of the present application may be practiced with the SINGLE NEEDLE RECIRCULATION SYSTEM FOR HARVESTING BLOOD COMPONENTS of U.S. Patent No. 5,437,624, issued August 1, 1995, the disclosure of which is incorporated herein by reference.

Preferably the fluid chamber 22 is initially primed with a low density fluid medium, such as air, saline solution, or plasma, having a density less than or equal to the density of liquid plasma. This priming fluid allows for efficient establishment of a saturated fluidized bed of platelets within the fluid chamber 22. When a saline solution is used, this liquid enters the channel 44 through supply line 78. The saline then flows into the outlet 56 and through the chamber 22 when controller 40 activates pump 36. Controller 40 also initiates operation of the motor 16 to rotate the centrifuge rotor 12 and fluid chamber 22 in the direction of arrow "B" in Fig. 3. During rotation, twisting of fluid lines 72, 74, 76, 78 and outflow tubing 38 connected to the centrifuge rotor 12 and fluid chamber 22 is prevented by a sealless one-omega/two-omega tubing connection as is known in the art and described in U.S. Patent No. 4,425,112.

After the apparatus is primed, and as the centrifuge rotates, whole blood or blood components are introduced through supply line 78 into the semi-rigid channel 44. When

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whole blood is used, the whole blood can be added to the semi-rigid channel 44 by transferring the blood directly from a donor through supply line 78. In the alternative, the blood may be transferred from a container, such as a blood bag, to supply line 78.

The blood within the channel 44 is subjected to a centrifugal force as the centrifuge rotor 12 continues to rotate in the direction of arrow "B" in Fig. 3. This centrifugal force acts in a radial direction away from the axis of rotation 13 of the rotor 12 as indicated by arrow "C" in Fig. 3.

The blood components undergo an initial separation within the channel 44. The components of whole blood stratify in order of decreasing density as follows: 1. red blood cells, 2. white blood cells, 3. platelets, and 4. plasma. The controller 40 regulates the rotational speed of the centrifuge rotor 12 to ensure that this particle stratification takes place. The blood particles form a buffy coat layer 58 and an outer layer 60 along an outer wall surface of the channel 44 within the separation chamber 46. The outer layer 60 includes particles having a density greater than the density of the particles in the buffy coat layer 58. Typically, the outer layer 60 includes red blood cells and white blood cells, while the buffy coat layer 58 includes platelets and white blood cells.

Plasma, the least dense blood component, flows within the channel 44 along the top surface of the buffy coat layer 58. When the height of the buffy coat layer 58 approaches the top of dam 50, the flowing plasma washes the platelets and some white blood cells of the buffy layer 58 over the dam 50. After these particles are washed over the dam 50, they enter the collect well 54. Some of the platelets may also flow past the collect well 54 and then reverse direction to settle back into the collect well 54, as described in U.S. Patent Application 08/422,598 entitled SPILLOVER COLLECTION OF SPARSE

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COMPONENTS SUCH AS MONONUCLEAR COMPONENTS OF WHOLE BLOOD, filed April 14, 1995, the disclosure of which is incorporated herein by reference.

The white blood cells and red blood cells within the outer layer 60 are removed through outlet line 74, while platelet poor plasma is removed through outlet line 72. The controller 40 may control optional pumps (not shown) connected to lines 72, 74, or 76 to remove these blood components, as is known in the art. After the red blood cells, white blood cells, and plasma are thus removed, they are collected and recombined with other blood components or further separated. Alternately, these removed blood components may be reinfused into a donor.

Plasma carries platelets and white blood cells from the collect well 54 into the fluid chamber 22, filled with the priming fluid, so that a saturated fluidized particle bed may be formed. The controller 40 maintains the rotation speed of the rotor 12 within a predetermined rotational speed range to facilitate formation of this saturated fluidized bed. In addition, the controller 40 regulates the pump 36 to convey plasma, platelets, and white blood cells at a predetermined flow rate through the tubing segment 42 and into inlet 28 of the fluid chamber 22. These flowing blood components displace the priming fluid from the fluid chamber 22.

When the platelet and white blood cell particles enter the fluid chamber 22, they are subjected to two opposing forces. Plasma flowing through the fluid chamber with the aid of pump 36 establishes a first viscous drag force when plasma flowing through the fluid chamber 22 urges the particles toward the outlet 32 in the direction "D", shown in Fig. 3. A second centrifugal force created by rotation of the rotor 12 and fluid chamber 22 acts in the direction "C" to urge the particles toward the inlet 28.

The controller 40 regulates the rotational speed of the rotor 12 and the flow rate of the pump 36 to collect platelets and white blood cells in the fluid chamber 22. As plasma flows through the fluid chamber 22, the flow velocity of the

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plasma decreases as the plasma flow approaches the maximum cross-sectional area 33. This flow reaches a minimum velocity at this maximum cross-sectional area 33. Because the rotating centrifuge rotor 12 creates a sufficient gravitational field in the fluid chamber 22, the platelets accumulate near the maximum cross-sectional area 33 rather than flowing from the fluid chamber 22 with the plasma. The white blood cells accumulate somewhat below the maximum cross- sectional area 33. However, density inversion tends to mix these particles slightly during this initial establishment of the saturated fluidized particle bed.

The larger white blood cells accumulate closer to inlet 28 than the smaller platelet cells, because of their different sedimentation velocities. Preferably, the rotational speed and flow rate are controlled so that very few platelets and white blood cells flow from the fluid chamber 22 during formation of the saturated fluidized particle bed.

The platelets and white blood cells continue to accumulate in the fluid chamber 22 while plasma flows through the fluid chamber 22. As the concentration of platelets increases, the interstices between the particles become reduced and the viscous drag force from the plasma flow gradually increases. Eventually the platelet bed becomes a saturated fluidized particle bed within the fluid chamber 22. Since the bed is now saturated with platelets, for each new platelet that enters the saturated bed in the fluid chamber 22, a single platelet must exit the bed. Thus, the bed operates at a steady state condition with platelets exiting the bed at a rate equal to the rate additional platelets enter the bed after flowing through inlet 28. This bed is depicted schematically in Fig. 5, where the "X" symbol represents platelets and the "O" symbol represents white blood cells. As explained below, and depicted in Fig. 5, the saturated fluidized particle bed substantially obstructs or prevents white blood cells, "O", from passing through the fluid chamber 22.

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The saturated bed establishes itself automatically, independent of the concentration of particles flowing into the fluid chamber 22. Plasma flowing into the fluid chamber 22 passes through the platelet bed both before and after the platelet saturation point.

The saturated bed of platelets occupies a varying volume in the fluid chamber 22 near the maximum cross-sectional area 33, depending on the flow rate and centrifugal field. The number of platelets in the saturated bed depends on a number of factors, such as the flow rate into the fluid chamber 22, the volume of the fluid chamber 22 and rotational speed. If these variables remain constant, the number of platelets in the saturated fluidized bed remains substantially constant. When the flow rate of blood components into the fluid chamber 22 changes, the bed self adjusts to maintain itself by either releasing excess platelets or accepting additional platelets flowing into the fluid chamber 22. For example, when the plasma flow rate into the fluid chamber 22 increases, this additional plasma flow sweeps excess platelets out of the now super-saturated bed, and the bed reestablishes itself in the saturated condition at the increased flow rate. Therefore, the concentration of platelets in the bed is lower due to the release of bed platelets.

After the saturated fluidized bed of platelets forms, flowing plasma carries additional platelets into the fluid chamber 22 and the bed. These additional platelets add to the bed and increase the viscous drag of the plasma flow through the bed. At some point the viscous drag is sufficient to cause platelets near the maximum cross-section area 33 to exit the saturated bed and fluid chamber 22. Thus, if the rotational speed and flow rate into the fluid chamber 22 remain constant, the number and concentration of platelets flowing into the saturated fluidized bed of platelets substantially equals the number and concentration of platelets released from the bed. This is in sharp contrast from the prior art.

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Although the bed is saturated with platelets, a small number of white blood cells may be interspersed in the platelet bed. These white blood cells, however will tend to "fall" or settle out of the platelet bed toward inlet 28 due to their higher sedimentation velocity. Most white blood cells generally collect within the fluid chamber 22 between the saturated platelet bed and the inlet 28, as depicted in Fig. 5 and described below.

The saturated fluidized bed of platelet particles functions as a filter or barrier to white blood cells flowing into the fluid chamber 22. When blood components flow into the fluid chamber 22, plasma freely passes through the bed. However, the saturated fluidized platelet bed creates a substantial barrier to white blood cells entering the fluid chamber 22 and retains these white blood cells within the fluid chamber 22. Thus, the bed effectively filters white blood cells from the blood components continuously entering the fluid chamber 22, while allowing plasma and platelets released from the saturated bed to exit the chamber 22. This replenishment and release of platelets is referred to as the bed's self-selecting quality. Substantially all of these filtered white blood cells accumulate within the fluid chamber 22 between the saturated fluidized platelet bed and the inlet 28.

The particle separation or filtration of the saturated fluidized particle bed obviates a number of limitations associated with prior art elutriation. For example, particles may be separated or filtered in a continuous steady state manner without batch processing. In addition, an additional elutriating fluid medium is not required. Furthermore, after the saturated fluidized particle bed is established, flow rates may be varied over a range without changing the size of the particles leaving the fluid chamber 22. Unlike prior art elutriation, the present invention establishes a saturated particle bed consisting of numerically predominant particles. This bed automatically passes the predominant particles while rejecting larger particles.

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The apparatus and method of the invention separate substantially all of the white blood cells from the platelets and plasma flowing through the fluid chamber 22. The barrier to white blood cells is created, at least in part, because white blood cells have a size and sedimentation velocity greater than that of the platelets forming the saturated fluidized particle bed. Therefore, particles of similar densities are separated according to different sizes or sedimentation velocities.

Because the initial separation at dam 50 and the saturated fluidized bed remove a majority of the red blood cells and white blood cells, the fluid exiting the fluid chamber 22 consists mainly of plasma and platelets. A device as described herein was operated 30 times using whole human blood. Each operation resulted in a leukopoor product having less than $3x10^6$ white blood cells per $3x10^{11}$ platelets. Based on these results it is expected that platelet product exiting the fluid chamber 22 will consistently (at least 99% of the time) meet the leukopoor standard of less than 5×10^6 white blood cells when at least 3×10^{11} platelets flow from the fluid chamber 22.

Unlike a conventional porous filter, where the filtered white blood cells are retained in the filter, the present invention allows a substantial fraction of white blood cells to be recovered and returned to the donor.

Preferably, 80% to 99% of the platelets initially entering the channel 44 may be recovered in a viable state. More preferably, at least 95% or at least 98% of the platelets initially entering the channel 44 are recovered from both the channel 44 and the fluid chamber 22.

When the blood components are initially separated with the separation chamber 46, a substantial number of platelets may become slightly activated. The saturated fluidized platelet bed allows white blood cells to be filtered from plasma and platelets despite this slight activation. Thus, the present invention does not require a waiting period to

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filter white blood cells after blood components undergo initial separation in a separation chamber 46. This is in contrast to methods using conventional filters.

After separation, the platelets and plasma exiting the fluid chamber 22 are collected in appropriate containers and stored for later use. The red blood cells and white blood cells removed from the semi-rigid channel 44 may be combined with the remainder of the plasma in the system for donor reinfusion or storage. Alternatively, these components may be further separated by the apparatus 10.

In an embodiment of the invention, the controller 40 regulates the rotational speed of the rotor 12 within a preferred range of 1,800 to 2,400 RPM. Preferably the rotation is controlled at 2,400 RPM to create a gravitational field within the fluid chamber 22 ranging from approximately 800G adjacent to the inlet 28 to approximately 500G adjacent to the outlet 32. The controller 40 maintains the flow rate into the fluid chamber 22 within a range of 1 ml/min to 15 ml/min. The preferred flow rate ranges from 2 ml/min to 8 ml/min. The specific flow rate is selected according to an initial platelet count and the total volume of whole blood being processed, among other things.

In an embodiment of the invention, filtering may take place at the same flow rate used to form the saturated fluidized bed. Optionally the flow rate during filtering may be greater than the flow rate used during the bed formation to increase the rate of particle filtration. For this optional arrangement, the controller 40 may increase the flow rate of the blood components entering the fluid chamber 22 while maintaining the saturated fluidized bed. The controller 40 increases flow rate by increasing the rate of pump 36.

The controller 40 maintains the saturated fluidized bed throughout the filtering process as blood components flow into the fluid chamber 22. The controller 40 ensures that the flow through the fluid chamber 22 is smooth and steady by regulating the supply of fluid and rotation of the centrifuge rotor 12. This regulation properly balances the forces in the

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fluid chamber 22 to maintain the saturated fluidized bed. As described in more detail below, the controller 40 may increase flow into the fluid chamber 22 while maintaining the saturated fluidized bed.

At the end of a blood component separation session, the controller 40 may recover platelets retained both in the buffy coat layer 58 of channel 44 and within the saturated fluidized bed of fluid chamber 22. The controller 40 recovers platelets in the buffy coat layer 58 by either decreasing rotational speed of the rotor 12 or increasing the amount of plasma exiting the channel 44. For example, in a preferred manner of recovering platelets in the buffy coat layer, the rotor speed is suddenly decreased from 2,400 RPM to 1,800 RPM, and then increased back to 2,400 RPM. This spills platelets and white blood cells retained in the buffy coat layer 58 over the dam 50 and into the fluid chamber 22. Within the fluid chamber 22 the saturated fluidized platelet bed blocks passage of the white blood cells from the buffy coat layer 58, while buffy coat layer 58 platelets simultaneously add to the bed and release platelets from the saturated bed. Thus, the apparatus may filter substantially all of the white blood cells from the buffy coat layer 58. This increases platelet yield significantly.

The buffy coat layer 58 may spill over the dam in the manner described in above-mentioned U.S. Patent Application 08/422,598. This is particularly effective in a mononuclear cell collection procedure, because the fluid chamber 22 may allow for separation of red blood cells from mononuclear cells.

In addition, platelets in the saturated fluidized bed are harvested to recover a substantial number of platelets from the fluid chamber 22. During bed harvest, the controller 40 increases the flow rate and/or decreases the centrifuge rotator 12 speed to release platelets from the bed. This flushes from the fluid chamber 22 most of the platelets that made up the saturated fluidized bed to substantially increase platelet yield. The harvesting continues until substantially

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all of the platelets are removed, just before an unacceptable number of white blood cells begin to flow from the fluid chamber 22.

The harvested platelets that made up the bed may be combined with the platelets previously collected. In addition, the remainder of contents of the fluid chamber 22, having a high concentration of white blood cells, can be separately collected for later use or recombined with the blood components removed from channel 44 for return to a donor.

The invention particularly allows trace or contaminating first particles to be separated from a liquid having a larger number of second particles. Preferably the first particles to be filtered, such as white blood cells, have a concentration insufficient to form a saturated fluidized particle bed. However, the invention in its broadest application is directed to either separating first particles from liquid or separating first from second particles without concern for particular particle concentrations.

Although the inventive device and method have been described in terms of removing white blood cells and collecting platelets, this description is not to be construed as a limitation on the scope of the invention. The invention may be used to separate any of the particle components of blood from one another. For example, the saturated fluidized bed may be formed from red blood cells to prevent flow of white blood cells through the fluid chamber 22, so long as the red blood cells do not rouleau (clump). Alternatively, the liquid for carrying the particles may be saline or another substitute for plasma. In addition, the invention may be practiced to remove white blood cells or other components from whole blood removed from an umbilical cord to collect stem cells. Further, one could practice the invention by filtering or separating particles from fluids unrelated to either blood or biologically related substances.

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The apparatus and method of the invention may separate white blood cells, including stem cells, and tumor cells by forming a saturated fluidized particle bed of stem cells to substantially prevent tumor cells from flowing through the fluid chamber 22. In the alternative, the tumor cells may form a saturated fluidized particle bed to substantially obstruct flow of stem cells through the fluid chamber 22.

In another aspect of the invention, smaller first particles, such as tumor cells, may be separated from larger second particles, such as stem cells, by forming a saturated fluidized particle bed with intermediate sized third particles. Initially, intermediate sized third particles are added to a liquid carrying the first and second particles. Preferably, the concentration of added third particles exceeds the concentration of both the first and second particles. These third particles are preferably magnetic micro-beads or some other substance readily separable from the other particles.

The liquid carrying the first, second, and third particles then passes into the fluid chamber 22. Eventually, the third particles form a saturated fluidized particle bed, in the same manner as described above. As more of the liquid and particles flow into the fluid chamber 22, the liquid and smaller first particles pass through the saturated third particle bed, while the bed and particle sedimentation characteristics obstruct movement of the second particles through the bed. Thus, the first and second particles separate within the fluid chamber 22.

The saturated fluidized bed may release third particles as more third particles flow into the bed or when flow rate into the fluid chamber 22 changes. These third particles may be removed from the liquid and first particles exiting the fluid chamber 22. In a preferred embodiment, a particle remover (not shown) having a magnet, magnetically attracts magnetic third particles to remove them from the liquid. Thus, a substantially purified concentration of first particles is obtained.

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This alternate method is useful to separate first and second particles both being present in low concentrations and having similar densities, but different sizes. Although the third particles for forming the bed are preferably added along with the first and second particles, they may also be introduced into the fluid chamber 22 in separate steps. This aspect of the invention may be particularly useful in separating tumor cells from stem cells or other blood components, as mentioned above. Alternatively, the first particles may be T cells and the second particles may be stem cells. However, this variant of the inventive method may be practiced to separate many different types of particles. For example, T cells can be separated from stem cells so as to reduce graft versus host disease after stem cell transfusion.

Additional embodiments of the invention will now be described where like or similar elements are identified throughout the drawings by reference characters having the same final two digits.

As shown in Fig. 6, another embodiment of the invention includes a fluid chamber 122 having an inlet 128 and an outlet 132. A groove 190 is formed on an inner surface of the fluid chamber 122 at a position of the maximum cross-sectional area 133. Top and bottom portions 191, 192, oriented substantially perpendicular to a longitudinal axis A-A of the fluid chamber 122, are joined by a side 193. Preferably, the side 193 is parallel to the axis A-A and surrounds this axis to form the substantially annular groove 190.

In an embodiment of the invention, the side 193 is 0.1 inches, while the top and bottom portions 191, 192 are each 0.08 inches. However, the groove 190 may be configured in many different shapes and sizes without departing from the invention.

The groove 190 helps to disperse Coriolis jetting within the fluid chamber 122. Thus, groove 190 improves the particle barrier capability of the saturated fluidized particle bed. Sudden increases in liquid flow rate during a particle separation procedure may limit the ability of the saturated

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fluidized particle bed to obstruct particle passage. Liquid flowing into the fluid chamber 22 undergoes a Coriolis jetting effect. This jetting flow reduces the filtration effectiveness of the saturated fluidized particle bed because liquid and particles may pass between the saturated fluidized particle bed and an interior wall surface of the fluid chamber 22 rather than into the bed itself. The fluid chamber 122 including groove 190 counteracts these effects by channeling Coriolis jetting flow in a circumferential direction partially around the axis A-A of fluid chamber 122. Therefore, the groove 190 improves the particle obstruction capability of the saturated bed, especially when liquid flow rates increase.

Figs. 16 and 17 depict fluid chambers 1022 and 1022', respectively, having alternate embodiments of grooves 1090, 1090'. As illustrated in Fig. 16, fluid chamber 1022 includes a groove 1090 having a side 1093 and top and bottom portions 1091 and 1092 formed circumferentially on the inner surface of the fluid chamber 1022 at a position of a maximum cross-sectional area 1033. These top and bottom portions 1091 and 1092 may be perpendicular to a longitudinal axis A-A, while the side 1093 may be parallel to the axis A-A to form a substantially annular groove 1090.

As shown in Fig. 16, a circumferential lip 1094, located closer to the axis A-A than the side 1093, extends from the top portion 1091. The bottom portion 1092 and lip 1094 define a groove entrance 1096. As shown in Fig. 16, this groove entrance 1096 may completely surround axis A-A.

Alternatively, as shown in Fig. 17, the groove entrance may include a plurality of slot-shaped entrances 1095' spaced about the circumference of the fluid chamber 1022' at the position of maximum cross-sectional area 1033'. In this embodiment, the lip 1094' extends to the bottom portion 1092' to form an inner groove wall 1097' located between the slot-shaped entrances 1095.

Preferably, a first entrance 1095' may be provided at a location corresponding to the location of Coriolis jetting, and a second entrance (not shown) may be provided at a

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diametrically opposite location. The Coriolis jet flow enters the groove 1090' at a first slot-shaped entrance 1095', travels circumferentially around the groove 1090' in both clockwise and counter-clockwise directions, and then exits at another slot-shaped opening.

The configurations of Figs. 16 and 17 are believed to improve direction of Coriolis jetting momentum and further improve performance. The groove configurations of Figs. 16 and 17 may be optionally employed in conjunction with any of the fluid chamber embodiments described herein.

Fig. 7 depicts another embodiment of a fluid chamber 222. A plurality of steps 294 are formed on an inner surface of the fluid chamber 222 between the position of the maximum cross section 233 and the inlet 228. Although only four steps 294 are illustrated, any number of steps 294 may be provided in the fluid chamber 222.

Each step 294 has a base surface 295 oriented substantially perpendicular to a longitudinal fluid chamber axis A-A. In addition, a side surface 296 is positioned orthogonal to the base surface 295. Although Fig. 7 depicts a corner where side surface 295 and base surface 295 intersect, a concave groove may replace this corner. In a preferred embodiment each step 294 surrounds the axis A-A to bound a cylindrical shaped area. Further, the fluid chamber 222 optionally includes a groove 290.

The base surface 295 is 0.05 inches and the side surface 296 is 0.02 inches in a preferred embodiment. However, the sizes for these surfaces and the configuration of each step 294 may be modified without departing from the scope or spirit of the invention.

Adding steps 294 to the fluid chamber 222, also improves the particle obstruction characteristics of the saturated fluidized particles bed, in particular during increases in the rate of fluid flow. The steps 294 provide this improvement by providing momentum deflecting and redirecting surfaces to reduce Coriolis jetting in fluid chamber 222. When Coriolis jetting takes place, the liquid and particles of the jet

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travel along an interior surface of the fluid chamber 222 that faces the direction of centrifuge rotation. Therefore, the jet may transport particles between the fluid chamber interior surface and either a saturated fluidized particle bed or an elutriation field positioned in the fluid chamber 222. Thus, particles traveling in the jet may exit the fluid chamber 222 without being separated.

Steps 294 direct or alter the momentum of the Coriolis jet flow of liquid and particles generally in a circumferential direction about axis A-A. Thus, a substantial number of particles originally flowing in the jet must enter the saturated fluidized bed or elutriation field to be separated.

As shown in Fig. 7, the fluid chamber 222 may include additional steps 225 shaped similar to steps 294. The additional steps 225 are located between the position of the maximum cross- section 233 and a fluid chamber outlet 232. In a fashion similar to that described above, these steps 225 tend to redirect the Coriolis jet flow in a circumferential direction surrounding axis A-A.

In addition to adding steps 294 and 225, the conical angle 234b of the second chamber section 230 may be decreased from 120° to 45° to reduce particle contamination caused by density inversion. If faster sedimenting particles should migrate past the maximum cross section 233, the smaller angled walls partially limit some of these particles from flowing directly to outlet 232 because density inversion does not exist in the section 230. Thus, the faster sedimenting particles will "fall" or migrate back between area 233 and inlet 228 under the influence of the gravity centrifugal field, rather than flowing from outlet 232. Optionally, any of the fluid chambers disclosed herein may include a second chamber section 230 with a conical angle 234b less than 120°.

Fig. 8 illustrates an additional embodiment of a fluid chamber 322 having steps 394 and an optional groove 390 similar to groove 190. As shown in Fig. 8, each step 394

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includes a base surface 395 substantially perpendicular to axis A-A. This embodiment also includes a side surface 396 oriented at an acute angle to the base surface 395.

In Fig. 9 a further embodiment of a fluid chamber 422 including flow limiting steps 494 and an optional groove 490 is depicted. A side surface 496 of each step 494 is substantially parallel to an axis A-A and forms an obtuse angle with base surface 495.

In Figs. 6-9, the grooves 190, 290, 390, 490 and steps 294, 394, 494 may either completely or only partially surround the chamber axis A-A. These features are provided to facilitate fluid flow rate increases, as described below, as well as to improve steady state performance of the fluid chamber. During blood component separation, the grooves 190, 290, 390, 490 and steps 294, 394, 494 greatly reduce the number of white blood cells that would otherwise bypass the saturated fluidized platelet bed.

The grooves 190, 290, 390, 490, steps 294, 394, 494, and additional steps 225 may be formed in many different configurations without departing from the scope, or spirit of the invention. For example, the base surface and/or side surface of one or more of the steps 294, 394, 494 may have a concave shape. In addition the steps 294, 394, 494 may be arranged in a spiral surrounding axis A-A. Further, a portion of the base surface 295, 395, 495 extending around axis A-A may be positioned lower than a remainder of this surface to form a concavity.

Although the fluid chambers 122, 222, 322, 422, 1022, 1022' are described for use in forming a saturated fluidized particle bed, this description is not intended to limit the scope of the invention in its broadest sense. Because particle separation difficulties, such as those discussed in Sartory, may be reduced or eliminated, a significant advancement from the prior art has been made. These fluid chambers 122, 222, 322, 422 may be used in any particle separation process. In particular, a fluid chamber having a channel, step, or additional step may be used in elutriation.

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The grooves 190, 290, 390, 490, steps 294, 394, 494, and additional step 225 may be formed in an injection molding process. Preferably, the fluid chambers 22, 122, 222, 322, 422, 1022, 1022' are initially formed by injection molding in multiple pieces, preferably two, and bonded together by any of several well known processes, such as RF welding, ultrasonic welding, hot plate welding, solvent bonding, or adhesive bonding. Alternatively, these fluid chambers may be formed from a unitary plastic material, as by blow molding. However, any known manufacturing process may be practiced to fabricate the chambers.

When one of the fluid chambers 122, 222, 322, 422, 1022, 1022' is substituted for the fluid chamber 22, the controller 40 may regulate flow of the liquid having first particles in number of preferred ways. Because these fluid chamber designs reduce Coriolis jetting and/or density inversion, the controller 40 may increase flow rate without disrupting the saturated fluidized particle bed.

While maintaining rotational speed of the rotor 12 at a substantially constant rate, the controller 40 may increase flow through the fluid chamber 122, 222, 322, 422, 1022, 1022' with one of, or a combination of, the following different routines. In one routine the controller 40 increases flow rate by rapidly or instantaneously increasing flow through the fluid chamber 122, 222, 322, 422, 1022, 1022'. In another routine, flow rate is increased gradually over time. In yet a further routine, the controller 40 increases flow rate in a sequential manner by gradually increasing the flow rate, maintaining this increased flow rate, and then gradually increasing flow rate again.

However, if the apparatus 10 includes the fluid chamber 22, shown in Figs 1-5, the flow rate control may be more limited. The flow velocity of the liquid and particles entering the fluid chamber 22 should not undergo rapid or extreme fluctuation, otherwise temporary disruption of the effectiveness of the bed may result. The flow velocity can drop suddenly without affecting the bed, however sudden

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increases in velocity, if large enough, may disrupt the bed to allow particles, such as white blood cells, to exit the fluid chamber 22.

The controller 40 increases flow into the fluid chamber 22 while maintaining the saturated fluidized bed. The controller 40 may perform this flow rate increase by gradually increasing flow in a continuous fashion until a final flow rate is achieved. In a preferred embodiment, including the fluid chamber 22 shown in Fig. 2, the controller 40 increases the flow rate into the fluid chamber 22 by a ratcheting process.

The controller 40 maintains the bed and increases the flow rate in the ratcheting process by initially reducing the rotational speed of the rotor 12. However, the rotational speed of the rotor 12 is not reduced to a level that allows red blood cells in outer layer 60 to spill over dam 50, otherwise a significant number of both red blood cells and white blood cells will flow into the fluid chamber 22. In an embodiment of the invention, the controller 40 lowers the rotational speed of the rotor 12 so that a centrifugal force at dam 50 remains above 850G. Then, the controller calculates a value for $K = Q_i/N_i^2$, where K is a constant, Q_i is the current flow rate into the fluid chamber 22, and N_i is the current rotational speed of the centrifuge rotor 12.

After the controller 40 reduces the rotational speed of the rotor 12 and calculates K, the controller 40 simultaneously increases both the flow rate into the fluid chamber 22 and the rotational speed of the rotor 12. Thus, an increasing centrifugal force in the fluid chamber 22 counteracts with increasing fluid flow forces in the fluid chamber 22 to maintain the saturated fluidized particle bed as a barrier to other particles. The new flow rate into the chamber, Q, and the new rotational speed N satisfy the equation: $Q/N^2 = K$. Therefore, Q/N^2 equals Q_i/N_i^2.

To increase the flow rate even further, the controller 40 may continue to simultaneously increase both flow rate and rotational speed. Also, if necessary, the controller 40 may

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repeat the ratcheting process to further increase flow rate. This is accomplished by repeating the steps of reducing rotational speed and simultaneously increasing both flow rate and rotational speed.

In addition, the controller 40 preferably returns the saturated fluidized particle bed to its original state if a pause in fluid flow to the fluid chamber 22 causes the bed to collapse. The controller 40 may constantly monitor both flow rate, Q, and rotational speed, N, to calculate a value for $K = Q/N^2$. If the flow into the fluid chamber 22 momentarily pauses to collapse the saturated fluidized bed, the particles that made up the bed temporarily remain in the fluid chamber 22. When fluid flow to the fluid chamber 22 is reinitiated, the controller 40 controls both the flow rate, Q, and rotational speed, N, so that these parameters satisfy the $K = Q/N^2$ relationship existing immediately before fluid flow to the fluid chamber 22 was interrupted. This automatically returns the particles of the collapsed bed back into a saturated fluidized bed form.

After a bed collapses the saturated fluidized particle bed may recover in many other different ways. For example, after a pause in fluid flow the flow rate may be increased in a stepwise or gradual fashion to provide bed recovery.

Fig. 10 illustrates another embodiment of the invention. In this embodiment a fluid chamber 522 is mounted on a centrifuge rotor 512. The rotor 512 includes an outer bowl 521 and a clip 523 for holding a separation chamber 546 formed in an elongated flexible tubular or belt shape from plastic material. The device depicted in Fig. 10 separates particles, in particular blood components, within the separation chamber 546 by generating centrifugal force. For further details concerning the configuration and operation of this device, refer to U.S. Patent 5,362,291 to Williamson, IV, U.S. Patent 5,360,542 to Brown et al., and U.S. Patent 5,078,671 to Dennehey et al., the disclosures of which are incorporated herein by reference.

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The fluid chamber 522 is mounted or held on the centrifuge rotor 512 with an outlet 532 facing substantially toward an axis of rotation 513 of the centrifuge rotor 512. Inflow tubing 542 supplies liquid and particles to the fluid chamber 522 after the particles undergo an initial separation within a portion of the separation chamber 546. In a similar fashion, outflow tubing 538 conveys substances from the fluid chamber 522 to another portion of the separation chamber 546.

In using the embodiment shown in Fig. 10, particles carried by a liquid are separated in the separation chamber 546 according to density and size differences of the particles. After being initially separated, the liquid and particles, for example plasma carrying platelets and white blood cells, flow into the fluid chamber 522. Within fluid chamber 522, a saturated fluidized particle bed forms to further separate particular particles from the flowing liquid.

Yet another embodiment of the invention is illustrated in Figs. 11 and 12. This embodiment includes both a separation chamber 646 shaped as a container and a collection container 627. Holders 629, 631 hold separation chamber 646 and container 627, respectively, on a centrifuge rotor 612. Flow lines 635, 638 provide fluid flow to and from the separation chamber 646 and container 627 as indicated by the arrows labelled with the symbol "E" shown in Fig. 11. Further components include a restraining collar 637 and container holder clamp assemblies 639. Particles are separated according to density and size differences within the separation chamber 646 in response to centrifugal force. For further details of how this device is configured and operates, refer to Baxter Heathcare Corporation's CS-3000® Plus Blood Separator Operator's Manual (7-19-3-136), the disclosure of which is incorporated herein by reference.

As depicted in Figs. 11 and 12, a holder 624 holds a fluid chamber 622 on the rotor 612. Inflow tubing 642 conveys liquid and particles initially separated in separation chamber 646 into the fluid chamber 622. In addition, an outflow tubing 638 fluidly couples the fluid chamber 622 to the

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collection container 627. With this configuration, a saturated fluidized particle bed may be formed in the fluid chamber 622, as explained with respect to the above embodiments, to filter particles.

Fig. 13 illustrates a further embodiment of the invention. This embodiment includes a separation chamber 746, preferably formed from rigid transparent plastic conduit, capable of being inserted into a centrifuge. An inlet 741 allows whole blood to flow into a first stage 743 of the separation chamber 746, so that red blood cells may be removed from a conduit 745, while platelet rich plasma flows through conduit 742. In addition, a conduit 747 and outlet 749 enable removal of platelet poor plasma and platelets, respectively, in a second stage 751. For further details regarding the structural configuration and operation of this embodiment, refer to the Brief Operating Instructions of the Fresenius MT AS 104 blood cell separator (4/6.90(OP)), the disclosure of which is incorporated herein by reference.

As shown in Fig. 13, a fluid chamber 722 may be coupled to the separation chamber 746. A saturated fluidized particle bed may be formed in the fluid chamber 722 to separate particles after initial particle separation in the separation chamber 746, in the manner described above.

In an alternate embodiment (not shown), the fluid chamber 722 may be coupled to outlet 749 of second stage 751. This alternate embodiment would allow for particles to be separated in a manner similar to the particle separation described for the embodiment shown in Figs. 1-5.

Fig. 14 illustrates yet another embodiment of the invention. As shown, a separation chamber 846 and a first fluid chamber 822a are provided on a centrifuge rotor 812 in a manner similar to that of the embodiment of Figs. 1-5. In addition, an outflow tubing 838 fluidly couples an outlet 832a of the fluid chamber 822a to an inlet 828b of an auxiliary fluid chamber 822b. Mounting brackets (holders) 824a, 824b

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maintain the fluid chamber and the auxiliary chamber 822a, 822b, respectively, at substantially the same radial distance from a rotation axis of the centrifuge rotor 812.

In using the embodiment shown in Fig. 14, centrifuge rotor 812 rotates to initially separate particles within separation chamber 846 according to density and/or sedimentation velocity. Liquid carries separated particles into the first fluid chamber 822a where particles further separate after formation of a saturated fluidized bed of particles or an elutriation field. Thereafter, the separated particles and liquid flow through tubing 838 into auxiliary fluid chamber 822b where particles are further separated by either a saturated fluidized bed of particles or an elutriation field. Thus, particles separate within chambers 822a, 822b by forming a saturated fluidized particle bed in one of the chambers 822a, 822b and an elutriation boundary in another of the chambers 822a, 822b, or, in the alternative, by forming either a saturated fluidized particle bed or an elutriation boundary in both of the chambers 822a, 822b.

Optionally the chambers 822a, 822b may have different dimensions, such as differing volumes, lengths or maximum diameters. For example, fluid chamber 822a may have a greater volume than that of auxiliary chamber 822b. These different dimensions allow for two different particle separations to take place within each of the chambers 822a, 822b.

The embodiment of Fig. 14 allows for multiple particle separations to take place simultaneously. Additionally, different types of particles may be harvested in one single procedure. Of course, one or more further fluid chambers may be added without departing from the scope of the invention. Furthermore, both of the chambers 822a and 822b may be cylindrical.

It will be apparent to those skilled in the art that various modifications and variations can be made to the structure and methodology of the present invention without departing from the scope or spirit of the invention.

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The fluid chambers 122, 222, 322, 422, 1022, or 1022' depicted in the embodiments of Figs. 6-9, 16 and 17, may be substituted for the fluid chambers 22, 522, 622, 722, 822a or 822b. Further, the invention can be modified by including supplemental fluid chambers or separation chambers. Although the invention has been described as having a separation chamber to initially separate particles from the liquid, the invention can be practiced without this initial separation taking place.

Although the controller 40 is described above as controlling rotor speed and flow rate, the controller 40 may also regulate other parameters. For example the controller may control the density or some other characteristic of the liquid used to carry particles into the fluid chamber.

In addition, while the invention is described herein in connection with blood component separation, the invention in its broadest sense is not so limited. The invention is applicable to other medical and non-medical uses.

The particles used to form the saturated fluidized bed in the fluid chamber can differ from the particles within the fluid passing through the fluid chamber for filtration. Additionally, it is possible to initially form the saturated fluidized bed with an extremely high concentration of platelets having very few white blood cells.

Further, the fluid chamber of the invention may be used in a separation process involving elutriation or any other particle separation means without departing from the scope of the invention.

In accordance with the invention there is also provided means for altering sedimentation velocity of particles used to form the saturated bed. Figs. 18-20 illustrate embodiments of the invention including examples of such means. As illustrated in Fig. 18, a portion of a tubing set 1100 preferably includes a primary container 1102 for containing a primary substance including liquid and particles to be separated.

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In a preferred embodiment of the invention, the primary substance in primary container 1102 is a peripheral cell collection including, for example, plasma, red blood cells, stem cells, T cells and optionally tumor cells. As mentioned above, devices for purifying blood to obtain a peripheral cell collection are known in the art. As described in more detail below, particular particles, such as red blood cells, in the primary substance are used to form a saturated fluidized particle bed in a fluid chamber 1122 or 1122' shown respectively in Figs 19 and 20. Fluid chambers 1122 and 1122' are preferably constructed in a manner similar to one of the fluid chambers 22, 122, 222, 322, 422, 522, 622, 722, 822a, 822b, 1022, or 1022' described above.

As shown in Fig. 18, the tubing set 1100 also preferably includes a series of additive containers 1104 containing additives for altering sedimentation velocity of the particles in the primary substance forming the saturated fluidized bed in the fluid chamber 1122, 1122'. A series of outflow tubes 1112 and 1114 respectively couple the primary container 1102 and each of the additive containers 1104 to a supply line 1121 of the tubing set 1100 so that the primary substance and additives flowing in the outflow tubes 1112 and 1114 mix in the supply line 1121. As shown respectively in Figs. 19 and 20, the supply line 1121 is coupled to an inlet 1140, 1140' of the fluid chamber 1222, 1222' (respectively).

A series of pumps 1124 and 1126, shown schematically in Fig. 18, regulate flow in the outflow tubes 1112 and 1114 from the primary container 1102 and additive containers 1104 to the supply line 1121. Preferably, the pumps 1124 and 1126 are peristaltic pumps connected to a controller 1106, similar to the controller 40 described above in connection with Fig. 3. Controller 1106 meters the amount of primary substance and additives flowing and mixing in the supply line 1121.

As will be recognized by those skilled in the art, other types of flow regulating devices, such as, for example, valves or impeller pumps, could be used in place of the peristaltic pumps 1124 and 1126. In its broadest sense, the invention

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does not require all of the above-described structure. For example, the additive substances could be introduced directly into the primary container 1102 without the use additive containers 1104, pumps 1126, and outflow tubes 1114. When the particles forming the saturated fluidized bed are magnetic, a variable magnetic field adjacent to the fluid chamber 1122, 1122' could alter sedimentation velocity of the bed forming particles.

With the structure described above, it is possible to alter the sedimentation velocity of particles forming a saturated fluidized bed in chamber 1122, 1122'. By changing sedimentation velocity, as described below, filtration characteristics of the saturated fluidized bed may be altered.

In use, one or more of the additive substances in containers 1104 are chosen because of their ability to change the sedimentation velocity of the bed forming particles to a sedimentation velocity greater than that of first particles in the primary substance and less than that of second particles in the primary substance. Controller 1106 regulates pumps 1126 to precisely control the sedimentation velocity of the particles in the saturated fluidized bed. After the sedimentation velocity of the bed forming particles is properly adjusted, the bed allows certain particles to pass through the fluid chamber 1122, 1122' while other particles are retained by the bed in fluid chamber 1122, 1122'.

When sedimentation velocity of the bed forming particles is increased, the saturated fluidized bed retains particles in the fluid chamber 1122 or 1122' that would normally pass through the bed if the sedimentation velocity of the bed forming particles was not altered. Conversely, when sedimentation velocity of the bed forming particles is decreased, the saturated fluidized bed allows particles to pass through the bed that would normally be retained in the fluid chamber 1122 or 1122' if the sedimentation velocity of the bed forming particles was not altered.

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In a preferred embodiment of the invention, red blood cells may be used to form the saturated fluidized bed, and one of the additive containers 1104 may contain an additive substance such as water or saline having a weak concentration of salt. For example, the additive substance in one of the additive containers 1104 may be a saline solution having about 0.4% sodium chloride by weight. Such additive substances are hypotonic as compared to red blood cells. Another of the additive containers 1104, preferably contains an additive substance, such as saline having a strong concentration of salt, which is hypertonic as compared to red blood cells. For example, the hypertonic additive solution in one of the additive containers 1104 may be a saline solution having about 7% sodium chloride by weight.

The hypotonic or hypotonic additive substances may be many different types of solutions containing a predetermined concentration of a particular solute. For example, these substances may include albumin as a solute.

As described in more detail below, hypotonic additive solutions tend to osmotically increase the size of red blood cells. Conversely, hypertonic solutions tend to osmotically decrease red blood cell size. Particle sedimentation velocity, as previously discussed, is directly related to the size of the particle according to Stokes law. Therefore, an increase in particle size increases sedimentation velocity, while a decrease in particle size decreases sedimentation velocity.

Another of the additive containers 1104 preferably holds a solution containing albumin or sucrose. Such solutions change the density and/or viscosity of liquid, such as plasma, flowing from the primary container 1102. As mentioned above, sedimentation velocity of a particle is also related to the density and viscosity of a fluid according to Stoke's law. Therefore, by adding density/viscosity altering components into supply line 1121, sedimentation velocity of the saturated fluidized bed particles may be altered.

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At least one of the additive containers 1104 preferably contains a substance that links a number of the saturated fluidized bed forming particles in the primary solution together to form a series of saturated bed forming particle groups having a size larger than that of the individual particles. Because the particles groups are larger than the individual particles, sedimentation velocity of the saturated bed forming particle groups is greater than that of the individual particles according to Stoke's law. In a preferred embodiment, such a particle group forming substance contains macromolecules of dextran or fibrogen. These substances cause red blood cells to rouleau -that is the red blood cells link together and form separate red blood cell groups.

In an embodiment of the invention shown in Fig. 19, the supply line 1121 is coupled to the inlet 1140 of fluid chamber 1122. The fluid chamber 1122 is mounted to a centrifuge rotor 1134 of a centrifuge device 1136 preferably including a motor, shaft, arm, holder, pump, and controller 1106 respectively similar or identical to the motor 16, shaft 18, arm 19, holder 24, pump 36, and controller 40 shown in Figs. 1 and 3.

In an alternate embodiment of the invention shown in Fig. 20, the supply line 1121 is coupled to an inlet 1140' of fluid chamber 1122'. The fluid chamber 1122' is mounted to a centrifuge rotor 1134' of a centrifuge device 1136' configured like the centrifuge device 1136 shown in Fig. 19.

In accordance with the invention there is also provided means for separating particles from liquid after the particles and liquid flow from the fluid chamber. As illustrated in Fig. 19, intermediate tubing 1138 couples an outlet 1142 of fluid chamber 1122 to an inlet 1144 of a supplemental chamber 1146. Supplemental chamber 1146 is removably mounted on the centrifuge rotor 1134.

As shown in Fig. 19, the fluid chamber 1122 and supplemental chamber 1146 are spaced at approximately the same distance from an axis of rotation of rotor 1134. A maximum cross-sectional area of the supplemental chamber 1146 is preferably larger than that of the fluid chamber 1122 so that

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the supplemental chamber 1146 retains particles without forming a saturated fluidized particle bed. In an alternate embodiment (not shown), the supplemental chamber 1146 is further than fluid chamber 1122 from an axis of rotation of rotor 1134. During rotation of rotor 1134, this spacing allows particles in the supplemental chamber 1146 to encounter a stronger centrifugal force than particles in fluid chamber 1122, thus allowing the supplemental chamber 1146 to have a maximum cross sectional area similar to that of fluid chamber 1122.

As described in more detail below, by controlling flow rate and rotation of rotor 1134, centrifugal force in the supplemental chamber 1146 causes particles passing from fluid chamber 1122 to be retained in chamber 1146 while permitting liquid to pass through an outlet 1148 and into an outlet line 1150.

As shown in Fig. 19, the supplemental chamber 1146 is preferably larger than the fluid chamber 1122, permitting the supplemental chamber 1146 to retain a substantial number of particles. Preferably, an interior of the supplemental chamber 1146 is shaped like that of the fluid chamber 1122.

In an alternative embodiment shown in Fig. 20, intermediate tubing 1138' couples an outlet 1142' of fluid chamber 1122' to an inlet 1152 of a separation channel 1154 mounted to centrifuge rotor 1134'. Adjacent to an outer portion of the centrifuge rotor 1134', the separation channel 1154 has a collection well 1156 for collecting particles flowing into the separation channel 1154. Rotation of centrifuge rotor 1134' sediments particles into the collection well 1156 while slower sedimenting liquid and possibly some slower sedimenting particles remain above a top boundary 1158 of the collection well.

As shown in Fig. 20, collection well 1156 has a particle concentrate outlet 1164 connected to a particle concentrate line 1160. The particle concentrate line 1160 removes particles retained in the collection well 1156. A liquid outlet 1166 is provided above top boundary 1158 and is

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connected to liquid outlet line 1162. The liquid outlet line 1162 removes liquid above the top boundary 1158. In addition, the liquid outlet line 1162 may remove slower sedimenting particles above the top boundary 1158.

Preferably, the particle collection well 1156, particle concentrate outlet 1164 and liquid outlet 1166 are located at or adjacent to one end of the separation channel 1154, and the inlet 1152 is located at or adjacent to an opposite end of the separation channel 1154. This spacing ensures ample time for separation of particles from liquid, collection of a substantial number of particles in the collection well 1156, and corresponding removal of a substantial number of particles through the concentrate line 1160.

Methods for separating T cells, tumor cells, stem cells, and/or plasma from a peripheral cell collection are discussed below with reference to Figs. 18-20. Although the invention is described in connection with separating these substances from a peripheral cell collection, it should be understood that the invention in its broadest sense is not so limited. For example, the invention may be readily practiced to separate substances in a bone marrow harvest collection or an umbilical cord cell collection harvested following birth. In addition, the method of the invention in its broadest sense could be practiced with structure different from that described in connection the embodiments shown in Figs, 18-20.

After a donation procedure in which a peripheral cell collection is obtained, the peripheral cell collection is placed in the primary container 1102. A substantial portion of the peripheral cell collection includes plasma, red blood cells, stem cells, and T cells. If the donor's blood included tumor cells, these cells are also present in the peripheral cell collection.

Ultimately, the red blood cells from the peripheral cell collection will be used to form a saturated fluidized bed in the fluid chamber 1122, 1122'. If the number of red blood cells in the peripheral cell collection is insufficient to form the saturated bed, additional red blood cells are

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preferably added to the primary container 1102 so that the number of red blood cells exceeds the number of stem cells, T cells, and any tumor cells in the primary container 1102.

At the beginning of a particle separation procedure, the pump 1124 associated with container 1102 is activated to convey the peripheral cell collection from the primary container 1102 to the supply line 1121. In addition, one or more of pumps 1126 associated with the additive substances from additive containers 1104 are used to supply additives to supply line 1121. In the supply line 1121, the peripheral cell collection and one or more of the additive substances mix to increase or decrease the sedimentation velocity of the red blood cells.

When hypotonic solution is added to supply line 1121, the red blood cells osmotically increase in size thereby increasing the sedimentation velocity of the red blood cells. Conversely, when the hypertonic solution is added to supply line 1121, the red blood cells decrease in size thereby reducing the sedimentation velocity of the red blood cells. When saline is used as the hypotonic or hypertonic solution, the mixture of the peripheral cell collection and additive substances in supply line 1121 may include about 0.6% to about 5% sodium chloride by weight. Preferably, the amount of sodium chloride or other solutes in the supply line 1121 is sufficient to prevent hemolysis (bursting) of the red blood cells if the red blood cells increase in size. For example, when saline is used, the amount of sodium chloride in the supply line 1121 is preferably above about 0.4% by weight.

When a solution containing albumin or sucrose is added to supply line 1121, the solution increases the density and/or viscosity of plasma in the supply line 1121, thereby reducing sedimentation velocity of the red blood cells. When a medium including macromolecules of dextran or fibrogen are added to the supply line 1121, the medium causes red blood cells in the supply line 1121 to rouleau, thereby increasing the sedimentation velocity of the red blood cells.

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The controller 1106 activates one or more of the pumps 1126 depending on the sedimentation velocity of the red blood cells and the sedimentation velocities of cells that will be separated. For example, to separate faster sedimenting stem cells from slower sedimenting T cells, additive introduction is controlled so that the sedimentation velocity of the red blood cells falls between the sedimentation velocity of the stem cells and the sedimentation velocity of the T cells.

The peripheral cell collection and additive substances flow through the supply line 1121 into the inlet 1140, 1140' of the fluid chamber 1122, 1122'. The controller 1106 controls the rotational speed of the rotor 1136, 1136' and the rate of flow into the fluid chamber 1122, 1122' to establish a saturated fluidized bed of red blood cells in the fluid chamber 1122, 1122'.

The saturated fluidized bed of red blood cells behaves like the earlier-described saturated fluidized bed of platelets. Plasma, additive substances, and slower sedimenting T cells pass through the saturated fluidized red blood cell bed and outlet 1142, 1142', while the bed retains faster sedimenting stem cells in the fluid chamber 1122, 1122'. As red blood cells continue to flow into the fluid chamber 1122, 1122' and enter the saturated fluidized bed, red blood cells flow from the outlet 1142, 1142'. Because the fluidized bed is saturated, the rate at which red blood cells enter the inlet 1140, 1140' equals the rate at which red blood cells pass through the outlet 1142, 1142'.

As the saturated fluidized red blood cell bed continues to filter faster sedimenting particles, the pump 1124 and one or more of additive pumps 1126 continue to mix the peripheral cell collection and additives in the supply line 1121. This ensures that red blood cells entering the saturated fluidized bed and red blood cells in the bed have a sedimentation velocity between that of the first and second particles being separated.

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In the embodiment of Fig. 19, plasma, additive substances, T cells, and the portion of red blood cells leaving the saturated fluidized bed flow through the outlet 1142 and intermediate tubing 1138 into the inlet 1144 of supplemental chamber 1146. In the supplemental chamber 1146, centrifugal force caused by rotation of the rotor 1134 retains the T cells and red blood cells. Meanwhile, the plasma and additive substances flow from the outlet 1148 into the outlet line 1150. This separates the T cells and red blood cells from the plasma and additive substances.

The stem cells and red blood cells in the fluid chamber 1122 and the T cells and red blood cells in the supplemental chamber 1146 may retain a residue of some of the additive substances, such as albumin, sucrose, dextran, or fibrogen. To wash this residue from these cells, one of pumps 1126 preferably pumps a washing medium such as saline from a corresponding additive container 1104 through the fluid chamber 1122 and supplemental fluid chamber 1146 before completion of the separation procedure. If necessary, rotational speed of the rotor 1134 may be altered to retain particles in the fluid chamber 1122 and supplemental fluid chamber 1146 during washing.

When all of the peripheral cell collection flows from primary container 1102, the controller 1106 terminates rotation of the centrifuge rotor 1134. To remove the stem cells and red blood cells from the fluid chamber 1222, a procedurist releases the fluid chamber 1122 from the centrifuge rotor 1134 and separates the supply line 1121 or intermediate tubing 1138 from the fluid chamber 1122. In a similar fashion, the procedurist removes T cells and red blood cells retained in the supplemental fluid chamber 1146.

In the embodiment of Fig. 20, plasma, additive substances, T cells, and the portion of red blood cells leaving the saturated fluidized bed flow through the outlet 1142' and intermediate tubing 1138' into the inlet 1152 of separation channel 1154. Centrifugal force generated by the rotation of centrifuge rotor 1134' sediments the T cells and

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red blood cells in the collection well 1156, while plasma and additive substances remain above the top boundary 1158 of the collection well 1156. As the T cells and red blood cells collect in the collection well 1156, the particle concentrate line 1160 removes them through outlet 1164. Simultaneously, the liquid outlet line 1162 removes plasma and additive substances through the liquid outlet 1166.

When the primary container 1102 empties, the controller 1106 terminates rotation of the rotor 1136'. A procedurist then removes the stem cells and red blood cells from the fluid chamber 1222' by releasing the fluid chamber 1122' from the centrifuge rotor 1134' and separating the supply line 1121' or intermediate tubing 1138' from the fluid chamber 1122'.

To separate faster sedimenting tumor cells from slower sedimenting stem cells, one or more of the pumps 1126 add additive substances from one or more of the additive containers 1104 into the supply line 1121. The additive substances adjust the sedimentation velocity of the red blood cells to a sedimentation velocity between the sedimentation velocity of tumor cells and the sedimentation velocity of stem cells.

As described above, a saturated fluidized bed of red blood cells forms in the fluid chamber 1122, 1122'. Because the tumor cells have a sedimentation velocity greater than that of the red blood cells, the saturated fluidized red blood cell bed retains tumor cells in the fluid chamber 1122, 1122'. Stem cells, which now have a sedimentation velocity less than that of the red blood cells, flow from the outlet 1142, 1142' of fluid chamber 1122, 1122' along with the portion of red blood cells leaving the bed.

In the supplemental chamber 1146 or the separation channel 1154, stem cells and red blood cells separate from the plasma and additive substances in the same way the T cells and red blood cells separate from the plasma and additive substances in the method described above. When the embodiment of Fig. 19 is used, washing medium, such as saline from one of

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additive containers 1104, preferably washes additive residue from the particles in fluid chamber 1122, and in supplemental fluid chamber 1146, as described above.

When the primary container 1102 is empty, a procedurist removes tumor cells and red blood cells from the fluid chamber 1122 or 1122'. Stem cells and the red blood cells are removed from the supplemental chamber 1146 shown in Fig. 19 or from the particle concentrate outlet shown in Fig. 20.

The invention may be used to separate slower sedimenting tumor cells from faster sedimenting stem cells by retaining stem cells in the saturated fluidized red blood cell bed, while allowing tumor cells to pass through the bed. The invention, in its broadest sense, may also be used to separate many different types of particles from one another. Thus, it should be understood that the invention is not limited to the examples discussed in this specification. Rather the invention is intended to cover modifications and variations provided they come within the scope of the following claims and their equivalents.

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Claims

1. A method of separating first particles from second particles, the method comprising the steps of:

rotating a centrifuge rotor about an axis of rotation, the rotor having an associated fluid chamber rotatable therewith, the fluid chamber having an inlet and an outlet;

controlling rotation of the rotor;

altering sedimentation velocity of the first particles;

passing a quantity of the first particles into the inlet of the rotating fluid chamber;

forming, with the first particles, a saturated fluidized bed within the fluid chamber; and

flowing into the fluid chamber inlet liquid having at least a quantity of the second particles dispersed therein while simultaneously maintaining the bed within the fluid chamber, so that the bed substantially prevents flow of the second particles from the fluid chamber inlet to the fluid chamber outlet while substantially permitting flow of the liquid and a portion of the first particles to the outlet.

2. The method of claim 1, wherein the liquid in the step of flowing additionally includes first particles disbursed therein.

3. The method of claim 1, wherein the first particles include red blood cells, and the second particles include cells chosen from a group consisting of stem cells and tumor cells.

4. The method of claim 1, further comprising the step of removing second particles retained in the fluid chamber.

5. The method of claim 1, wherein the altering step includes the substep of changing size of the first particles.

6. The method of claim 1, wherein the altering step includes the substep of contacting the first particles with a solution that is hypertonic as compared to the first particles so that osmosis decreases size of the first particles.

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7. The method of claim 1, wherein the altering step includes the substep of contacting the first particles with a solution that is hypotonic as compared to the first particles so that osmosis increases size of the first particles.

8. The method of claim 1, wherein the altering step includes the substep of changing tonicity of the liquid so that osmosis decreases size of the first particles.

9. The method of claim 1, wherein the altering step includes the substep of changing tonicity of the liquid so that osmosis increases size of the first particles.

10. The method of claim 1, wherein the altering step includes the substep of changing at least one of density and viscosity of the liquid.

11. The method of claim 1, wherein the altering step includes the substep of linking a number of the first particles to form a series of first particle groups.

12. The method of claim 1, wherein the first particles are red blood cells, and wherein the altering step includes the substep of contacting the red blood cells with a substance for causing the red blood cells to rouleau.

13. The method of claim 1, wherein the altering step precedes the flowing step.

14. The method of claim 1, wherein at least a portion of the altering step is simultaneously conducted with the flowing step.

15. The method of claim 1, further comprising the step of separating the portion of first particles flowing to the outlet of the fluid chamber from the liquid flowing to the outlet of the fluid chamber.

16. A method of separating first particles from second particles having a sedimentation velocity different from a sedimentation velocity of the first particles, the method comprising the steps of:

passing liquid into a fluid chamber, the liquid carrying at least the first and second particles;

altering sedimentation velocity of third particles;

introducing the third particles into the fluid chamber;

forming within the fluid chamber a saturated fluidized bed of third particles; and

obstructing with the saturated fluidized third particle bed movement of second particles through the fluid chamber while permitting the liquid and the first particles to pass through the fluid chamber.

17. The method of claim 16, further comprising the step of adding the third particles to the liquid before the step of passing so that the steps of passing and introducing are performed substantially simultaneously.

18. The method of claim 16, wherein the first particles include stem cells, the second particles include tumor cells and the third particles include red blood cells.

19. The method of claim 16, wherein the first particles include cells chosen from a group consisting of tumor cells and T cells, the second particles include stem cells, and the third particles include red blood cells.

20. The method of claim 16, further comprising the step of removing second particles retained in the fluid chamber.

21. The method of claim 16, wherein the altering step includes the substep of changing size of the third particles.

22. The method of claim 16, wherein the altering step includes the substep of contacting the third particles with a solution that is hypertonic as compared to the third particles so that osmosis decreases size of the third particles.

23. The method of claim 16, wherein the altering step includes the substep of contacting the third particles with a solution that is hypotonic as compared to the third particles so that osmosis increases size of the third particles.

24. The method of claim 16, wherein the altering step includes the substep of changing tonicity of the liquid so that osmosis decreases size of the third particles.

25. The method of claim 16, wherein the altering step includes the substep of changing tonicity of the liquid so that osmosis increases size of the third particles.

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26. The method of claim 16, wherein the altering step includes the substep of changing at least one of density and viscosity of the liquid.

27. The method of claim 16, wherein the altering step includes the substep of linking together third particles to form a series of third particle groups.

28. The method of claim 16, wherein the third particles are red blood cells, and wherein the altering step includes the substep of contacting the red blood cells with a substance that causes the red blood cells to rouleau.

29. The method of claim 16, wherein the altering step precedes the passing step.

30. The method of claim 16, wherein at least a portion of the altering step is performed simultaneously with the passing step.

31. The method of claim 16, wherein the first and second particles are of substantially equal density, and wherein the altering step further includes the substep of changing size of the third particles so that the third particles are larger than the first particles and smaller than the second particles.

32. The method of claim 16, further comprising the step of separating the first particles permitted to pass through the fluid chamber from the liquid permitted to pass through the fluid chamber.

33. A method of separating first particles from second particles, the method comprising the steps of:

flowing a liquid having first, second, and third particles into a fluid chamber;

forming within the fluid chamber a saturated fluidized bed of the third particles;

obstructing flow of the second particles through the fluid chamber with the saturated fluidized third particle bed; and

permitting the liquid, the first particles, and a portion of the third particles to pass through the fluid chamber.

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34. The method of claim 33, wherein the first particles include stem cells, the second particles include tumor cells, and the third particles include red blood cells.
35. The method of claim 33, wherein the first particles are cells chosen from a group consisting of tumor cells and T cells, the second particles include stem cells, and the third particles include red blood cells.
36. The method of claim 33, further comprising the step of removing second particles retained in the fluid chamber.
37. The method of claim 33, further comprising the step of altering sedimentation velocity of the third particles.
38. The method of claim 37, wherein the altering step includes the substep of changing size of the third particles.
39. The method of claim 37, wherein the altering step includes the substep of contacting the third particles with a solution that is hypertonic as compared to the third particles so that osmosis decreases size of the third particles.
40. The method of claim 37, wherein the altering step includes the substep of contacting the third particles with a solution that is hypotonic as compared to the third particles so that osmosis increases size of the third particles.
41. The method of claim 37, wherein the altering step includes the substep of changing tonicity of the liquid so that osmosis decreases size of the third particles.
42. The method of claim 37, wherein the altering step includes the substep of changing tonicity of the liquid so that osmosis increases size of the third particles.
43. The method of claim 37, wherein the altering step includes the substep of changing at least one of density and viscosity of the liquid.
44. The method of claim 37, wherein the altering step includes the substep of linking together third particles to form a series of third particle groups.
45. The method of claim 37, wherein the third particles are red blood cells, and wherein the altering step includes the substep of contacting the red blood cells with a substance that causes the red blood cells to rouleau.

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46. The method of claim 37, wherein the altering step precedes the flowing step.

47. The method of claim 37, wherein at least a portion of the altering step is performed simultaneously with the flowing step.

48. The method of claim 37, wherein the first and second particles are of substantially equal density, and wherein the altering step further includes the substep of changing size of the third particles so that the third particles are larger than the first particles and smaller than the second particles.

49. The method of claim 33, further including, after the permitting step, the step of separating the first particles passing through the fluid chamber from the portion of third particles passing through the fluid chamber.

50. The method of claim 49, wherein the separating step includes the substep of magnetically separating the portion of third particles.

51. The method of claim 33, further comprising the step of separating the first particles and portion of second particles passing through the fluid chamber from the liquid passing through the fluid chamber.

52. The method of claim 33, further comprising the step of adding third particles to the liquid so that a number of third particles in the liquid exceeds both a number of first particles and a number of second particles in the liquid.

53. A method of separating first and second particles, comprising the steps of:

introducing red blood cells into a fluid chamber;

forming within the fluid chamber a saturated fluidized bed of the red blood cells;

passing liquid into the fluid chamber, the liquid carrying at least the first and second particles; and

obstructing with the saturated fluidized red blood cell bed movement of second particles through the fluid chamber while permitting the liquid, first particles, and a portion of the red blood cells to pass through the fluid chamber.

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54. The method of claim 53, wherein the steps of passing and introducing are performed substantially simultaneously.

55. The method of claim 53, wherein the first particles include stem cells and the second particles include tumor cells.

56. The method of claim 53, wherein the first particles include cells chosen from a group consisting of tumor cells and T cells and the second particles include stem cells.

57. The method of claim 53, further comprising the step of altering sedimentation velocity of the red blood cells.

58. The method of claim 57, wherein the step of altering includes the substep of contacting the red blood cell with saline solution to osmotically change size of the red blood cells.

59. The method of claim 57, wherein the step of altering includes the substep of contacting the red blood cells with a substance that causes red blood cells to rouleau.

60. The method of claim 57, wherein the step of altering includes the substep of changing at least one of the density and viscosity of the liquid.

61. The method of claim 53, further including the step of removing second particles retained in the fluid chamber.

62. The method of claim 53, further comprising the step of separating the first particles and portion of red blood cells passing through the fluid chamber from the liquid passing through the fluid chamber.

63. A method of separating first particles from second particles, the method comprising the steps of:

rotating a centrifuge rotor about an axis of rotation, the rotor having an associated fluid chamber rotatable therewith, the fluid chamber having an inlet and an outlet;

controlling rotation of the rotor;

altering sedimentation velocity of the first particles;

passing a quantity of the first particles into the inlet of the rotating fluid chamber;

forming, with the first particles, a saturated fluidized bed within the fluid chamber;

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flowing into the fluid chamber inlet liquid having at least a quantity of the second particles dispersed therein while simultaneously maintaining the bed within the fluid chamber, so that the bed substantially prevents flow of the second particles from the fluid chamber inlet to the fluid chamber outlet while substantially permitting flow of the liquid and a portion of the first particles from the outlet; and

separating the portion of first particles flowing from the outlet of the fluid chamber from the liquid flowing from the outlet of the fluid chamber.

64. An apparatus for separating first particles from second particles, the apparatus comprising:

a motor;

a centrifuge rotor coupled to the motor for rotation about an axis of rotation;

a holder for holding a fluid chamber on the rotor with an outlet of the fluid chamber positioned closer to the axis of rotation than an inlet of the fluid chamber;

means for supplying liquid and first and second particles to the inlet of the fluid chamber;

means for altering sedimentation velocity of the first particles; and

means for controlling at least one of the motor and the supplying means to maintain a saturated fluidized bed of first particles within the fluid chamber and to cause second particles to be retained in the fluid chamber.

65. The apparatus of claim 64, wherein the means for altering sedimentation velocity of the first particles includes means for adjusting tonicity of the liquid to osmotically change size of the first particles.

66. The apparatus of claim 64, wherein the means for altering sedimentation velocity of the first particles includes means for adjusting at least one of density and viscosity of the liquid.

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67. The apparatus of claim 64, wherein the means for altering sedimentation velocity of the first particles includes means for linking together first particles to form a series of first particle groups.

68. The apparatus of claim 64, further comprising a fluid chamber in the holder and means for separating particles flowing from the outlet of the fluid chamber from liquid flowing from the outlet of the fluid chamber.

69. The apparatus of claim 68, wherein the means for separating particles includes a supplemental chamber having an inlet in fluid communication with the outlet of the fluid chamber.

70. The apparatus of claim 68, wherein the means for separating particles includes a separation channel having a collection well for retaining particles therein, the separation channel including an inlet, a particle concentrate outlet located in the collection well, and a liquid outlet located in a portion of the separation channel outside of the collection well, the inlet of the separation channel being flow connected to the outlet of the fluid chamber.

71. An apparatus for separating first particles from second particles, the apparatus comprising:

a motor;

a centrifuge rotor coupled to the motor for rotation about an axis of rotation;

a fluid chamber connected to the rotor, the fluid chamber having an inlet and an outlet;

means for supplying liquid and first and second particles to the inlet of the fluid chamber;

means for controlling at least one of the motor and the supplying means to maintain a saturated fluidized bed of first particles within the fluid chamber and to cause second particles to be retained in the fluid chamber; and

means for separating particles flowing from the outlet of the fluid chamber from liquid flowing from the outlet of the fluid chamber.

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72. The apparatus of claim 71, wherein the means for separating particles includes a supplemental chamber having an inlet in fluid communication with the outlet of the fluid chamber.

73. The apparatus of claim 71, wherein the means for separating particles includes a separation channel having a collection well for retaining particles therein, the separation channel including an inlet, a particle concentrate outlet located in the collection well, and a liquid outlet located in a portion of the separation channel outside of the collection well, the inlet of the separation channel being flow connected to the outlet of the fluid chamber.

74. An apparatus for filtering first particles from a liquid, the apparatus comprising:

a motor;

a centrifuge rotor coupled to the motor for rotation about an axis of rotation;

a holder for holding a fluid chamber on the rotor with an outlet of the fluid chamber positioned closer to the axis of rotation than an inlet of the fluid chamber;

means for supplying a substance to the inlet of the fluid chamber; and

means for controlling at least one of the motor and the supplying means to maintain a saturated fluidized bed of second particles within the fluid chamber and to cause first particles to be retained in the fluid chamber.

75. The apparatus of claim 74, wherein the means for supplying substance to the inlet of the fluid chamber includes a pump for fluid connection to the fluid chamber, and wherein the controlling means regulates the pump.

76. The apparatus of claim 74, further comprising means on the rotor for receiving a separation chamber capable of separating particles in response to centrifugal force.

77. The apparatus of claim 76, wherein the separation chamber includes a conduit and the receiving means includes a passageway on the rotor for receiving the conduit.

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78. The apparatus of claim 77, wherein the passageway includes a ridge positioned therein for contacting the conduit to form a dam in the conduit.

79. The apparatus of claim 76, wherein the separation chamber receiving means includes a holder for a container.

80. The apparatus of claim 74, wherein the controlling means increases a supply of substance to the fluid chamber by sequentially decreasing a rotational speed of the rotor, and then increasing both rotational speed of the centrifuge rotor and a flow of substance provided by the supply means.

81. The apparatus of claim 74, further comprising an auxiliary fluid chamber holder for holding an auxiliary fluid chamber on the rotor with an outlet of the auxiliary fluid chamber positioned closer to the axis of rotation than an inlet of the auxiliary fluid chamber.

82. A method of separating first particles from second particles, the method comprising the steps of:

rotating a centrifuge rotor about an axis of rotation, the rotor having a fluid chamber;

controlling rotation of the rotor;

passing second particles into an inlet of the fluid chamber;

forming, with the second particles, a saturated fluidized bed within the fluid chamber; and

flowing the liquid having at least first particles into the fluid chamber inlet while maintaining the bed within the fluid chamber, so that the bed substantially prevents flow of first particles from the fluid chamber inlet to a fluid chamber outlet while substantially permitting flow of the liquid to the outlet.

83. The method of claim 82 wherein the step of flowing includes flowing liquid and second particles.

84. The method of claim 82, wherein both the step of passing and the step of flowing includes conveying plasma into the fluid chamber.

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85. The method of claim 82, wherein the first particles include white blood cells and the second particles include platelets.

86. The method of claim 82, wherein the first particles include white blood cells and the second particles include red blood cells.

87. The method of claim 82, wherein the first particles include stem cells and the second particles include tumor cells.

88. The method of claim 82, wherein the first particles include tumor cells and the second particles include stem cells.

89. The method of claim 82, wherein the step of controlling includes the substeps of sequentially lowering, and then increasing a rotational speed of the rotor, and the step of flowing includes the substep of increasing flow of liquid having first particles simultaneously with the substep of increasing rotational speed of the rotor.

90. The method of claim 82, wherein the step of controlling includes the substeps of sequentially lowering the speed of the rotor to a first speed N_i, and then increasing the rotor speed to a second speed, N, and wherein the step of flowing includes the substeps of sequentially maintaining flow of liquid having first particles at a first flow rate, Q_i, and then, simultaneously with the substep of increasing the rotor speed, increasing the flow rate to a second flow rate, Q, wherein $Q/N^2=Q_i/N_i^2$.

91. The method of claim 82, wherein the step of controlling includes the substep of substantially maintaining rotational speed of the rotor, and the step of flowing includes the substep of rapidly increasing a flow rate of the liquid having first particles.

92. The method of claim 82, wherein the step of controlling includes the substep of substantially maintaining rotational speed of the rotor, and the step of flowing includes the substep of gradually increasing a flow rate of the liquid having first particles.

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93. The method of claim 82, wherein the step of controlling includes the substep of substantially maintaining rotational speed of the rotor, and the substep of flowing includes the substeps of gradually increasing a flow rate of the liquid having first particles to a first flow rate, maintaining the first flow rate of the liquid, and gradually increasing the flow rate of the liquid.

94. The method of claim 82, wherein a fluid flow rate during the flowing step is within a range of 1 ml/min to 15 ml/min.

95. The method of claim 82, wherein the step of controlling includes the substep of regulating rotation of the rotor in a speed range to maintain a gravitational field in the fluid chamber ranging from approximately 500G to 800G.

96. The method of claim 82, further comprising, after the step of flowing, the step of removing second particles retained in the fluid chamber.

97. The method of claim 96, further comprising the step of removing first particles from the fluid chamber after the step of removing second particles.

98. The method of claim 82, wherein the step of flowing includes the substeps of conveying blood components into a separation chamber, separating the blood components within the separation chamber, and directing at least a portion of the separated components into the fluid chamber inlet.

99. The method of claim 98, wherein the portion of separated components includes at least plasma, platelets, and white blood cells.

100. The method of claim 98, wherein the portion of separated components includes at least plasma, platelets, and red blood cells.

101. The method of claim 98, wherein the portion of separated components includes at least plasma, red blood cells, and white blood cells.

102. The method of claim 98, further comprising the step of directing platelets retained in the separation chamber into the fluid chamber inlet while maintaining the bed within the fluid chamber.

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103. The method of claim 82, further comprising the step of flowing the liquid from the fluid chamber outlet into an inlet of an auxiliary fluid chamber.

104. An apparatus for separating constituent components of a fluid, the apparatus comprising:

a conduit configured to be received by a centrifuge rotor, the conduit having at least one inlet and at least one outlet;

at least one inlet line connected to the conduit inlet;

a fluid chamber having an inlet and an outlet;

means for fluidly coupling the conduit outlet with the fluid chamber inlet; and

an outflow line connected to the outlet of the fluid chamber.

105. The apparatus of claim 104, wherein an interior surface of the fluid chamber extends along a longitudinal axis thereof and the interior surface of the fluid chamber has a maximum cross sectional area at a position intermediate the fluid chamber inlet and the fluid chamber outlet.

106. The apparatus of claim 104, wherein the fluid chamber interior converges along the longitudinal axis from the position of the maximum cross sectional area toward the fluid chamber inlet.

107. The apparatus of claim 104, wherein the fluid chamber interior converges along the longitudinal axis from the position of the maximum cross sectional area toward the fluid chamber outlet.

108. A tubing set for use with a centrifuge including a rotor provided with a generally annular groove and a fluid chamber holder, said tubing set comprising:

a channel having a generally annular configuration adapted to interfit with the annular groove of the centrifuge rotor, the channel including a platelet rich plasma outlet;

a plurality of lines being in fluid communication with the channel, the plurality of lines including at least a whole blood inlet line, a red blood cell outlet line, and a platelet poor plasma outlet line; and

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a fluid chamber including a first section diverging from an inlet of the fluid chamber to a position of maximum cross-sectional area of the fluid chamber and a second section converging from the position of the maximum cross-sectional area to an outlet of the fluid chamber, the inlet of the fluid chamber being in fluid communication with the platelet rich plasma channel outlet.

109. An apparatus for separating particles from a liquid, the apparatus comprising:

a motor;

a centrifuge rotor coupled to the motor for rotation about an axis of rotation;

a holder for holding a fluid chamber on the rotor with an outlet of the fluid chamber positioned closer to the axis of rotation than an inlet of the fluid chamber; and

means on the rotor for receiving a separation chamber capable of separating particles in response to centrifugal force.

110. The apparatus of claim 109, wherein the separation chamber includes a conduit and the receiving means includes a passageway on the rotor for receiving the conduit.

111. The apparatus of claim 110, wherein the passageway includes a ridge positioned therein for contacting the conduit to form a dam in the conduit.

112. The apparatus of claim 109, wherein the separation chamber receiving means includes a holder for a container.

113. The apparatus of claim 109, further comprising a separation chamber mounted within the receiving means and a fluid chamber mounted within the fluid chamber holder, the separation chamber being flow connected to the fluid chamber.

114. A method of separating white blood cells from a liquid, the method comprising the steps of:

passing at least particles into an inlet of a fluid chamber;

forming within the fluid chamber a substantial barrier to white blood cell flow through the fluid chamber, the barrier including a saturated fluidized bed of the particles;

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flowing into the fluid chamber a liquid having at least the particles and the white blood cells to be separated;

obstructing with the fluidized bed, while permitting the liquid to pass through the fluid chamber, white blood cell movement through the fluid chamber; and

releasing a portion of the particles from the fluidized bed while maintaining a saturated bed of the particles in the fluid chamber.

115. The method of claim 114, wherein the particles include platelets.

116. The method of claim 115, further comprising the step of separating particle constituents from the white blood cells before the flowing step.

117. The method of claim 114, wherein the particles include red blood cells.

118. The method of claim 114, wherein the liquid includes components of blood removed from an umbilical cord.

119. The method of claim 114, further including the step of priming the fluid chamber with a priming fluid having a density less than a density of the liquid.

120. The method of claim 119, wherein said priming fluid comprises one of saline solution and air.

121. The method of claim 114, further including the step of priming the fluid chamber with the liquid.

122. A method of separating first particles from second particles, the method comprising the steps of:

passing liquid into a fluid chamber, the liquid carrying at least the first and second particles to be separated;

introducing third particles into the fluid chamber;

forming within the fluid chamber a saturated fluidized bed of third particles; and

obstructing with the saturated fluidized third particle bed movement of second particles through the fluid chamber while permitting the liquid and the first particles to pass through the fluid chamber.

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123. The method of claim 122, further comprising the step of adding the third particles to the liquid before the step of passing so that the steps of passing and introducing are performed simultaneously.

124. The method of claim 122, wherein the first particles include tumor cells and the second particles include stem cells.

125. The method of claim 122, wherein the first particles include stem cells and the second particles include tumor cells.

126. The method of claim 122, wherein the third particles are magnetic and the method further comprises the step of separating first and third particles by magnetically attracting the third particles.

127. The method of claim 122, wherein the first and second particles have a substantially equal density, and the third particles have a size larger than the first particles and smaller than the second particles.

128. A method of separating smaller first particles from larger second particles, the method comprising the steps of:

adding third particles to a liquid having the first particles and second particles, the third particles being larger than the first particles and smaller than the second particles;

flowing the liquid having the first, second, and third particles into a fluid chamber;

forming within the fluid chamber a saturated fluidized bed of at least one of the first and third particles;

obstructing flow of the second particles through the fluid chamber with the fluidized bed; and

permitting the liquid, first, and third particles to pass through the fluid chamber.

129. The method of claim 128, further including the step of removing the third particles from the liquid after the permitting step.

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130. The method of claim 128, wherein the number of third particles added during the adding step exceeds both the number of first particles and the number of second particles in the liquid.

131. The method of claim 128, wherein the first particles include tumor cells and the second particles include stem cells.

132. The method of claim 128, wherein the first particles include stem cells and the second particles include tumor cells.

133. An apparatus for separating portions of a substance, the apparatus comprising:

means for generating a centrifugal field;

a fluid chamber connected to the generating means, the fluid chamber having an inlet and outlet;

means for supplying a substance to the chamber, the substance including at least particles;

means for establishing a saturated fluidized bed of the first particles within the fluid chamber;

means for supplying a substance to be filtered to the fluid chamber; and

means for maintaining the saturated fluidized bed in the chamber so that at least a first portion of the substance to be filtered is retained in the fluid chamber while at least a second portion of the substance to be filtered passes through the fluid chamber.

134. The apparatus of claim 133, further comprising means in fluid communication with the fluid chamber for separating particles from the liquid.

135. An apparatus for separating particles from a liquid, the apparatus comprising:

a fluid chamber having an inlet, an outlet, and a wall extending between and connecting the inlet and the outlet, the wall defining an interior, such that, the interior has a maximum cross- sectional area at a position intermediate the inlet and the outlet, and the wall converges from the position of the maximum cross-sectional area toward the inlet;

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a separation chamber configured to be received by a centrifuge rotor to centrifugally separate particles within the separation chamber; and

means for fluid coupling the fluid chamber to the separation chamber, the fluid coupling means being connected to the separation chamber at a location permitting particles in the separation chamber to pass into the fluid chamber, while substantially preventing non-separated particles from passing through the fluid coupling.

136. The apparatus of claim 135, wherein the separation chamber comprises at least a conduit.

137. The apparatus of claim 135, wherein the separation chamber comprises a container.

138. The apparatus of claim 135, further comprising a auxiliary chamber having an inlet and an outlet, the auxiliary chamber inlet being in fluid communication with the fluid chamber outlet, the auxiliary chamber further including an interior diverging from the auxiliary chamber inlet to a position of a maximum cross-sectional area.

139. A method of separating blood components, the method comprising the steps of:

applying a centrifugal force to blood to separate the blood into components including at least plasma, platelets, and white blood cells,

whereby at least a portion of the platelets become at least partially activated during the applying step; and

filtering the components to remove white blood cells, while a substantial number of platelets remain activated.

140. The method of claim 139, further comprising, after the step of filtering, the step of recovering at least 95% of the platelets separated in the applying step.

141. The method of claim 139, further comprising, after the step of filtering, the step of recovering at least 98% of the platelets separated in the applying step.

142. The method of claim 139, wherein the filtering step includes the substep of flowing the components into a saturated fluidized bed of platelets.

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143. An apparatus for separating particles from a liquid, the apparatus comprising:

means for initially separating within a separation chamber particles according to at least one of different densities and different sedimentation velocities; and

means, including a fluid chamber fluidly coupled to the initial separating means, for further separating particles according to sedimentation velocity.

144. A method of separating particles in a liquid, the method comprising the steps of:

initially separating particles in a liquid according to at least one of different densities and different sedimentation velocities;

flowing at least a portion of the particles separated in the initial separating step into a fluid chamber; and

further separating the particles within the fluid chamber according to different sedimentation velocities.

145. The method of claim 144, wherein the particles comprises blood components.

146. A method of separating blood components, the method comprising the steps of:

rotating a centrifuge rotor about an axis of rotation, the rotor having a separation chamber and fluid chamber;

controlling rotation of the rotor;

conveying blood components into the separation chamber;

separating the blood components within the separation chamber into at least first blood components and second blood components;

directing second blood components and at least a portion of the first blood components from the separation chamber into the fluid chamber; and

filtering within the fluid chamber the first blood components to remove at least a portion of first particles from the second blood components.

147. The method of claim 146, wherein the step of filtering includes the substep of obstructing passage of first particles using a saturated fluidized bed of second particles.

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148. The method of claim 146, wherein the directing step includes the substep of flushing a substantial number of second components retained in the separation chamber into the fluid chamber.

149. A method of separating first and second particles within a fluid chamber provided on a centrifuge rotor, the method comprising the steps of:

rotating the centrifuge rotor about an axis of rotation;

flowing liquid carrying at least first and second particles from a source into an inlet of the fluid chamber without adding a substantial amount of a diluting fluid, the second particles entering the fluid chamber inlet at a first concentration; and

preventing a substantial number of first particles from flowing from the fluid chamber inlet to a fluid chamber outlet while permitting liquid and a concentration of second particles to flow to the outlet, the concentration of second particles being substantially equal to the first concentration.

150. A fluid chamber for separating particle constituents from a liquid, the fluid chamber comprising:

an inlet;

an outlet;

a wall extending between the inlet and outlet to form a fluid chamber interior along a longitudinal axis of the fluid chamber, the interior having a maximum cross sectional area at a position intermediate the inlet and outlet, the interior converging from the position of the maximum cross sectional area toward the inlet; and

at least one groove formed on an inner surface of the wall.

151. The fluid chamber of claim 150, wherein the groove is located in the fluid chamber at the position of the maximum cross sectional area.

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152. The fluid chamber of claim 150, wherein the groove includes top and bottom portions orientated substantially perpendicular to the longitudinal axis of the fluid chamber and a side connecting the top and bottom portions.
153. The fluid chamber of claim 152, wherein the side of the groove surrounds the longitudinal axis of the fluid chamber.
154. The fluid chamber of claim 150, wherein the groove extends from an inner position of the wall to an outer position of the wall, the inner position being located closer to the longitudinal axis than the outer position, and wherein the groove has a width extending in a direction parallel to the longitudinal axis, the fluid chamber further including a lip located proximate the inner position for defining at least one entrance into the groove, a dimension of the entrance extending in a direction parallel to the longitudinal axis being less than the width of the groove.
155. The fluid chamber of claim 154, wherein the lip forms an inner groove wall extending between a top and bottom portion of the groove and the entrance includes an opening in the inner groove wall extending along a portion of the groove.
156. The fluid chamber of claim 154, wherein the lip defines first entrance and second entrances extending along portions of the groove, the first entrance being located proximate a Coriolis jetting region.
157. The fluid chamber of claim 154, wherein the entrance is located between the lip and the inlet of the fluid chamber.
158. The fluid chamber of claim 150, further comprising at least one step formed on the inner surface of the wall between the position of the maximum cross sectional area and the inlet.
159. The fluid chamber of claim 150, further comprising at least one step formed on the inner surface of the wall between the position of the maximum cross sectional area and the outlet.

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160. A fluid chamber for separating particle constituents from a liquid, the fluid chamber comprising:

an inlet;

an outlet;

a wall extending between the inlet and outlet to form a fluid chamber interior along a longitudinal axis of the fluid chamber, the interior having a maximum cross sectional area at a position intermediate the inlet and outlet, the interior converging from the position of the maximum cross sectional area toward the inlet; and

at least one step formed on an inner surface of the wall.

161. The fluid chamber of claim 160, wherein the step includes a base surface orientated substantially perpendicular to the longitudinal axis of the fluid chamber.

162. The fluid chamber of claim 161, further including a side surface connected to the base surface, the side surface being substantially orthogonal to the base surface.

163. The fluid chamber of claim 161, further including a side surface connected to the base surface, the side surface being orientated at an acute angle with respect to the base surface.

164. The fluid chamber of claim 160, wherein the step includes a side surface orientated substantially parallel to the longitudinal axis.

165. The fluid chamber of claim 160, wherein the step is located between the position of the maximum cross-sectional area and the inlet.

166. The fluid chamber of claim 160, wherein the step is located between the position of the maximum cross-sectional area and the outlet.

167. The fluid chamber of claim 160, wherein the step includes a top surface formed into a concavity.

168. A method of particle separation within a fluid chamber provided on a centrifuge rotor, the method comprising the steps of:

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providing at least one flow directing member on an interior wall surface of the fluid chamber, the flow directing member being shaped to reduce Coriolis jetting within the fluid chamber;

rotating the centrifuge rotor about an axis of rotation;

flowing liquid carrying particles into the fluid chamber, such that the flow directing member directs the liquid to substantially prevent the liquid from flowing between a wall of the fluid chamber and a separation area within the chamber; and

separating particles within the fluid chamber at the separation area of the chamber according to differences in sedimentation velocity.

169. The method of claim 168, wherein the separation area comprises one of a fluidized particle bed and an elutriation field.

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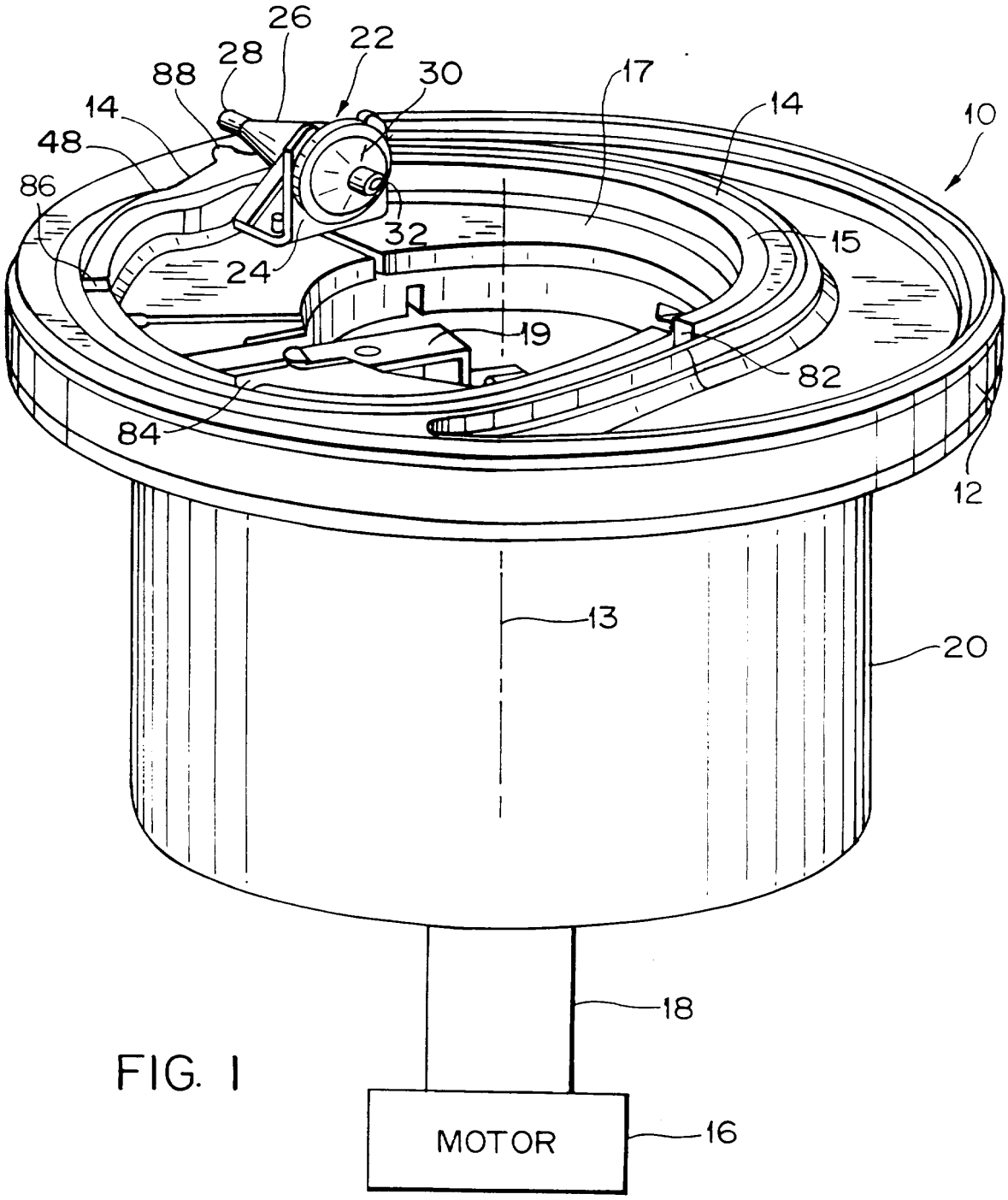


FIG. 1

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-0995

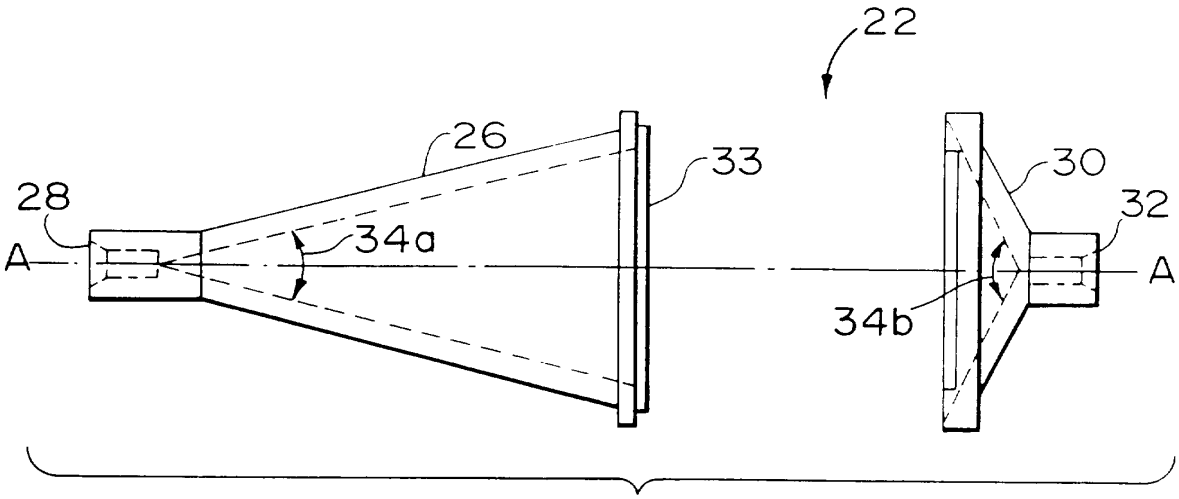

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FIG. 2

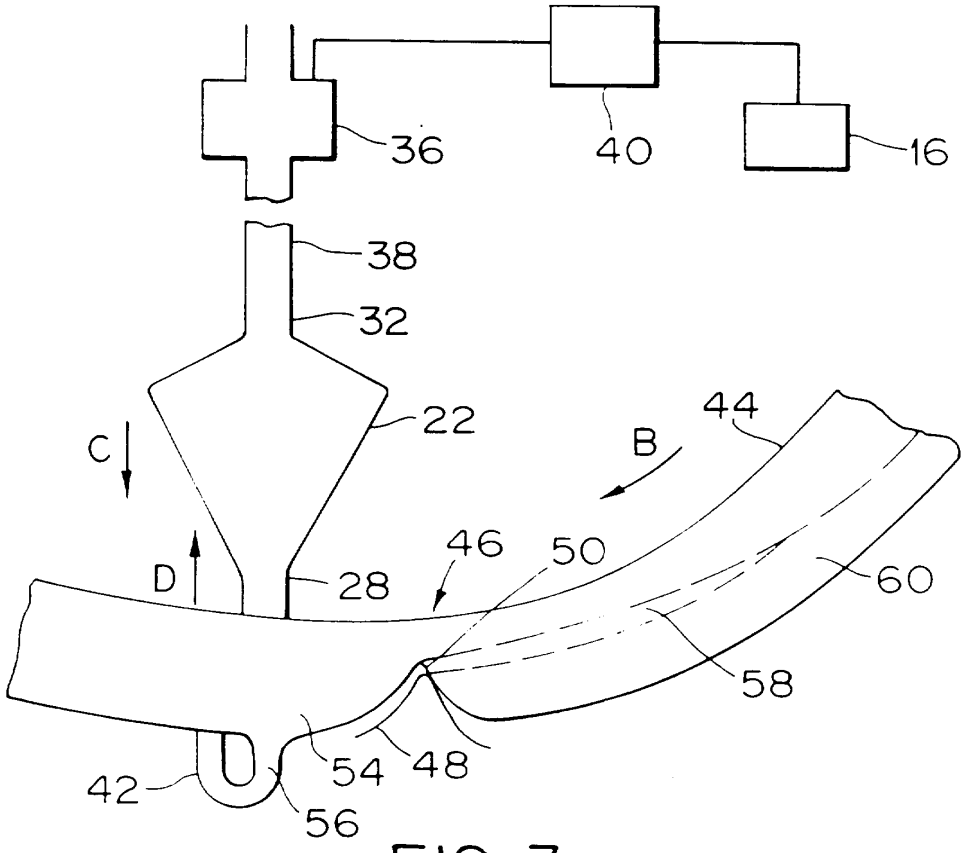

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FIG. 3

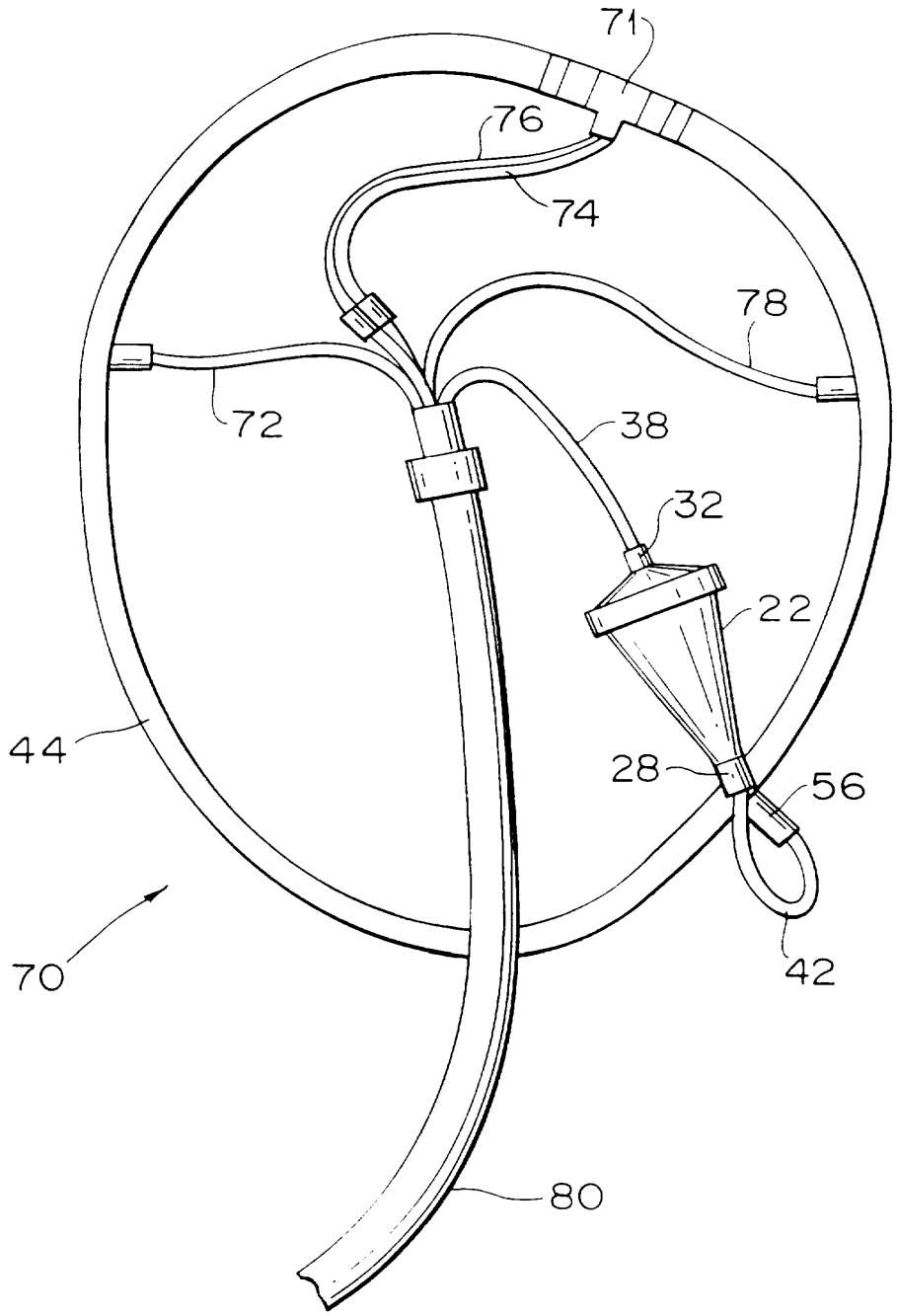


FIG. 4

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Petitioner Terumo Exhibit 1021-0997

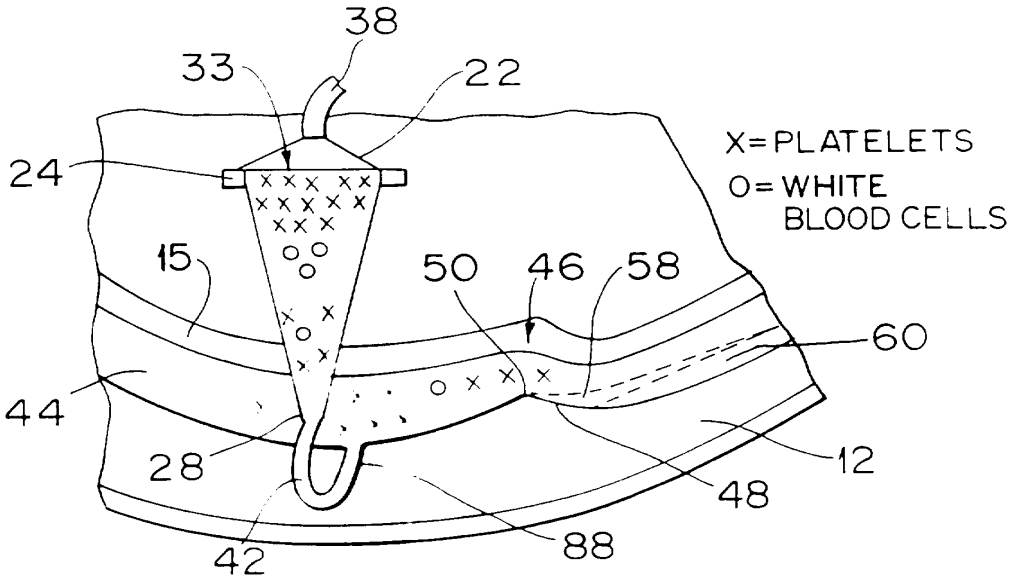


FIG. 5

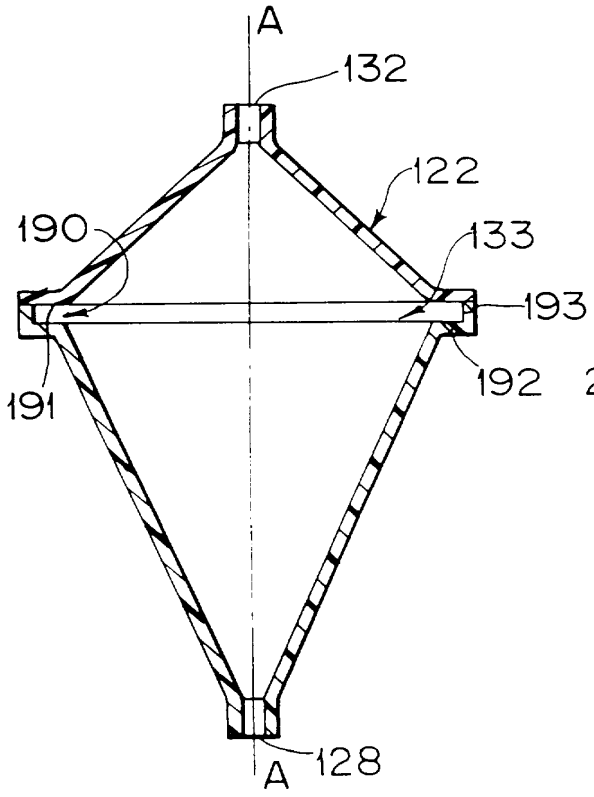


FIG. 6

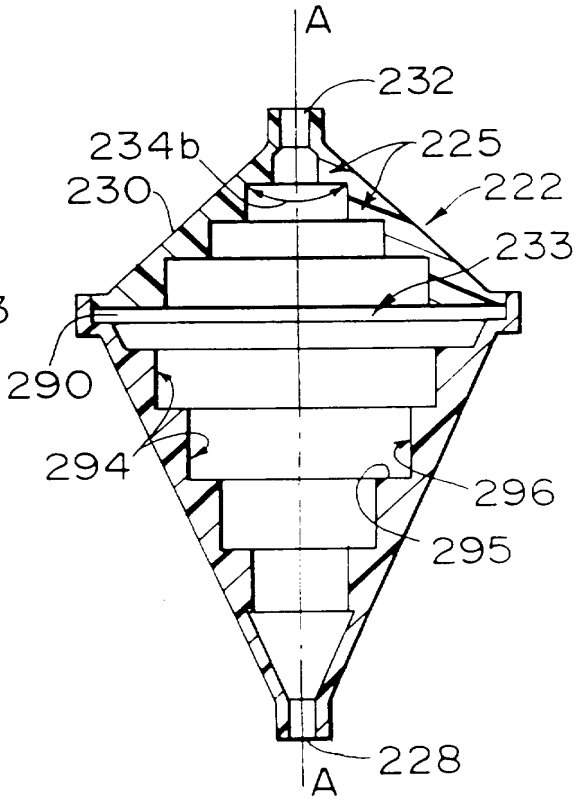


FIG. 7

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Petitioner Terumo Exhibit 1021-0998

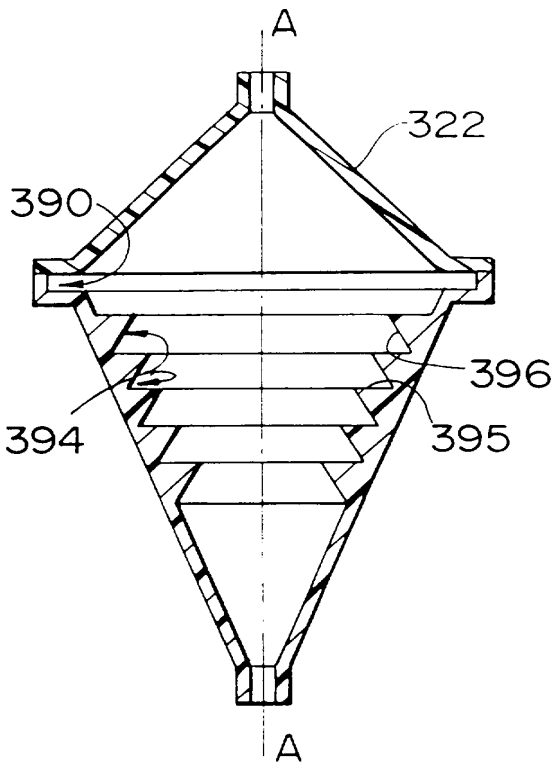


FIG. 8

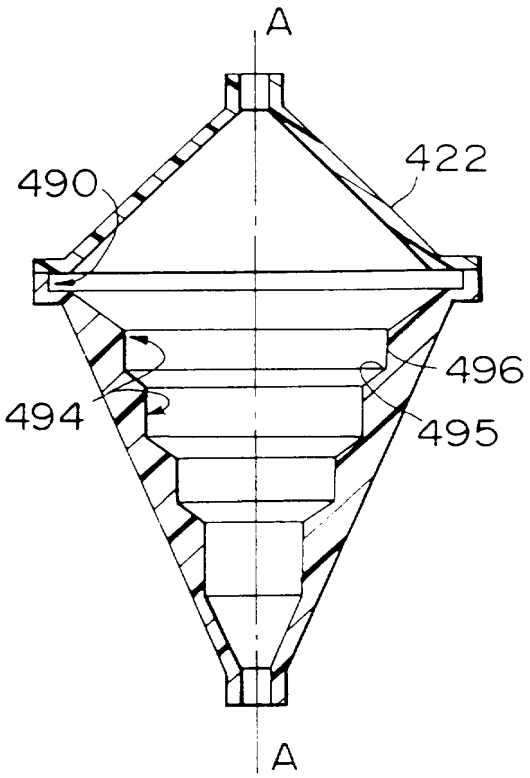


FIG. 9

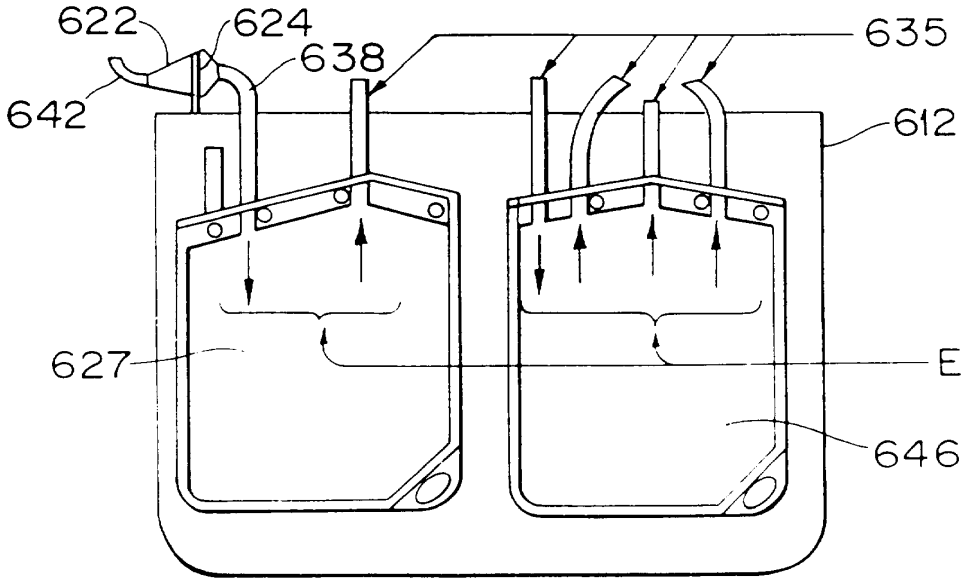


FIG. 11

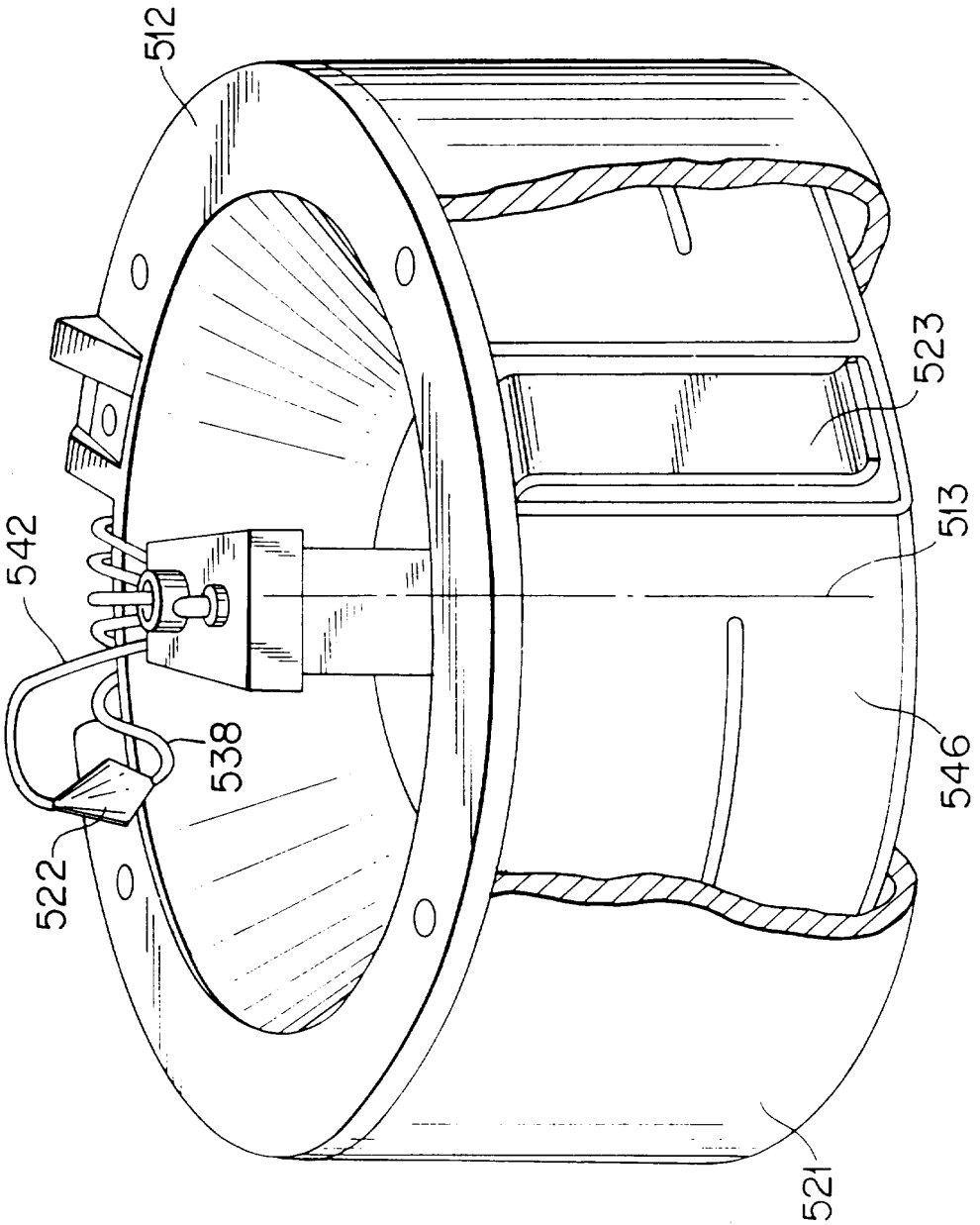


FIG. 10

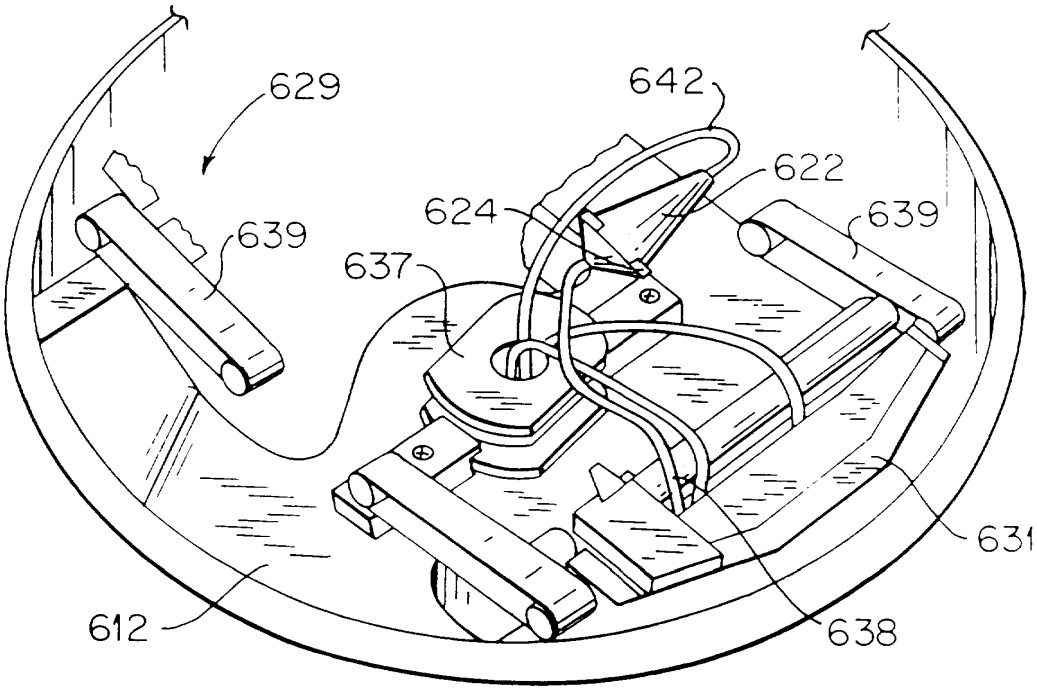


FIG. 12

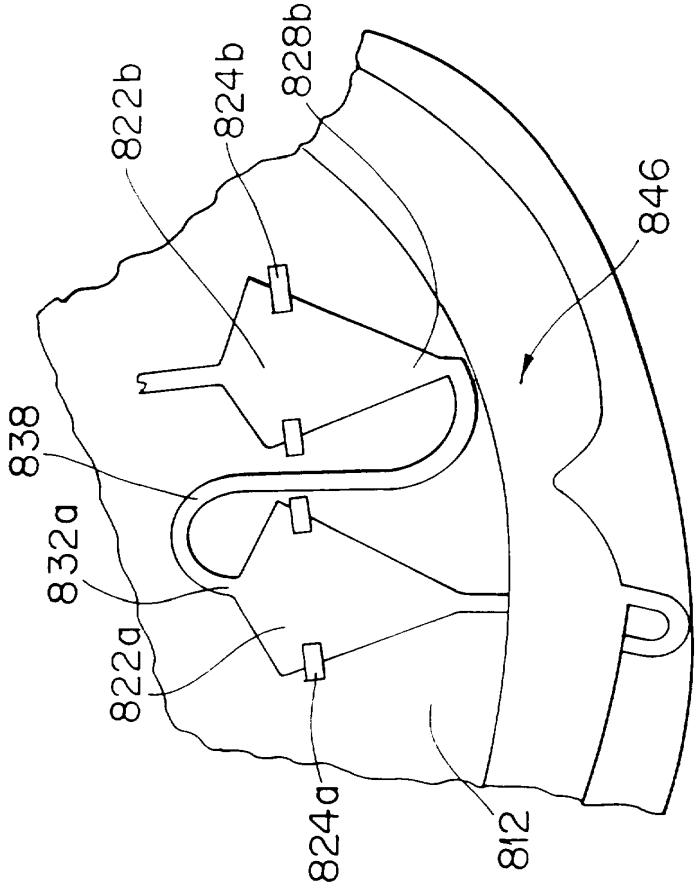

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FIG. 14

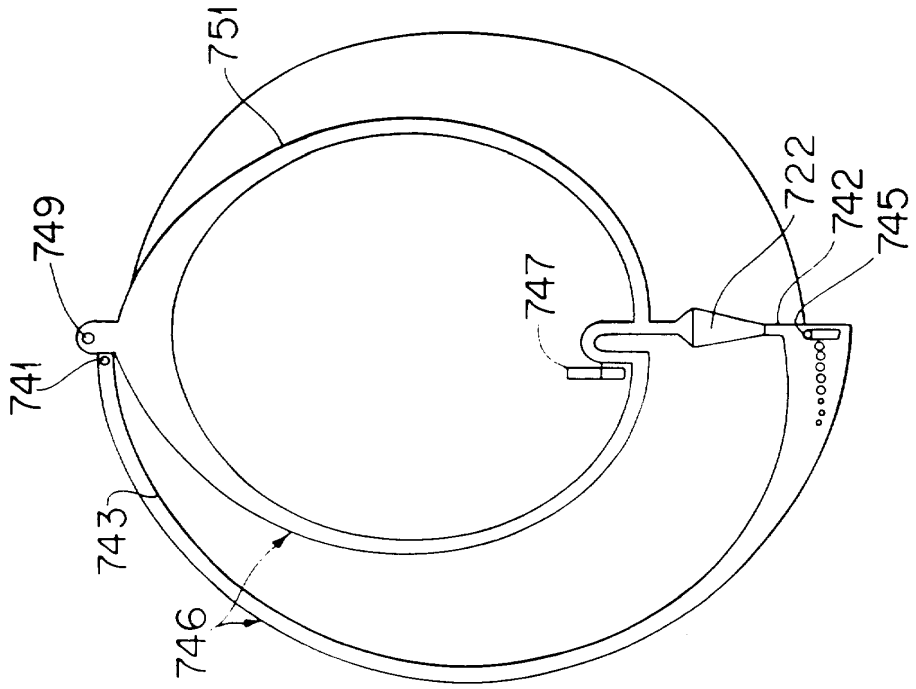

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FIG. 13

FIG. 15

WO 96/33023 PCT/US96/05505

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Petitioner Terumo Exhibit 1021-1003

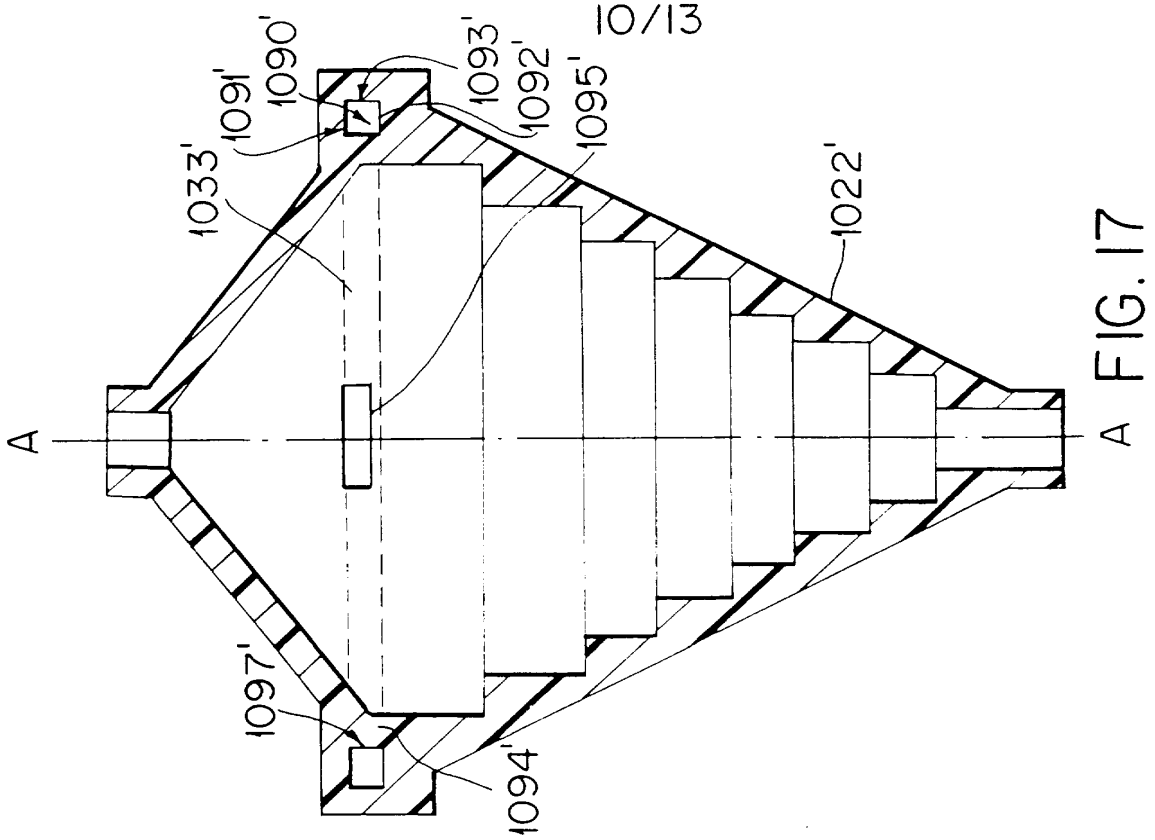

1091'
1090'
1093'
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1095'
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1022'
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1097'
1094'

FIG. 17

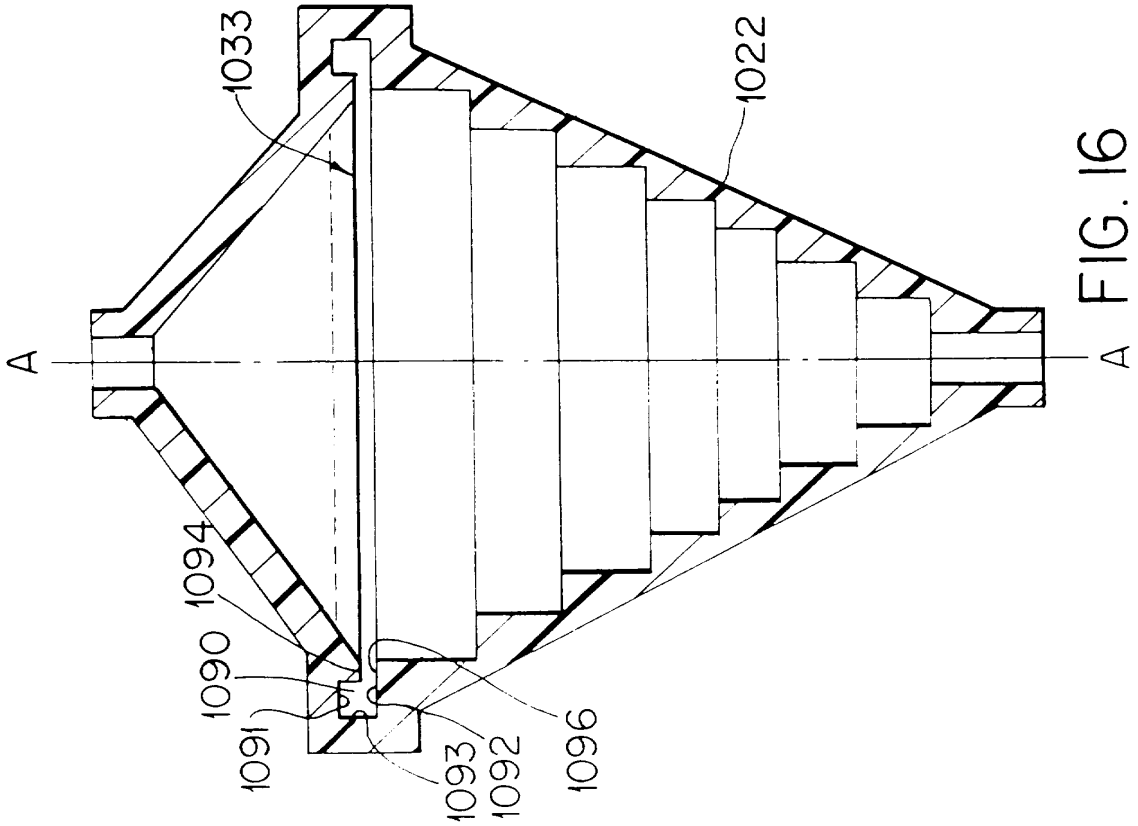

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FIG. 16

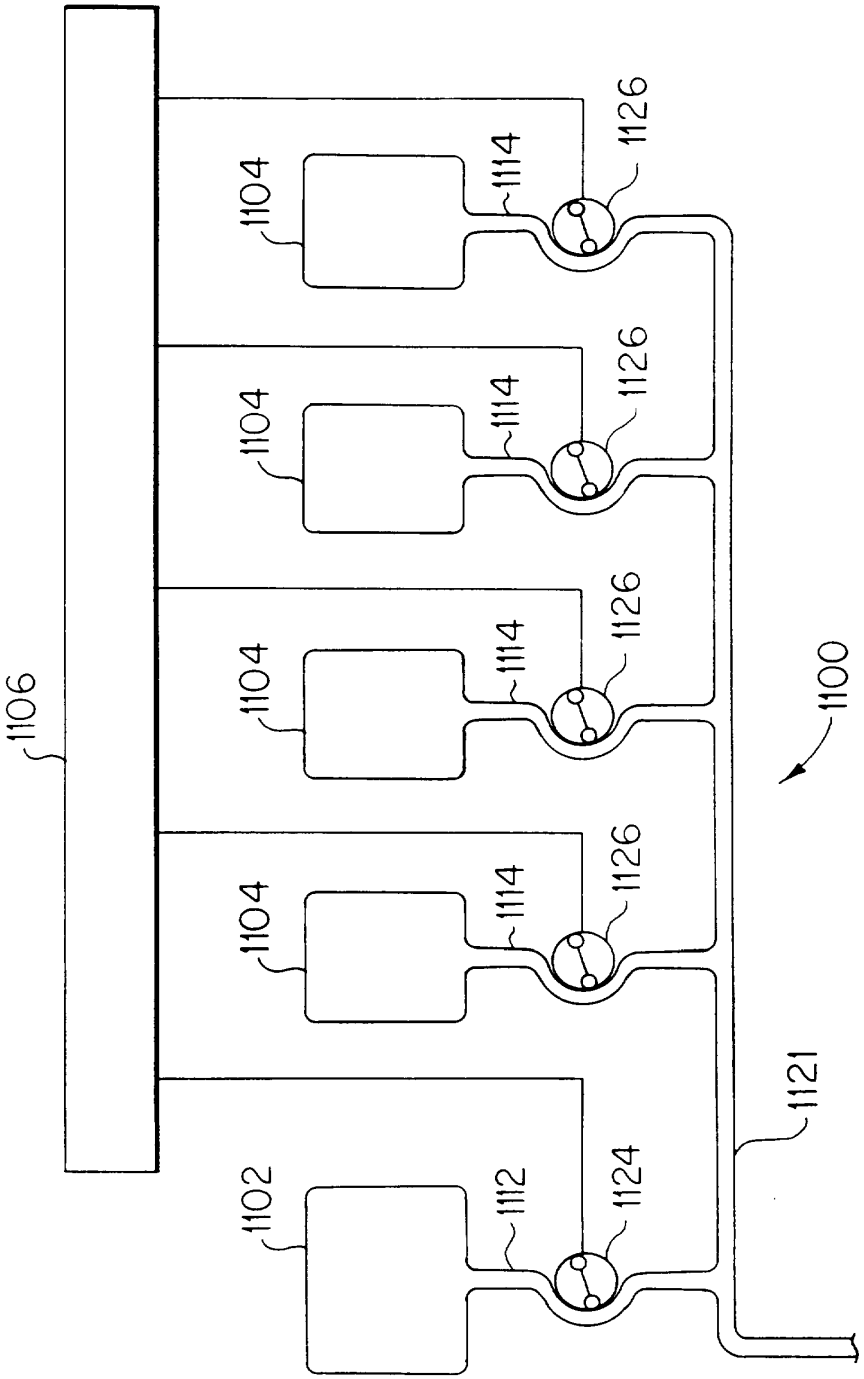

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FIG. 18

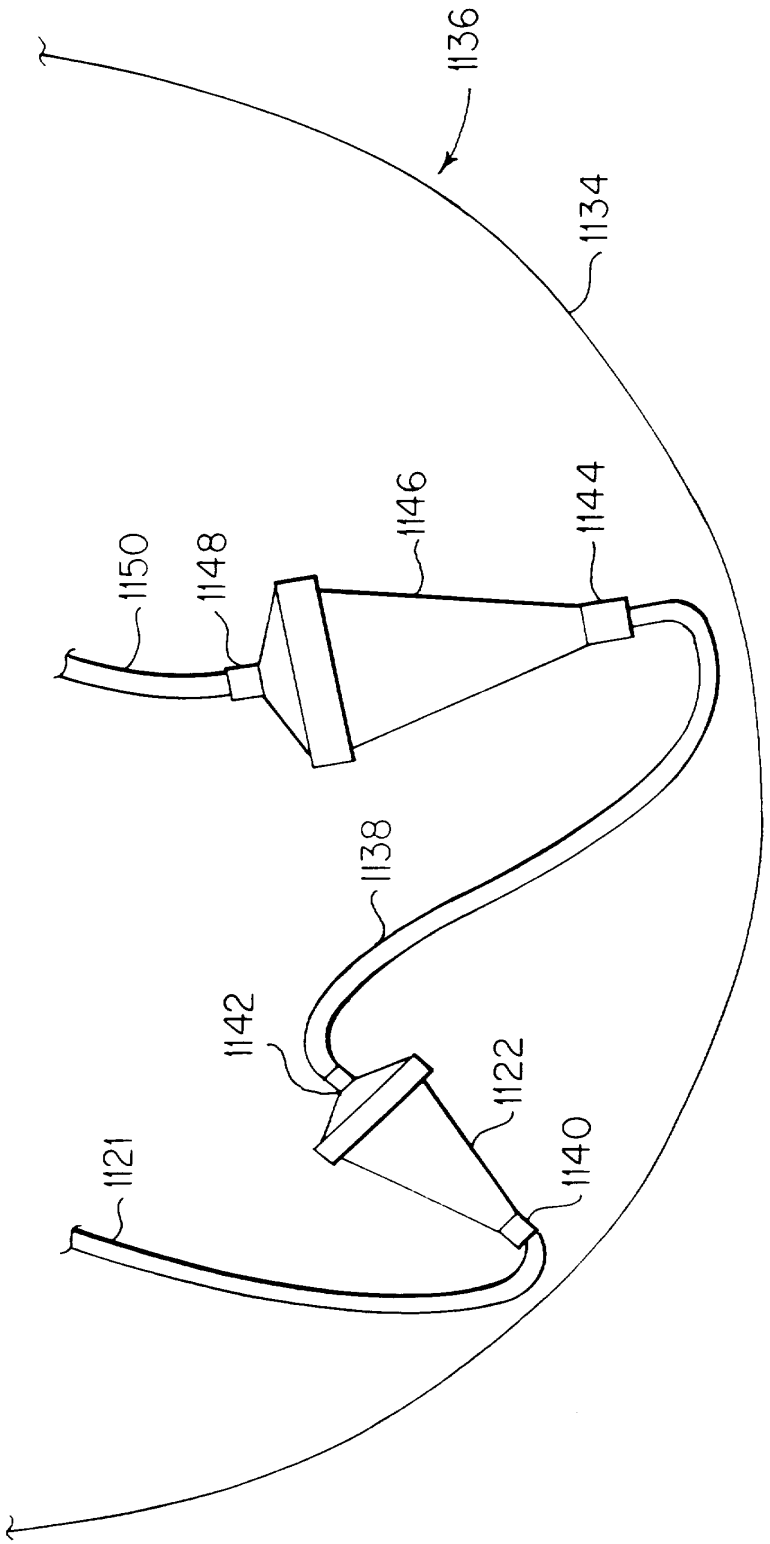


FIG. 19

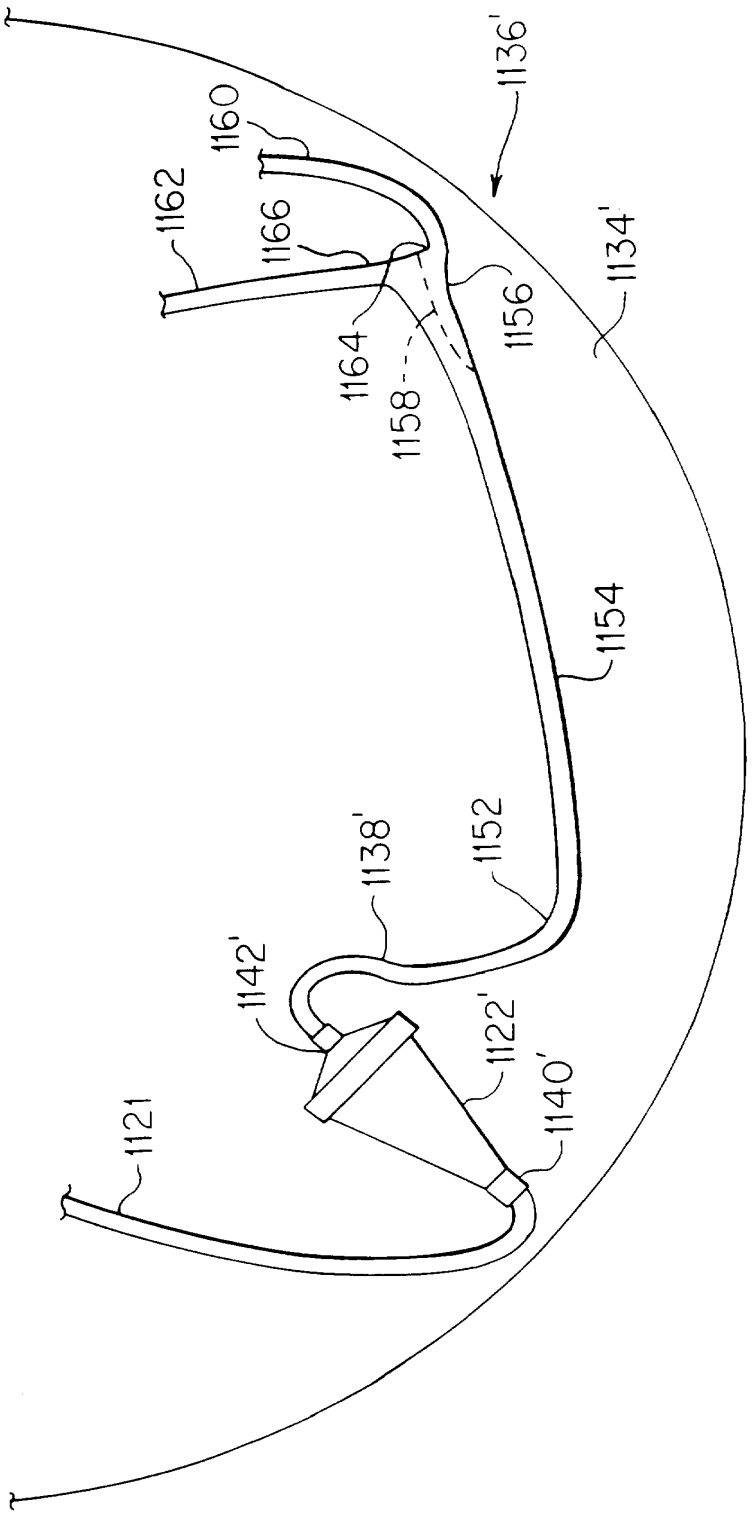


FIG. 20

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1007

INTERNATIONAL SEARCH REPORT

Ir itional Application No
PCT/US 96/05505

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B04B5/04 A61M1/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B04B A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 27698 (BAXTER INTERNATIONAL INC.) 8 December 1994	143-146
Y	see the whole document	1-70,87, 88, 124-127, 131,132, 139-142, 147,148

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
20 August 1996	26.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leitner, J

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Petitioner Terumo Exhibit 1021-1008

INTERNATIONAL SEARCH REPORT

Ir ıtional Application No
PCT/US 96/05505

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 187 979 (H.M. CULLIS) 12 February 1980	71,72, 74-76, 82-86, 96,97, 103,109, 114-123, 128,130, 133,134, 149
Y		1-70,73, 77-79, 87,88, 104-108, 110-113, 124-127, 131,132, 135-142, 147,148
A	see the whole document	80,81, 98-102, 150,160, 168

Y	US,A,4 708 712 (A.P. MULZET) 24 November 1987 cited in the application see abstract; figures	73, 77-79, 104-108, 110-113, 135-138

A	US,A,4 350 283 (A.L. LEONIAN) 21 September 1982	

A	US,A,4 322 298 (M.D. PERSIDSKY) 30 March 1982	

A	US,A,4 416 654 (D.W. SCHOENDORFER) 22 November 1983	

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A	DE,A,37 00 122 (M. LUTZ) 14 July 1988	

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/05505

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9427698	08-12-94	CA-A-	2140455	08-12-94
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US-A-4187979	12-02-80	NONE		
US-A-4708712	24-11-87	CA-A-	1298822	14-04-92
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		FR-A-	2596294	02-10-87
		GB-A,B	2188569	07-10-87
		JP-B-	1044104	26-09-89
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		GB-A-	1455203	10-11-76
		JP-A-	50032562	29-03-75
		SE-A-	7407053	09-12-74
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		DE-A-	3117710	08-04-82
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		JP-A-	57026619	12-02-82
		SE-A-	8102776	06-11-81
DE-A-3700122	14-07-88	NONE		
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		WO-A-	9300937	21-01-93
US-A-5397479	14-03-95	AU-B-	6635894	21-11-94

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Petitioner Terumo Exhibit 1021-1010

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/05505

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5397479		CA-A-	2161408	10-11-94
		EP-A-	0696933	21-02-96
		WO-A-	9425135	10-11-94
		US-A-	5482829	09-01-96

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Petitioner Terumo Exhibit 1021-1011

Espacenet

Bibliographic data: WO0205059 (A2) — 2002-01-17

MEDICAL SYSTEM, METHOD AND APPARATUS EMPLOYING MEMS

Inventor(s): CORK WILLIAM H [US]; ULMES JAMES J [US]; WEST RICHARD L [US]; LO YING-CHEN [US]; WEBER MARK C [US]; MIN KYUNGYOON [KR] + (CORK, WILLIAM H, ; ULMES, JAMES, J, ; WEST, RICHARD, L, ; LO, YING-CHEN, ; WEBER, MARK, C, ; MIN, KYUNGYOON)

Applicant(s): BAXTER INT [US]; CORK WILLIAM H [US]; ULMES JAMES J [US]; WEST RICHARD L [US]; LO YING CHEN [US]; WEBER MARK C [US]; MIN KYUNGYOON [KR] + (BAXTER INTERNATIONAL INC, ; CORK, WILLIAM H, ; ULMES, JAMES, J, ; WEST, RICHARD, L, ; LO, YING-CHEN, ; WEBER, MARK, C, ; MIN, KYUNGYOON)

Classification: - international: ***A61B5/00; A61B5/145; A61M1/36; A61M1/38; A61M37/00; B01D17/00; B01D37/00; B01D61/00; B01D61/22; B01L99/00; C02F1/00; C12M1/34; G01N33/48; G01N33/49; G01N33/50; G01N35/08; G06F1/00;*** *A61B19/02; A61M1/02; G01N35/00;* ***G06F;*** (IPC1-7): G06F

- cooperative: **A61B5/14546**; **A61B5/14557**; **A61B5/417**; **A61B50/13**; **A61M1/3609**; **A61M1/367**; **A61M1/3696**; **A61M1/38**; **B01D61/22**; **G01N33/491**; **G01N33/5005**; **G01N33/5094**; **G01N35/08**; A61B2562/028; A61M1/0209; A61M2205/12; A61M2205/33; A61M2205/52; A61M2230/20; G01N2035/00237; Y10T436/117497

Application number: WO2001US21188 20010703 Global Dossier

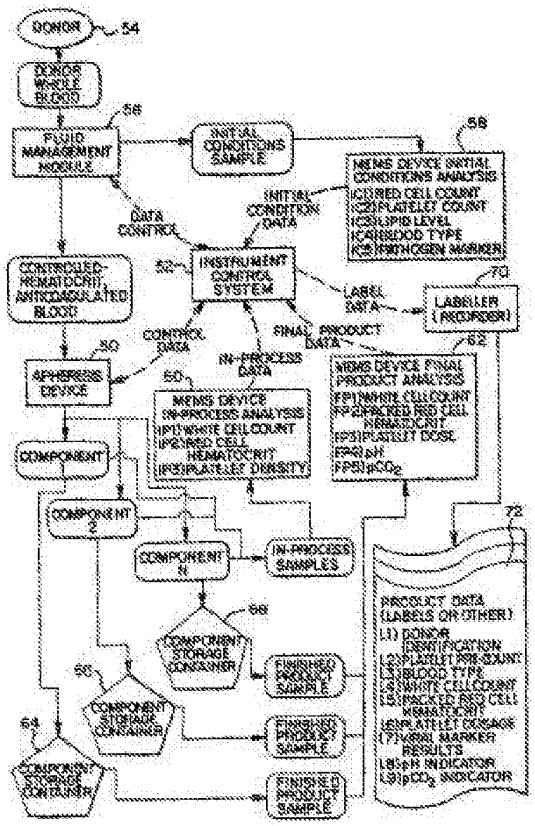
Priority number(s): US20000216640P 20000707

Also published as: WO0205059 (A3) AU7181001 (A) AU777087 (B2) BR0106942 (A) CA2382371 (A1) more

Abstract of WO0205059 (A2)

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Petitioner Terumo Exhibit 1021-1012

A biological suspension processing system is disclosed that may include a suspension treatment device for treating one or more components of a biological suspension, a first fluid flow path for introducing a suspension into the treatment device and a second fluid flow path for withdrawing a constituent of the suspension from the device. At least on microelectromechanical (MEM) sensor communicates with one of the fluid flow paths for sensing a selectedcharacteristic of the fluid therewith. The MEM sensor may be located elsewhere, such as on a container or bag and communicate with the interior for sensing a characteristic of the fluid contained therein. A wide variety of characteristics may be sensed, such as flow rate, pH, cell type, cell antigenicity, DNA, viral or bacterial presence, cholesterol, hematocrit, cell concentration, cell count, partial pressure, pathogen presence, or viscosity.



Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1013

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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(43) International Publication Date
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number
WO 02/05059 A2

(51) International Patent Classification[7]: G06F

(21) International Application Number: PCT/US01/21188

(22) International Filing Date: 3 July 2001 (03.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/216,640 7 July 2000 (07.07.2000) US

(71) Applicant *(for all designated States except US)*: **BAXTER INTERNATIONAL INC.** [US/US]; One Baxter Parkway, Deerfield, IL 60015 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CORK, William H.** [US/US]; ** (**). **ULMES, James, J.** [US/US]; ** (**). **WEST, Richard, L.** [US/US]; 37162 North Lake Shore Drive, Lake Villa, IL 60046 (US). **LO, Ying-Chen** [US/US]; 225 Fox Run Road, Green Oaks, IL 60048 (US). **WEBER, Mark, C.** [US/US]; 800 Birch Street, Algonquin, IL 60102 (US). **MIN, Kyungyoon** [KR/KR]; 7267 Clem Drive, Gurnee, IL 60031 (US).

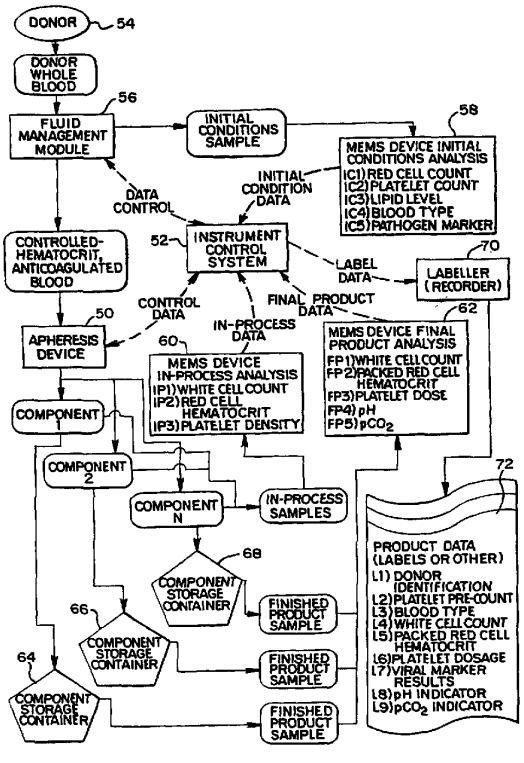
(74) Agents: **PRICE, Bradford, R., L.**; Baxter Healthcare Corporation, Route 120 and Wilson Road, Round Lake, IL 60073 et al. (US).

(81) Designated States *(national)*: AU, BR, CA, CH, CN, DE, ES, GB, IN, JP, MX, US.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

[Continued on next page]

(54) Title: MEDICAL SYSTEM, METHOD AND APPARATUS EMPLOYING MEMS



(57) Abstract: A biological suspension processing system is disclosed that may include a suspension treatment device for treating one or more components of a biological suspension, a first fluid flow path for introducing a suspension into the treatment device and a second fluid flow path for withdrawing a constituent of the suspension from the device. At least on microelectromechanical (MEM) sensor communicates with one of the fluid flow paths for sensing a selectedcharacteristic of the fluid therewith. The MEM sensor may be located elsewhere, such as on a container or bag and communicate with the interior for sensing a characteristic of the fluid contained therein. A wide variety of characteristics may be sensed, such as flow rate, pH, cell type, cell antigenicity, DNA, viral or bacterial presence, cholesterol, hematocrit, cell concentration, cell count, partial pressure, pathogen presence, or viscosity.

WO 02/05059 A2

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Published:
— *without international search report and to be republished upon receipt of that report*

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Petitioner Terumo Exhibit 1021-1015

MEDICAL SYSTEM, METHOD AND APPARATUS EMPLOYING MEMS

William H. Cork
James J. Ulmes
Richard L. West
Ying-Cheng Lo, Ph.D.
Mark C. Weber
Kyungyoon Min

The present invention relates generally to medical systems, methods and apparatus for processing biological suspensions including, but not limited to, blood. More specifically, the present invention relates to novel medical systems, methods and apparatus (for processing biological suspensions) that employ microelectromechanical systems ("MEMS") as sensors, detectors or other elements for improving product quality, purity, consistency, characterization, and/or production.

The present invention is described below in connection with the processing of blood and blood components, a field in which it is expected to find substantial application and benefit. However, it should be understood that the present invention is not limited to blood or blood component processing and may be employed in connection with the processing of other biological suspensions, for example, bone marrow or cell growth media.

The processing of blood and blood components has taken on increased significance in recent years due to

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the increased demand for blood and blood components for therapeutic application. Blood is a suspension of cells or cell fragments that are suspended in a liquid. The cells include red cells, for carrying oxygen from the lungs to the muscles and returning carbon dioxide from the muscles to the lungs, white cells, for fighting infection, and platelets, for clotting. The cells are suspended in a liquid called plasma, and the plasma itself has constituents that can be separated through a process called fractionation. For purposes of this description, blood "component" and blood "constituent" are used interchangeably.

Red cells are typically needed by patients suffering from significant blood loss. Platelets are required by many patients undergoing chemotherapy or radiation treatment, which reduces the ability of the body to make new bloods cells (and platelets are among the shortest-lived blood cell). Plasma may be administered to patients for a variety of reasons, or may be subjected to further fractionation to isolate and concentrate certain blood proteins.

As the demand for blood components has increased, it has become routine to separate collected blood into its constituent parts so that only the required constituent is given to the patient, and the other components or constituents remain available for other patients, or are returned to the donor. A term commonly used for separation of blood into one or more constituents is "apheresis." Apheresis may be done manually, after whole

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blood is collected, or it may be carried out in an automated or semi-automated procedure.

Automated apheresis typically employs a reusable device or instrument and a disposable, single use tubing set through which the blood flows for processing. The collected constituent, such as platelets, red cells or plasma, is typically withdrawn and directed to a storage container, or collected within a container inside the device, and the other blood constituents are either returned to the donor or separately withdrawn and stored for other uses. A variety of devices, based on different principles, have been used in automated apheresis. The most common devices are based on centrifugation principles, and separate the blood components based on their different densities. The CS-3000® and Amicus separators by Baxter Healthcare Corporation of Deerfield, Illinois, and the Trima® and Spectra® separators by Gambro BCT of Lakewood, Colorado, are examples of centrifugal blood separators or apheresis devices. The Autopheresis-C separator by Baxter Healthcare Corporation is another type of apheresis device. It operates on a principle of membrane separation using Taylor vortices, which is much different than the above-identified centrifugation devices. The present invention is not limited to a particular treatment device or principle of operation, and may be of significant benefit in any of these and other blood or suspension treatment devices.

In addition to collection of blood constituents from healthy donors, the same equipment and processes may be used therapeutically, to treat ill patients. For

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example, when it is believed that a patient may benefit by depleting the amount of white cells or by removing plasma, the same equipment used with donors may be used to collect those constituents from patients, returning the remainder of the blood to the patient. Blood processing as a therapeutic procedure for a wide variety of conditions has also grown in recent years.

Although blood constituent collection or depletion has been performed for many years, and advances have been made, there remain significant areas where further improvements are needed. One area where there is significant need for improvement is in reducing the potential for human error in the collection and testing of blood components. In a normal platelet collection procedure, for example, a number of tests are conducted on the blood withdrawn from the donor and on the platelet concentrate that is collected. For example, an incoming blood sample may be withdrawn from the tubing set and sent to a laboratory for testing regarding platelet count, the presence of pathogens, blood type, and a variety of other tests.

A sample of the collected blood constituent may also be subjected to similar tests. For platelets, for example, the amount of collected platelets is a particularly important number, because a certain amount of platelets (4×10^{11}) is usually necessary to constitute a standard "dose" or "unit" of platelets. In addition to determining the number (or, alternatively, the density) of platelets collected, the collected platelet product also may be tested for the presence of white cells, which

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are a suggested source of adverse reactions in some patients.

Many of these tests either are not conducted at the same place the blood component is collected or require 24-48 hours to complete. Great care must be taken, and numerous administrative steps completed, to assure that the sample is properly traceable to the collected blood product, and that the laboratory results are properly recorded in connection with the particular blood product collected. Notwithstanding such care, because of the number of individuals and steps involved, the risk of human error in this process is real, even if small. Accordingly there is a continuing need for advances that reduce the amount of human handling and intervention required, and thus the potential for error as well as the cost associated with collecting and testing blood constituents. More specifically, there is a need for collection or treatment systems that provide a product, such as blood platelets, red cells or plasma, which is fully or partially characterized, such as by cell count, pathogen presence, white cell count, blood type, et cetera, with minimum human intervention and with minimum need for testing procedures that separate the testing from the treatment process itself and thereby introduce opportunity for human error.

Because the demand for blood components is not constant, it also is not unusual for certain blood constituents to be wasted due to outdating before they are used. Although red cells, which may be refrigerated and stored for lengthier periods of time, blood platelets

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are normally stored at room temperature, and have a limited shelf life of about 5-7 days under the best of circumstances. Both, however, have limited shelf life, and, as a result, it is not uncommon for a significant amount of collected blood constituent product to be wasted because it is not used within the allowed shelf life period. Thus, in light of the limited donor pool that is available to contribute platelets and other blood components, there is a need for better efficiencies in collecting and using blood components.

In addition to the above, there is a continuing need for devices that make the collection process itself more efficient. For example, the hematocrit and platelet count of a donor may be of significant value in tailoring or optimizing the collection procedure to obtain the desired amount of the collected product, in the desired amount of time, with the desired amount of purity or freedom from undesirable components, and with minimum adverse effects to the donor or patient. Although the donor's hematocrit may be measured reasonably easily prior to a collection procedure, platelet count is an expensive and time consuming procedure, and typically is not done prior to the procedure. In most platelet collection procedures, the best available information is an estimated platelet count, based on an average of prior donations, which can vary widely. Accordingly, there is a need for more current information that can be used to optimize the collection procedure.

In summary, there is a continuing need for improvement in providing blood constituents regarding (1)

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the consistency of the collected product, for example in terms of the yield or amount of constituent collected and available for transfusion or the quality (e.g., viability) of the blood constituent collected, (2) the purity of the collected product, for example the absence of undesirable contaminants and better assurance of completion of all the necessary testing with reduced chance of human error, (3) the efficiency of collection and usage of collected blood constituent, (4) the cost and error potential in the collection and associated testing and administrative burden and (5) the safety afforded to the donor.

Within the past decade significant progress has also been made in the field of microelectromechanical systems (MEMS). MEMS is a class of systems that are physically very, very small. These systems typically, but not exclusively, have both electrical and mechanical or optical components. Modified integrated circuit fabrication techniques and materials were originally used to create these very small devices or systems, but currently many more fabrication techniques and materials are available.

MEMS devices have been conceived for a variety of sensing and actuating functions. MEMS devices have been conceived for typing blood, counting cells, identifying DNA, performing chemical assays, measuring pH, sensing partial pressures, and performing a wide variety of other procedures and tests. Recently, various manufacturers have even claimed to have developed a "lab on a chip" that is suitable for carrying out a variety of blood or

blood constituent assays or tests. However, progress in integrating MEMS devices into pre-existing medical procedures to enhance performance and reduce potential for human error has been limited.

SUMMARY

To achieve one or more of the above objectives, the present invention employs a MEMS sensor in a system for processing a biological suspension, for example blood, in a treatment device, wherein the MEMS sensor is employed to sense one or more fluid characteristics of fluid flowing into or from the treatment device. More specifically, the present invention may be embodied in a biological suspension processing system comprising a suspension treatment device for treating one or more components of a biological suspension, a first fluid flow path communicating with the treatment device for introducing a suspension into the treatment device, and a second fluid flow path communicating with the treatment device for withdrawing a constituent of the suspension from the treatment device. In accordance with the present invention, at least one microelectromechanical (MEMS) sensor communicates with one of said fluid flow paths for sensing a selected characteristic of the fluid within the flow path. The treatment device may be an apheresis device for separating and collecting one or more blood constituents, but in its broader aspects, the present invention is not necessarily limited to a particular suspension treatment device or to a particular apheresis device or separator.

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Turning back to aspects of the present invention, the MEMS sensor may be operable to sense a characteristic such as, for example, one of those selected from the group consisting of flow rate, pH, cell type, cell antigenicity, cell concentration, cell count, viscosity, cholesterol, hematocrit, DNA, viral or bacterial presence, pathogen presence, and/or partial pressure of a selected gas or other characteristics.

To aid in control of the system, the sensor may communicate with the first fluid flow path and generate a signal responsive to one or more selected characteristics of the fluid (e.g. platelet count) in the first fluid flow path. The suspension treatment device may include a controller adapted to receive the sensor signal and to control the treatment device in response to the signal. This system could be used, for example, to optimize the treatment procedure time, to provide a more consistent product, to provide a product that has a certain minimum quantity of suspension constituent, or to better safeguard patient affects. A sensor may also communicate with the second fluid flow path, which conducts the fluid being withdrawn from the treatment device, for example to count desired or non-desired components, such as platelets or white cells, or for other desired purposes.

For even better control the system may include sensor adapted to sense a selected characteristic a plurality of times at discrete intervals. This sensor may generate a signal each time it senses the characteristic, and the suspension treatment device may

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include a controller that is adapted to receive the sensor signal and to control the treatment device in response thereto. Thus, periodic sensing may be used to better optimize or improve the treatment procedure over all or part of the treatment procedure. For example, the sensor may communicate with the second fluid flow path and sense the approximate quantity or concentration of a selected cell, with the controller controlling the system to collect a desired quantity of the selected cell, or alternatively, to reduce the collected amount of the selected cell.

The system may further comprise a container communicating with the second fluid flow path for receiving the withdrawn constituent, with the system being adapted to provide tracking information for associating with the container the particular characteristic sensed by at least one sensor. A machine readable or human readable data storage media may be carried by the container to store information regarding the particular characteristics sensed by at least one sensor. The data storage media is not limited to a particular type, and may comprises a graphic indicator such as a bar code label on the container, an electronic data storage device, such as one with a non-volatile semiconductor memory, or an icon or other graphic carried by the container representative of the sensed characteristic. This tracking may be entirely carried out by the system, thereby reducing the possibility of human error in mishandling of the sample or information.

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When the suspension includes one or more blood components and the blood component withdrawn is a cellular component, the system may include a container for storing the cellular component withdrawn, and the data storage media may include data regarding, for example, the type, quality, purity, quantity and/or concentration of the cellular component in the container. More specifically, the system may include a first sensor communicating with the first fluid flow path and a second sensor communicating with the second flow path and the treatment device may comprise an apheresis device. When the suspension comprises whole blood, the first sensor may sense inter alia, platelets to determine a platelet count in the suspension introduced into the apheresis device and the second sensor may sense inter alia, platelets withdrawn to determine a platelet count in the second flow path. A container communicating with the second flow path may be provided to store the blood platelets withdrawn, and the system may further comprises machine readable or human readable data storage media carried by the container for storing information regarding platelet count sensed by one or both of said sensors. To reduce the number of human interventions required, the system may itself include a data recording device for receiving a signal from one or more of the sensors and recording the data regarding the sensed characteristic. The data recording device may be a printer for printing a human or machine readable report of the characteristic sensed, such as directly on the container or on a label affixed to the container.

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Alternatively, the container may carry a machine readable electronic data storage device, and the data recording device be adapted to transfer data regarding the selected characteristic sensed by the sensor to the electronic data storage device. An electronic data storage device may preferably comprise a non-volatile semiconductor memory, or "write once, reads many times" memory so that the data is not inadvertently lost or destroyed by power loss. In other words, a memory or processing chip may be added to the blood constituent storage container, such as permanently mounted in the tail flap of the container, with a non-volatile memory, for receiving and storing data for later access by the appropriate electronic reading instrument.

The blood component storage container also may include a microelectromechanical sensor carried by the container and communicating with the container compartment for sensing a selected characteristic, for example just before administration to a patient, of the blood component received or stored therein. Such a sensor similarly may include a non-volatile semiconductor memory or so-called "write once, read many times" data storage.

In accordance with another aspect, the present invention may be directed to a blood processing system for providing a characterized blood constituent product in which the system comprises: an apheresis device for separating one or more desired cellular blood constituents from a suspension comprising whole blood, a first fluid flow path communicating with the apheresis

device for introducing a suspension comprising whole blood into the device, a second fluid flow path communicating with the apheresis device for withdrawing at least one desired cellular blood constituent from the device, a container communicating with the second fluid flow path for receiving the blood constituent withdrawn from the apheresis device, machine readable or human readable data storage media carried by the container, at least one microelectromechanical sensor communicating with the first fluid flow path for sensing at least one characteristic of the whole blood and for generating at least one electrical signal responsive to such sensing, at least one microelectromechanical sensor communicating with the second flow path for sensing the quantity of cellular blood constituent withdrawn from the apheresis device and for generating an electrical signal responsive to such sensing, a data recorder adapted to receive the electrical signals from the sensors and to record data regarding the sensed characteristics on the data storage media, whereby a user may readily identify the sensed characteristic regarding the whole blood and the quantity of the desired cellular constituent in the container with a minimum of human intervention.

This system may further include a sensor communicating with the second fluid flow path for sensing the quantity of a non-desired biologic constituent in the flow path and generating an electrical signal responsive to the quantity, the data recorder being adapted to receive such signal and record data regarding the quantity of non-desired cellular constituent in the data

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storage media for access by a user of the product in the container. The non-desired biologic component may be a viral constituent, or a cellular constituent, such as white cells.

As before, the system may include a controller adapted to receive the signals from the sensors communicating with the first and second fluid flow paths and to control the apheresis device in response to one or more of such signals to provide a desired cellular blood constituent product characterized by data recorded in the data storage media in accordance with characteristics sensed by the sensors. The data storage media may comprise machine readable graphics carried on the container, for example, a bar code. The system may also, when withdrawing blood from a donor or patient, for example, generate a human-readable report for the donor or patient containing selected data regarding one or more of the sensed characteristics.

In accordance with another aspect of the present invention, a biological suspension processing system may be provided which includes: a blood treatment device for treating one or more components of a biological suspension, a human subject, a first fluid flow path communicating with the vascular system of the human subject and the treatment device for introducing blood from the human subject into the treatment device, a second fluid flow path communicating with the treatment device for withdrawing a constituent of the blood from the treatment device, a third fluid flow path communicating with the treatment device from withdrawing

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another constituent of the blood from the treatment device, and at least one microelectromechanical sensor communicating with one of said fluid flow paths for sensing a selected characteristic of the fluid within the flow path.

The sensor may generate a signal responsive to one or more selected characteristic of the fluid in one of the fluid flow path, with the suspension treatment device including a controller adapted to receive the sensor signal and to control the treatment device in response thereto. In the situation where the third fluid flow path communicates with the human subject, and the treatment device is adapted to add anticoagulant to the blood in the first fluid flow path, the selected characteristic may include the hematocrit of blood in the first fluid flow path. In that setting, the controller may control the addition of anticoagulant into the first fluid flow path to prevent too much anticoagulant from being returned to the donor or patient, because, as is well known excess anticoagulant flow to the donor or patient may have deleterious consequences.

The signal from the sensor and the control of the treatment device is not limited, however, to the safety of the human subject. The controller may, for example, in response to the signal control the treatment device to withdraw a constituent of desired quality, to withdraw a constituent of desired quantity, to withdraw a constituent that is depleted of an undesired component, or to withdraw a selected minimum quantity of constituents, such as platelets, red cells or plasma, or

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to withdraw a certain amount of constituent in a maximum or minimum procedure time.

In a more specific embodiment of the present invention, the MEMS sensor(s) or other MEMS devices are located on a common disposable carrier or cassette. The carrier includes internally defined fluid flow passageways that may be selectively opened or closed by macro or MEMS scale valves to control flow of fluid to the sensors in response to control signals from the device controller. The carrier is preferably adapted to interfit with a reusable reader/controller which cooperates with the MEMS devices located in the cassette to provide a signal responsive to the sensed characteristic, which signal may be used to optimize the treatment procedure or to identify the sensed characteristic for later association with or labeling of the collected blood product, or to control the flow of fluid through the cassette.

Although the carrier may take several different forms, in one form of a cassette, it is comprised of a rigid plastic base that mounts a plurality of MEMS sensors or other MEMS devices such as valves or pumps, and has preformed passageways defined in the base with fluid flow control valve modules located to control the flow of selected fluid to the desired MEMS sensor. The cassette may include preformed open passageways that are closed by a resilient membrane which overlies one side of the cassette and is sealed to the passageway walls (either temporarily by pressure exerted by the reader or permanently by solvent or sonic bonding) to close the

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passageways. The membrane may cooperate, such as by mechanical or pneumatic actuation, with the valve modules to control the flow of fluid through passageways in the MEMS cassette.

The present invention is not limited to a particular type of MEMS sensor or to a particular principle of operation. The MEMS devices useful in the present invention may be static or dynamic, purely mechanical, biomechanical or electro-mechanical. They may also include optical components, and they may be dry or used in combination with liquid reagents or other liquids.

One type of MEMS sensor that holds promise for apheresis procedures is a microcytometer in which particles, for example cells, or cell fragments, are fed through a narrow, microfluidic channel in single file. Other MEMS sensors may be based, for example, on centrifugal microfluidics analysis employing a rotating compact disc that employs, for example, a micro-fluidics manifold and spectrophotometric cuvette formed on the surface of the disc, which may be read by an optical disc reader.

Because certain MEMS devices may require special or separate sterilization procedures as compared to other MEMS devices, the present invention also contemplates that there may be more than one MEMS carrier or cassette. For example, MEMS employing reagents may require a different sterilization technique, such as ethylene oxide sterilization, as compared to purely mechanical or electro/mechanical, optical/mechanical or optical/electrical MEMS devices, which may be suitable

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for radiation or heat sterilization. There may also be other reasons for having more than one MEMS cassette, including ease of manufacturing, ease of mounting or assembly on the treatment device, and the like. In such case, the MEMS cassette may be attached to the remainder of the fluid circuit after sterilization, as by sterile docking or other sterile connection procedure.

Fluid may be pumped through the MEMS cassette by the peristaltic pumps that are typically employed on apheresis devices for moving blood and blood components through the tubing set or, alternatively, the MEMS cassette itself may include macro and/or MEMS-scale pumps for circulating fluid through the MEMS cassette and to the desired MEMS sensor. Similarly, liquid flow through the cassette may be controlled by MEMS scale valves, or by macro scale valves such as those employed in the fluid flow control modules of the Amicus apheresis centrifuge marketed by Baxter Healthcare.

Additional aspects and features of the present invention are set forth in the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is schematic flow chart of a suspension treatment system embodying the present invention.

Figure 2 is a software/data flow chart for a control and data flow system that may be employed in the present invention.

Figure 3 is a perspective view of a reusable suspension treatment device, specifically an apheresis device, embodying the present invention.

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Figure 4 is an enlarged perspective view of a portion of the device of Figure 3, showing the reader/controller for a MEMS cassette or carrier.

Figure 5 is a plan schematic of a disposable fluid circuit, including a MEMS cassette or carrier, for use with the device of Figure 3 and employing the present invention.

Figure 6 is an exploded perspective view of a MEMS cassette or carrier that may be used in the disposable fluid circuit of Figure 5, embodying the present invention.

Figure 7a is a top view of the assembled MEMS cassette of Figure 6.

Figure 7b is a side view of the MEMS cassette of Figure 7a.

Figure 8 is a perspective view of the reader/controller for the MEMS cassette.

Figure 9 is an enlarged perspective view of the device of Figure 3, embodying an alternative MEMS cassette reader/controller.

Figure 10 is an exploded perspective view of a MEMS cassette that may be used with the reader/controller shown in Figure 9.

Figure 11 is a rear perspective view of the assembled MEMS cassette of Figure 10, illustrating macro-scale valve modules for fluid flow control.

Figure 12 is an enlarged perspective view showing the interfit between the MEMS cassette of Figure 10 and the reader/controller of Figure 9.

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Figure 13 is a schematic view of MEMS microcytometer that may be used in the present invention.

Figure 14 is a view of the microcytometer of Figure 13, illustrating the focusing of blood cells using sheath flow.

Figures 15a and 15b are cross-section views of a bistable valve that may be used in the MEMS cassette of the present invention.

Figure 16 is a top plan view of an alternative MEMS cassette embodying the present invention, which includes fluid pumping chambers for pumping fluid through the cassette.

Figure 17a is a plan view of a compact disc employing a microfluidic manifold and a spectrophotometric cuvette.

Figure 17b is an elevational view of a reader for the compact disc of Figure 17a.

Figure 18a is a plan view of a blood component storage container having a MEMS sensor mounted in or carried on the container wall for accessing the contents.

Figure 18b is a plan view of the container of Figure 18a with a reader for reading the MEMS sensor.

DETAILED DESCRIPTION OF DRAWINGS

Turning now to a more detailed description of the drawings, Figure 1 is a flow chart illustrating a treatment system embodying the present invention. Although the flow chart in Figure 1 is in the context of a blood apheresis system, the flow chart and the steps indicated therein have application to other suspension treatment systems as well.

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Before describing the treatment system in more detail, it should be understood that the flow chart is intended to reflect general system features and functions, and not necessarily the system structure. For example, it should be understood that features shown in a single box or grouping of the flow chart may represent what are actually two or more physical modules or structures in the actual product, and more than one box or grouping in the flow chart may be a single physical module or structure in the final product. The purpose of the flow chart is simply to illustrate one embodiment of an overall system and function, and not to limit the actual physical structure.

As applied to apheresis, the system in Figure 1 includes an apheresis device 50, such as a centrifuge, spinning membrane separator or other apheresis device or instrument, and an instrument or device control system 52. The control system 52, which may comprise a programmable microprocessor, performs a variety of control and monitoring functions for carrying out an apheresis procedure. It receives and sends data regarding various initial, in-process and final product characteristics, it controls the fluid flow through the system, it controls the operation of the apheresis device and it tracks and stores data for labeling the final product or for communicating with data storage media associated with the container in which product is collected during the apheresis procedure.

In the system shown in Figure 1, whole blood is collected from a donor 54, such as a healthy adult human.

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The flow of blood (and other liquids such as priming solution and anticoagulant) through the system is controlled by a fluid management module 56. In accordance with the present invention, one or more characteristics of the blood flowing into the system may be sensed by one or more MEMS sensors. For example, an initial sample of the whole blood, before processing, may brought into contact with one or more initial condition MEMS sensors 58 for sensing or measuring red cell count, platelet count, lipid level, blood type or markers representative of pathogen (viral or bacteria) presence. As used here, "sensor" or "sensing" is used broadly and includes detecting, measuring, monitoring, analyzing, characterizing, sampling and any other tests or analysis that may be desired.

Data from the initial conditional sampling, typically in the form of an electrical signal, may be fed back to the control system 52 for purposes, for example, of controlling the fluid management module or the apheresis separation process or for tracking or storing information relating to the sensed characteristic for later association with the collected product. For example, data as to blood type may be saved for recording on a machine readable or human readable data storage media carried by the container for the collected product, such as a descriptive label, bar code or electronic memory device. Data regarding initial platelet count may be used, for example, to optimize the apheresis procedure to minimize procedure time, to maximize the amount of

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platelets collected or to better assure collection of a certain minimum number of platelets.

The anticoagulated whole blood is directed by the fluid management module to the apheresis device or instrument 50. There, the blood is separated into one or more components, such as components nos. 1, 2 and up to "n" components. During the apheresis procedure, in-process data may be sensed by one or more of the in-process condition MEMS sensors 60, for detecting characteristics such as white cell count, red cell hematocrit and platelet density. Data from the in-process condition MEMS sensor(s) may be fed back to the control system 52, typically for controlling the apheresis process and/or fluid flow. The in-process condition MEMS sensor may sample fluid one or more times during the procedure, as desired. To provide periodic adjustment of the apheresis device or fluid flow throughout the apheresis procedure, a plurality of MEMS sensors may be employed in the in-process sensing. These MEMS sensors may be activated by the control system to sense one or more selected characteristic at selected time intervals throughout the procedure or upon occurrence of certain triggering events, such as power outage, red cell spill over or other event.

The separated blood components not returned to the donor are directed to storage containers 64, 66 and 68, respectively. It is not necessary, of course, for the storage containers to be outside of the apheresis device. In the Baxter CS-3000® and Amicus® centrifuges, for example, blood components may be collected in containers

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that reside inside the rotating centrifuge until the apheresis procedure is completed.

As one or more components are collected, one or more characteristics of the final collected product may be sensed by the MEMS final product condition sensor(s) 62 and data relayed back to the controller 52. The final product condition MEMS sensor 62 may be provided to sense one or more characteristics of the collected product, such as white cell count, packed red cell hematocrit, platelet dose, pH, or gas (e.g., CO_2) partial pressure. The final product condition MEMS may feed data back to the control system 52 for optimizing the apheresis procedure, controlling fluid flow and/or storing/tracking data for association with the final collected product.

One of the benefits of certain aspects of the present invention is the providing of a final product that is fully or partially characterized according to the initial condition, in-process and/or final product condition MEMS sensors, with the characteristics sensed being tracked or stored for association with the final product container, all occurring with reduced human intervention and opportunity for error. For example, having received data from the various MEMS condition sensors 58, 60 and 62, the instrument control system 52 may relay that data to a recorder or labeler 70, which records the data onto data storage media 72 carried by the storage container. The data or storage media may be human readable, or machine readable (e.g., graphic or bar code), or a combination of both or other form. The recorder may, for example, print a label for attachment

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to the container, or transfer the data to a machine readable electronic storage device, such as a memory chip, carried by the container. The result is a blood component product characterized as needed, with reduced need for human intervention or opportunity for human error.

Figure 2 is an outline of certain aspects of a programmable operation control system. As shown there, the procedure process master control module 74 may instruct (shown by dashed lines) various elements of the system to perform certain functions, and receive (shown by solid lines) data from one or more of those elements. For example, the master control may direct the sample pre-measurement module 76 to carry out certain initial condition sensing. This may be carried out by opening a macro or MEMS-scale valve that directs incoming whole blood into contact with the desired initial condition MEMS sensor 58. The information or data regarding the sensed characteristic is then relayed back through the pre-measurement module to the master control module for storage or for later association with the collected blood product.

Similar steps may be carried out as between the master control module 74 and the in-process module 78 and in-process MEMS sensor(s) 60, and as between the master control module and the final product configuration module 80 and final product condition sensor(s) 62.

Information from the various MEMS sensors may then be relayed to the recorder/labeler 70 for associating the data with the final product container. In one simple

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form, this may be by way of printing a label for attachment to the container or for printing the desired information on a pre-attached label, although the present invention also contemplates that data could be transferred optically or electrically to an electronic data storage device (such as a non-volatile memory chip or "write once, read many times" storage device) attached to the final product container. If the operator desires that only certain information be displayed with the product, the system permits less than all of the characteristics that are sensed to be displayed on or in connection with the collected product.

Figure 3 shows a biological suspension treatment device, and specifically an Amicus® apheresis instrument 82 of the general type made and sold by Baxter Healthcare Corporation of Deerfield, Illinois. The Amicus® separator is described in detail in U.S. Patent No. 5,462,416, which is incorporated by reference, and that description will not be repeated in full here.

Briefly, the Amicus® separator is based on centrifugation principles, and separates blood components by reason of their different densities. The Amicus® separator is intended to work with a disposable, one-time use plastic tubing set, which will be described later, through which blood and blood components flow during the apheresis procedure.

The Amicus® separator includes a base portion, generally at 84, a fluid management and sensor panel area 86, and a display screen and touch control panel 88. The machine base 84 contains the rotating centrifuge chamber

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drive hardware and control electronics. The centrifuge chamber is accessible through a drop-down front door 90 for loading and removing the disposable tubing set.

The fluid management and sensor panel includes three pump and valve stations, each of which has a pair of peristaltic pumps 92 and adjacent flow control module 94 for pumping fluid through the system and controlling the direction of fluid flow. User information regarding the apheresis procedure is displayed on the display screen 88, which also includes touch input capability for operator entry of information or control commands prior to and during the apheresis procedure.

In accordance with a preferred version of the present invention, the MEMS sensors and other devices are mounted on a single MEMS carrier or cassette 96 (Figure 5), which is part of the disposable fluid circuit and intended for one-time use only. The apheresis instrument 82 (Figure 3) includes a MEMS cassette reader/controller 98 into which the MEMS cassette is mounted when the disposable fluid circuit is installed on the instrument. The reader/actuator 98 cooperates with the MEMS cassette for reading or transferring data from the MEMS sensors on the cassette and for controlling flow of fluid through the MEMS cassette and to the desired MEMS sensor or other MEMS device.

The MEMS cassette reader/controller shown in Figure 3, and shown in larger view in Figure 4, employs a base 100 adapted to receive the MEMS cassette and a door 102 pivotally mounted on the base for closing over the cassette to block out ambient light and cooperate with

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optical, electronic or mechanical devices located in the base portion for reading or interpreting the MEMS sensors or other devices and/or for actuating valves or pumps located in the MEMS cassette.

Figure 5 is a schematic view of a disposable one-time-use processing assembly or fluid circuit 104 embodying the MEMS cassette/carrier 96 of the present invention for use on the apheresis instrument shown in Figure 3. A detailed description of the disposable fluid circuit may be found in U.S. Patent No. 5,462,416, which was previously incorporated by reference, and will not be repeated here.

The processing assembly 104 includes an array of flexible tubing that forms the fluid circuit through which blood and blood components flow. The fluid circuit conveys liquid to and from a processing chamber 106 that is mounted in the rotating centrifuge chamber during use. The fluid circuit includes a number of containers 110a-f that fit on hangers on the centrifuge assembly to dispense and receive liquids during the apheresis process.

The fluid circuit 104 also includes one or more in-line fluid control cassettes 112, which are not to be confused with the MEMS cassette (although the fluid control cassettes could also include MEMS sensors or other MEMS devices and thus incorporate features of the present invention, if desired). Figure 5 shows three such cassettes designated 112a , 112b and 112c. The cassettes serve in association with the pump and valve stations on the centrifuge assembly to direct liquid flow

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among the multiple liquid sources and destinations. During a blood processing procedure the cassettes centralize the valving and pumping functions to carry out the selected procedure. Further details of these functions are described in the above mentioned U.S. Patent No. 4,562,416.

A portion of the fluid circuit 108 leading between the cassettes 112a-c and the processing chamber 106 is bundled together to form an umbilicus 114. The umbilicus links the rotating parts of the processing assembly (principally the fluid management processing chamber) with the non-rotating, stationary parts of the processing assembly (principally the cassettes and containers and fluid circuit tubing and MEMS carrier or cassette). The umbilicus links the rotating and stationary parts of the processing assembly without using rotating seals, by employing the well known one-omega two-omega principle, which has long been successfully used in the CS-3000® centrifuge marketed by Baxter Healthcare Corporation.

In the illustrated and preferred embodiment, the fluid circuit 104 pre-connects the processing chamber 106, the containers 110, the fluid control cassettes 112 and the MEMS carrier/cassette 96. The assembly thereby preferably forms an integral pre-assembled sterile unit, although it is recognized that if separate sterilization is required for the MEMS cassette, it may require subsequent attachment, such as by sterile connection procedure, to the remainder of the fluid circuit.

During a typical dual needle platelet collection procedure, whole blood is drawn into an inlet needle 116

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and combined at a junction 118 with anticoagulant such as ACD, which is pumped from the ACD container 110d, through fluid control cassette 112a and from there into the separation/processing chamber 106. In the separation chamber, platelet rich plasma is separated from packed red cells, and each is withdrawn from the separation chamber. The platelet rich plasma is withdrawn through the umbilicus 114 upwardly through cassette 112c and then, after passing through an optical sensor 120, returned to a collection chamber in the centrifuge. There, platelet concentrate is separated from the platelet rich plasma, and platelet-depleted or platelet-poor plasma is withdrawn from the collection chamber and collected in a platelet-poor plasma storage container 110c and/or returned to the donor, with red cells through fluid control cassette 112a and return needle 117. Although illustrated as a dual needle set, the present invention is equally applicable for a single needle fluid circuit of the type also previously sold by Baxter Healthcare Corporation for use on the Amicus® centrifuge.

In accordance with the present invention, as illustrated in Figure 5, the fluid circuit 104 includes at least one MEMS cassette or carrier 96. As shown in Figure 5 for purposes of illustration and not limitation, the MEMS cassette 96 is shown having five fluid connections. The number of connections, however, depends on the fluid characteristics to be sensed, and fewer fluid connections may suffice for many blood-related applications, as will be discussed later.

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As illustrated in Figure 5, the MEMS cassette 98 has a fluid inlet 120 connected to the packed red cell line. Fluid in this line may be monitored by MEMS sensors to determine the packed red cell hematocrit for the purpose, for example, of optimizing the separation procedure.

MEMS cassette fluid inlet 122 is connected to the whole blood inlet line. Fluid from this line may be sensed by MEMS sensors, for example, to determine any of the initial condition data such as red cell count, platelet count, lipid level, blood type or the presence of a pathogen (viral or bacteria) indicator or marker.

The next fluid entry inlet line 124, is shown communicating to the platelet rich plasma line. This may be used to perform in-process analysis of white cell count, red cell hematocrit, platelet density and the like.

Fluid connection 126 is connected to the platelet-depleted plasma line. MEMS sensors associated with this connection may be used to sense any of the desired final product characteristics of the plasma. Similarly, fluid connection 128 is attached to the platelet concentrate collection tubing for MEMS sensing of one or more of the final characteristics of the platelet concentrate, such as platelet dose or density, white cell count, platelet size, and the like.

A MEMS cassette or carrier 98 as presently contemplated is depicted in greater detail in Figure 6. As shown there, the cassette includes a rigid MEMS holder or support 130, a plurality of MEMS sensors or other MEMS devices 132, front cover 134 and membrane backing 136.

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The holder or support 130 is preferably made of rigid plastic or other suitable material. A plurality of passageways 138 for fluid flow are provided in the MEMS holder, for communicating the desired fluid to the desired MEMS sensor or other device. As illustrated in Figure 6, three such fluid passageways 138 are shown for initial condition, in-process, and finished product characteristic sensing. The passageways are pre-formed into the MEMS holder, and communicate with three arrays of MEMS device-receiving areas 140, which are adapted to receive the desired MEMS sensors or other devices. The center fluid passageway communicates with two rows of MEMS device receiving areas that flank the passageway. The other two passageways communicate with a single row of MEMS devices. The size of the array and number of MEMS sensors or other devices may be varied as needed for a given treatment procedure to provide the desired sensing capability. For those MEMS sensors or other devices that require an electrical power source, the rigid holder may include a plurality of electrical contacts 142. Embedded or embossed electrical leads in the holder may extend between the contacts and the appropriate areas 140 for mounting MEMS sensors or other devices that require a voltage source.

The MEMS holder and MEMS sensors/devices are contained beneath the clear cover plate 134, which is sealed to the holder 130, as by adhesive, sonic or solvent bonding, to form the passageways 138. The clear cover allows for the transmission of light to or from associated optical light sources or receivers in the MEMS

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cassette reader. The flexible membrane 196 attached to the underside of the MEMS holder allows for actuation of valves, pumps or other devices associated with the MEMS cassette, as described in more detail later.

Turning to Figure 7A, which is a plan view of the MEMS cassette or carrier 98, the initial condition analysis sample line 144 communicates with a first fluid passageway 138a in the MEMS cassette that communicates with a plurality of MEMS sensors for sensing viral or pathogen markers (e.g., a DNA analysis that may reveal the presence of an unwanted virus or bacteria), blood type, lipid level, platelet count and red cell count. The inlet to each MEMS sensors may be controlled by a valve 141, which may be macro-scale valve that controls flow of the initial fluid to the MEMS sensor or by MEMS-scale valves, which are available from a variety of sources using various principles, such as surface tension, flexing membranes or the like. It is contemplated that the initial condition line would communicate, in an apheresis procedure, with the whole blood inlet line. Additionally, although the passageways 138 are shown as having closed ends, the passageways may also continue through the cassette and return to the fluid circuit so that, for example, the sample lines are receiving a constant throughput of the fluid to be analyzed.

The next inlet line is the in-process analysis sample line 146, which communicates with the fluid flow passageway 138b in the MEMS cassette for sampling various characteristics of the fluid while the apheresis process

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is carried out. For example, the in-process fluid may flow through the center passageway 138b to platelet density MEMS sensors, red cell MEMS sensors and MEMS sensors for counting the number of white cells. The in-process flow line may be attached to the platelet-rich plasma line, the packed red cell line or, if desired, with the processing chamber itself.

The final product analysis sample line 148 communicates with the third passageway 138c in the MEMS cassette for determining final product characteristics, such as partial pressure of CO_2, the pH, the platelet density, hematocrit or white cell count. It is anticipated that this final product sample line would be connected to the flow line communicating with the final product collection container, although other connection sites, such as the processing chamber itself, are within the scope of this invention.

Although the characteristics described above are these that may be determined in the platelet collection procedure, the user may select or the manufacturer may employ different MEMS sensors with different objectives or for sensing different characteristics, as desired.

As shown in Figure 8, in use, the MEMS cassette or carrier 96 is preferably mounted within a recessed area in the base 100 of the MEMS cassette reader/controller 98. For MEMS devices employing optical read-out, the base preferably includes an array of light emitting fibers or diodes 150 in registration with the appropriate MEMS devices, and the door 102 may include an array of light collectors or receivers 152 in registration with

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the MEMS devices for the purpose of reading the optical transmission, reflection or refraction by the particular MEMS sensor. The base and/or door also include electrical contacts 153 for connecting with electrical contacts 142 of the cassette for MEMS needing an electrical voltage source. Therefore, it is apparent that the present invention is not limited to a particular type of MEMS sensor or device or to MEMS sensors or devices operating on a particular principle.

One example of a MEMS sensor for use in the present invention is illustrated in Figure 13. The MEMS sensor shown there is a MEMS microcytometer 149, and is believed to have particular promise for cell-related applications. As may be seen there, the microcytometer includes a light source 150 for emitting light, such as coherent laser light, at a single file stream of components, such as cells which may be received from the initial condition, in process or final condition flow lines. Light receivers 152 and 154, receive reflected and refracted light from the particles which, in turn, is used to count or characterize the cells flowing through the line, such as by cell type, cell density or number of cells. Fluorescence detection and light scattering can be used to count and characterize the cells. Such detection may also be combined with immunossays techniques to detect and characterize antibody coated beads and antibody-antigen complexes. This type of MEMS sensor has been previously described by, and may be available from Micronics, Inc., of Redmond, Washington.

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As shown in Figure 14, the microcytometer 149 employs a micro-fluidic channel 151 in which fluid flowing in a sheath flow arrangement resulting from liquid flow from the intersecting flow channels 153 forms the cells into single file for analysis. Accordingly, it is within the concept of the present invention that the MEMS cassette may also include additional fluid channels 153, as appropriate, for receiving liquids or gases (such as saline, water, reagents, or other liquids or gases) that may be used in connection with the MEMS sensors.

Another MEMS device that may be suitable for application in the present invention is a MEMS sensor based on centrifugal microfluidics analysis. One or more small rotating compact discs may be mounted in the MEMS cassette, which disc may be read by an optical disc reader. The disc employs, for example, a micro-fluidics manifold and spectrophotometric cuvette formed on the surface of the disc. Figure 17 diagrammatically depicts such a device, which has been proposed by and may be available from Gamera Bioscience of Medford, Massachusetts.

Microfluidic mixing devices, capillary connectors employing microchannels, and membrane micro-valves available from TMP of Enscheda, Netherlands, and thin-walled compliant plastic structures, micro-fluidic circuits, silicone button pneumatic actuators and micro-valves as disclosed by Lawrence Livermore National Laboratory at the July 15-16, 1999 Knowledge Foundation conference on Novel Microfabrication Options for Biomems, in San Francisco, California, are but a few of other MEMS

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devices that may be incorporated into the MEMS cassette of the present invention.

As noted earlier, the MEMS cassette may include macro-scale valves, for example, as used in the Baxter Amicus® separator for controlling flow through the fluid circuit module sets. These valves and their operation is described in more detail in previously cited U.S. Patent No. 5,462,416. However, the MEMS cassette may also employ MEMS-scale valves 141, as illustrated in Figure 7a.

A wide variety of MEMS-scale valves are available. For example, Figures 15a and 15b show a bi-stable valve 156 employing a membrane 158 that flexes between a closed position, blocking inlet passageway 160 as shown in Figure 15a and an open position as shown in Figure 15b allowing flow between the inlet passageway and outlet passageway 162. The valve presumably opens when the pressure in the valve chamber exceeds a threshold amount, at which time the membrane moves from the stable closed position to the stable open position. The valve moves to the stable closed position when the pressure in the valve chamber drops below a certain threshold value, causing the membrane to move from the stable open position to the stable closed position. Such a bistable microvalve was described by the Institute for Mikrostukturtechnik, at the July, 1999 "Novel Microfabrication Options for Biomems, Technologies & Commercialization Strategies" conference sponsored by the Knowledge Foundation. This is but one example of a MEMS scale valve that may be used in the MEMS cassette. It is also known to use micro-

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channels and surface tension to form MEMS scale valves, with the valve opening when fluid pressure exceeds a certain threshold to overcome the effects of surface tension. Such valves may also find use in a MEMS cassettes of the type disclosed here.

An alternative design for the MEMS carrier or cassette and the cassette reader/controller is shown in Figures 9-11. As shown in Figure 9, a cassette reader/controller 164 comprises a pair of upstanding walls 166 defining a MEMS cassette-receiving slot between them. One wall has a function similar to the base 100 of the prior embodiment and the other wall functions in a manner similar to the door of the prior embodiment. In other words, one wall includes an array of light emitting fibers, diodes or the like, and any appropriate electrical contacts for cooperation with the MEMS devices in the MEMS cassette. The facing wall includes an array of light receivers for cooperating with the MEMS sensors and for reading the characteristics sensed. As before, one of these upstanding walls may also include macro-scale valves for actuating or controlling flow through the MEMS cassette, or the MEMS cassette may include MEMS-scale valves for controlling fluid.

Figure 10-11 depicts an alternative MEMS cassette 168 for use with reader/controller 164. The MEMS cassette 168 includes a base 170 having preformed fluid passageways 172 and pre-formed MEMS receiving or mounting areas 174 that may be connected to the passageways as desired for allowing fluid flow from the passageway to the MEMS sensor. As may be seen in Figure 10, the three

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fluid pathways extend fully through the base from inlets 176 to outlets 178. A clear 180 cover is mounted on one side of the base and a flexible membrane 182 on the other side of the base.

As shown in an underside view, in Figure 11, valve module areas 184 are provided in the cassette which may be opened or closed by macro-scale valve members which depress the flexible membrane to contact and close against a valve module to block flow between the passageway and MEMS device or, upon release, to open a particular valve module to fluid flow. The valve opening and closing arrangement is preferably comparable to that already employed in the Baxter Amicus® centrifuge, which is described in detail in the U.S. Patent No. 5,462,416.

As illustrated in Figure 12, this alternative embodiment of the MEMS reader 164 and cassette 168 permits very easy loading of the cassette during installation of the disposable by sliding the cassette downwardly between the upstanding walls 166 of the MEMS cassette reader/controller.

Figure 16 illustrates another embodiment of a MEMS cassette or carrier 186 in accordance with the present invention. The earlier described cassettes rely on pressure within the tubing set (created by peristaltic pumps 92) for moving the selected fluid into and through the MEMS cassette. However, the MEMS cassette may itself have pumping chambers for moving fluid through the cassette and, indeed, through the tubing set, if desired. Figure 16 shows such a MEMS cassette 186.

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As illustrated in Figure 16, MEMS cassette 186, comparable to previously described embodiments, includes three internal passageways 188 communicating with inlet flow tubing for sensing initial condition, in-process and final condition characteristics. In the Figure 16 embodiment, however, each passageway also communicates with a respective pumping chamber 190. The pumping chamber preferably has one wall defined a flexible membrane bonded to one side of the cassette. Flexing of the membrane by mechanical or pneumatic pressure alternatively reduces and increases the size of the chamber, resulting in a pumping action. Inlet and outlet valves 192 at each end of the pumping chamber, which are alternatively opened and closed, control the direction of flow through the pump. As pointed out earlier, this pumping may be used only to move the desired fluid through the MEMS cassette or may also be used to move fluid through the entire disposable fluid circuit, if desired.

Figure 18a shows a blood component container 194 with a MEMS sensor 196 carried by or embedded in the wall of the container for sensing a selected characteristic of the blood component in the container. The MEMS sensor may be adapted to access the container contents through a frangible part of the container wall or through a piercing member associated with the sensor, and may be adapted to test for bacterial contamination and/or pH of the stored blood component. This would have particular application in sensing the blood component just before

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administration to a patient to assure that the pH and bacteria levels are acceptable.

After a suitable assay period required by the MEMS sensor, the results may be read directly from the MEMS sensor. Alternatively, the MEMS sensor may be read by a reader 198 such as an automated optical, magnetic or electronic device, suitable for the particular MEMS sensor mounted on the bag.

Although described in terms of one or more specific embodiments, the present invention is not limited to the specific structures disclosed for illustrative purposes, and includes such changes or modifications as may be apparent to one skilled in the field upon reading this description.

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CLAIMS:

1. A biological suspension processing system comprising:

a suspension treatment device for treating one or more components of a biological suspension;

a first fluid flow path communicating with the treatment device for introducing a suspension into the treatment device;

a second fluid flow path communicating with the treatment device for withdrawing a constituent of the suspension from the treatment device; and

at least one microelectromechanical sensor communicating with one of said fluid flow paths for sensing a selected characteristic of the fluid within the flow path.

2. The system of claim 1 in which a sensor senses one or more characteristics selected from the group consisting of flow rate, pH, cell type, cell antigenicity, cell concentration, cell count, viscosity, cholesterol, hematocrit, DNA, viral or bacterial presence, pathogen presence, and partial pressure of a selected gas.

3. The system of claim 1 in which a sensor communicates with the first fluid flow path and generates a signal responsive to one or more selected characteristic of the fluid in the first fluid flow path, the suspension treatment device including a controller adapted to

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receive the sensor signal and to control the treatment device in response thereto.

4. The system of claim 1 in which a sensor communicates with said second fluid flow path and generates a signal responsive to a selected characteristic of the fluid in the second fluid flow path, the suspension treatment device including a controller adapted to receive the sensor signal and to control the treatment device in response thereto.

5. The system of claim 1 in which the sensor is adapted to sense the selected characteristic a plurality of times at discrete intervals.

6. The system of claim 5 in which the sensor generates a signal responsive to a selected characteristic of the fluid in the flow path, the suspension treatment device including a controller adapted to receive the sensor signal and to control the treatment device in response thereto.

7. The system of claim 6 in which sensor communicates with the second fluid flow path and senses the approximate quantity or concentration of a selected cell.

8. The system of claim 1 further comprising a container communicating with the second fluid flow path for receiving the withdrawn constituent, the system being adapted to provide tracking information for associating

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with the container the particular characteristic sensed by at least one sensor.

9. The system of claim 8 in which the system comprises machine readable or human readable data storage media carried by the container, the data storage media storing information regarding the particular characteristic sensed by at least one sensor.

10. The system of claim 9 in which the data storage media comprises a bar code label on the container.

11. The system of claim 9 in which the data storage media comprises an electronic data storage device.

12. The system of claim 11 in which the electronic data storage device has a non-volatile semiconductor memory.

13. The system of claim 9 in which the data storage media comprises at least one icon carried by the container and representative of the sensed characteristic.

14. The system of claim 9 in which the suspension includes one or more blood components and the blood component withdrawn is a cellular component, and the container is for storing the cellular component withdrawn, and the data storage media includes data regarding the type, quality, purity, quantity or

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concentration of the cellular blood component in the container.

15. The system of claim 1 in which the at least one sensor includes a first sensor communicating with the first fluid flow path and a second sensor communicating with the second flow path and the treatment device comprises an apheresis device and the suspension comprises whole blood, the first sensor sensing platelets to determine a platelet count in the suspension introduced into the apheresis device and the second sensor sensing platelets to determine a platelet count in the second flow path, wherein the system includes a container communicating with the second flow path for storing blood platelets withdrawn, and the system further comprises machine readable or human readable data storage media carried by the container, the data storage media storing information regarding platelet count sensed by one or both of said sensors.

16. The system of claim 1 in which a sensor communicates with said second fluid flow path, and said system includes a container for storing the constituent withdrawn, the sensor generating a signal responsive to a characteristic of the constituent withdrawn, and the system includes a data recording device for receiving the signal and recording data regarding the sensed characteristic of the constituent withdrawn.

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17. The system of claim 16 in which the data recording device comprises a printer for printing a report of the characteristic sensed.

18. The system of claim 17 in which the report is in machine readable graphic format.

19. The system of claim 16 wherein the container carries a machine readable electronic data storage device, and in which the data recording device is adapted to transfer data regarding the selected characteristic sensed by the sensor to the electronic data storage device.

20. The system of claim 19 in which the electronic storage device comprises a non-volatile semiconductor memory.

21. A disposable plastic blood component storage container defining an interior compartment for receiving a blood component, and at least one microelectromechanical sensor carried by the container and communicating with the compartment for sensing a selected characteristic of the blood component received therein.

22. The container of claim 21 in which the sensor is adapted to sense bacterial presence or pH in the blood component just before it is administered to a patient.

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23. The container of claim 21 in which the sensor includes write once, read many times data storage, and is adapted to be read by an automated reading device.

24. A blood processing system for providing a characterized blood constituent product, the system comprising:

an apheresis device for separating one or more desired cellular blood constituents from a suspension comprising whole blood;

a first fluid flow path communicating with the apheresis device for introducing a suspension comprising whole blood into the device;

a second fluid flow path communicating with the apheresis device for withdrawing at least one desired cellular blood constituent from the device;

a container communicating with the second fluid flow path for receiving the blood constituent withdrawn from the apheresis device;

machine readable or human readable data storage media carried by the container;

at least one microelectromechanical sensor communicating with the first fluid flow path for sensing at least one characteristic of the whole blood and for generating at least one electrical signal responsive to said sensing;

at least one microelectromechanical sensor communicating with the second flow path for sensing the quantity of cellular blood constituent withdrawn from the

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apheresis device and for generating an electrical signal responsive to said sensing;

a data recorder adapted to receive the electrical signals from the sensors and to record data regarding the sensed characteristics on the data storage media, whereby a user may readily identify the sensed characteristic regarding the whole blood and the quantity of the desired cellular constituent in the container.

25. The system of claim 24 including a sensor communicating with the second fluid flow path for sensing the quantity of a non-desired biologic constituent in the flow path and generating an electrical signal responsive to the amount, the data recorder being adapted to receive such signal and record data regarding the quantity of non-desired cellular constituent in the data storage media for access by a user of the product in the container.

26. The system of claim 25 in which the non-desired biologic component is a viral constituent.

27. The system of claim 25 in which the non-desired biologic component is a cellular constituent.

28. The system of claim 27 wherein the desired cellular blood constituent is platelets or red cells and wherein the non-desired cellular constituent is white cells.

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29. The system of claim 24 further comprising a controller adapted to receive the signals from the sensors communicating with the first and second fluid flow paths and to control the apheresis device in response to one or more of such signals to provide a desired cellular blood constituent product characterized by data recorded in the data storage media in accordance with characteristics sensed by the sensors.

30. The system of claim 29 in which the desired cellular blood constituent is platelets, red cells, stem cells or white cells.

31. The system of claim 24 in which the data storage media comprises machine readable graphics carried on the container.

32. The system of claim 31 in which the machine readable graphics comprises a bar code.

33. The system of claim 24 in which the first fluid flow path communicates with the vascular system of a human donor, and the system includes means for generating a human-readable report for the donor containing selected data regarding one or more of the sensed characteristics.

34. A biological suspension processing system comprising:

a blood treatment device for treating one or more components of a biological suspension;

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a human subject;

a first fluid flow path communicating with the vascular system of the human subject and the treatment device for introducing blood from the human subject into the treatment device;

a second fluid flow path communicating with the treatment device for withdrawing a constituent of the blood from the treatment device;

a third fluid flow path communicating with the treatment device from withdrawing another constituent of the blood from the treatment device; and

at least one microelectromechanical sensor communicating with one of said fluid flow paths for sensing a selected characteristic of the fluid within the flow path.

35. The system of claim 34 in which the sensor generates a signal responsive to one or more selected characteristic of the fluid in one of the fluid flow path, the suspension treatment device including a controller adapted to receive the sensor signal and to control the treatment device in response thereto.

36. The system of claim 35 in which the third fluid flow path communicates with the human subject, the treatment device is adapted to add anticoagulant to the blood in the first fluid flow path, the selected characteristic includes the hematocrit of blood in the first fluid flow path, and the controller controls the addition of anticoagulant into the first fluid flow path.

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37. The system of claim 35 in which the controller controls the treatment device in response to the signal to avoid one or more deleterious consequences to the human subject.

38. The system of claim 35 in which the controller controls the treatment device in response to the signal to withdraw a constituent of desired quality.

39. The system of claim 35 in which the controller controls the treatment device in response to the signal to withdraw a constituent of desired quantity.

40. The system of claim 35 in which the control controls the treatment device in response to the signal to withdraw a constituent that is depleted of an undesired component.

41. The system of claim 40 in which the undesired component is white cells.

42. The system of claim 35 in which the controller controls the treatment device in response to the signal to withdraw a desired constituent.

43. The system of claim 42 in which the desired constituent is platelets.

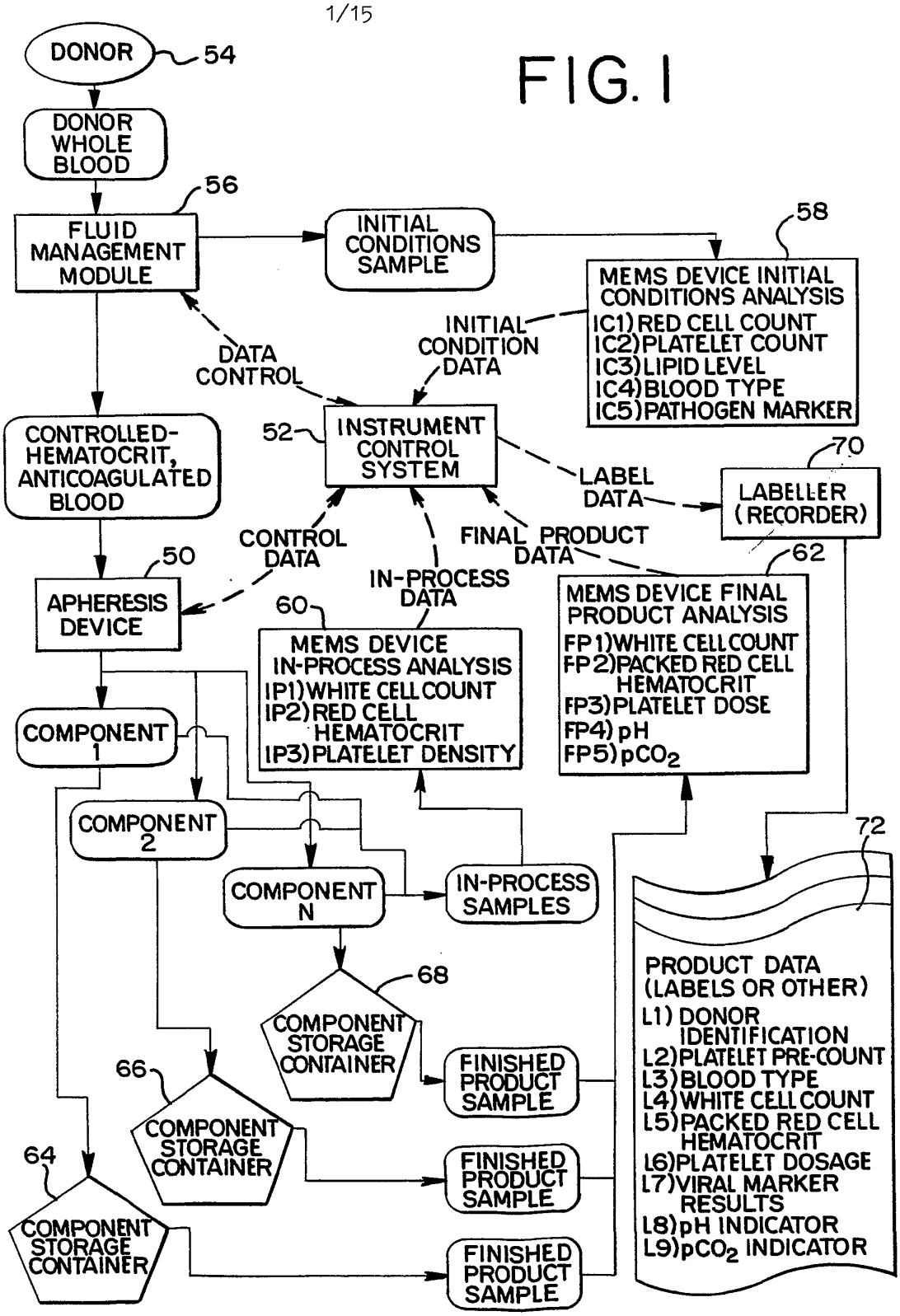
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44. The system of claim 42 in which the desired constituent is red cells or plasma.

45. The system of claim 35 in which the sensor senses platelets and the controller controls the treatment device to withdraw a selected minimum quantity of platelets.

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FIG. 1



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FIG. 2

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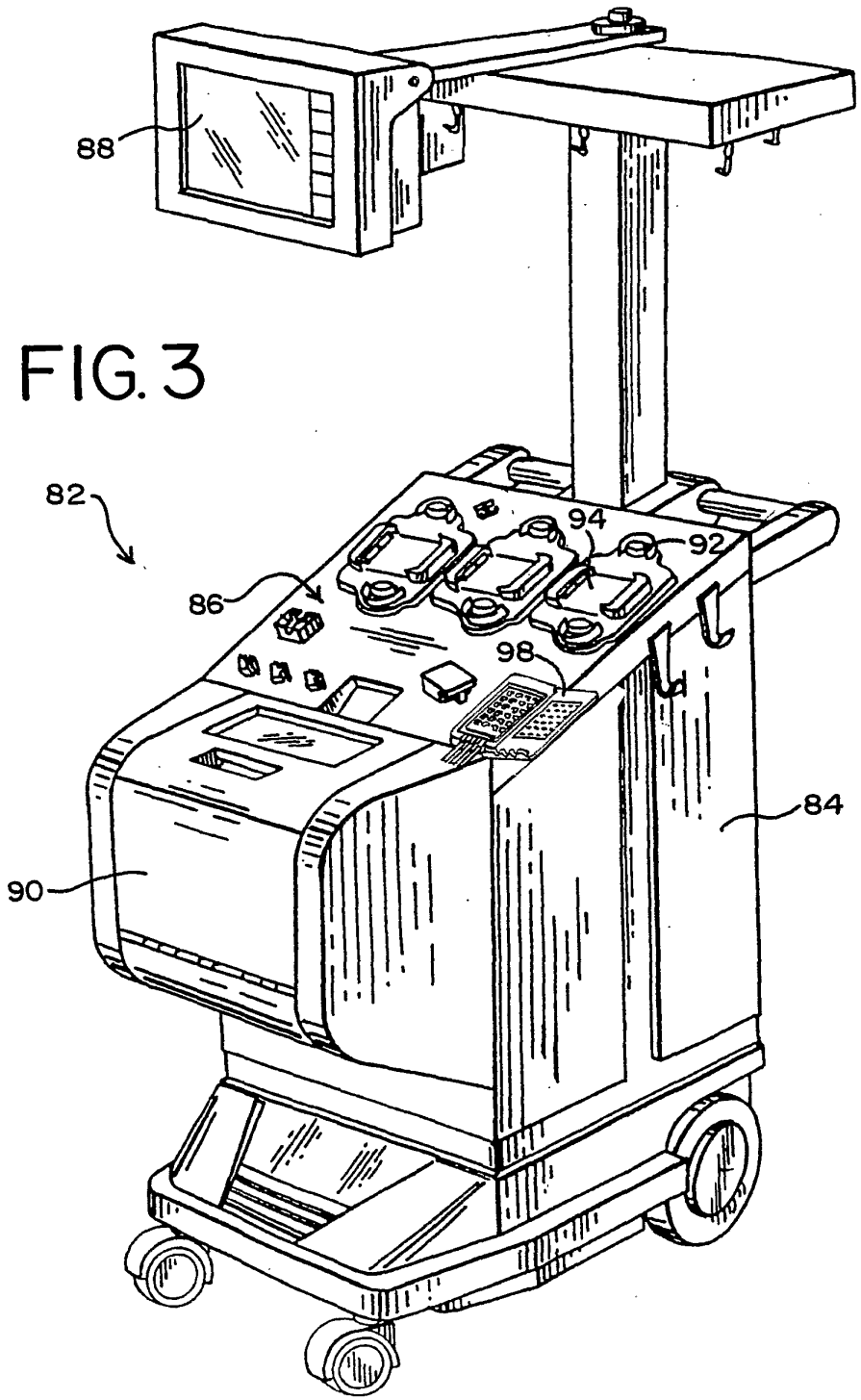


FIG. 3

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FIG. 4

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FIG. 5

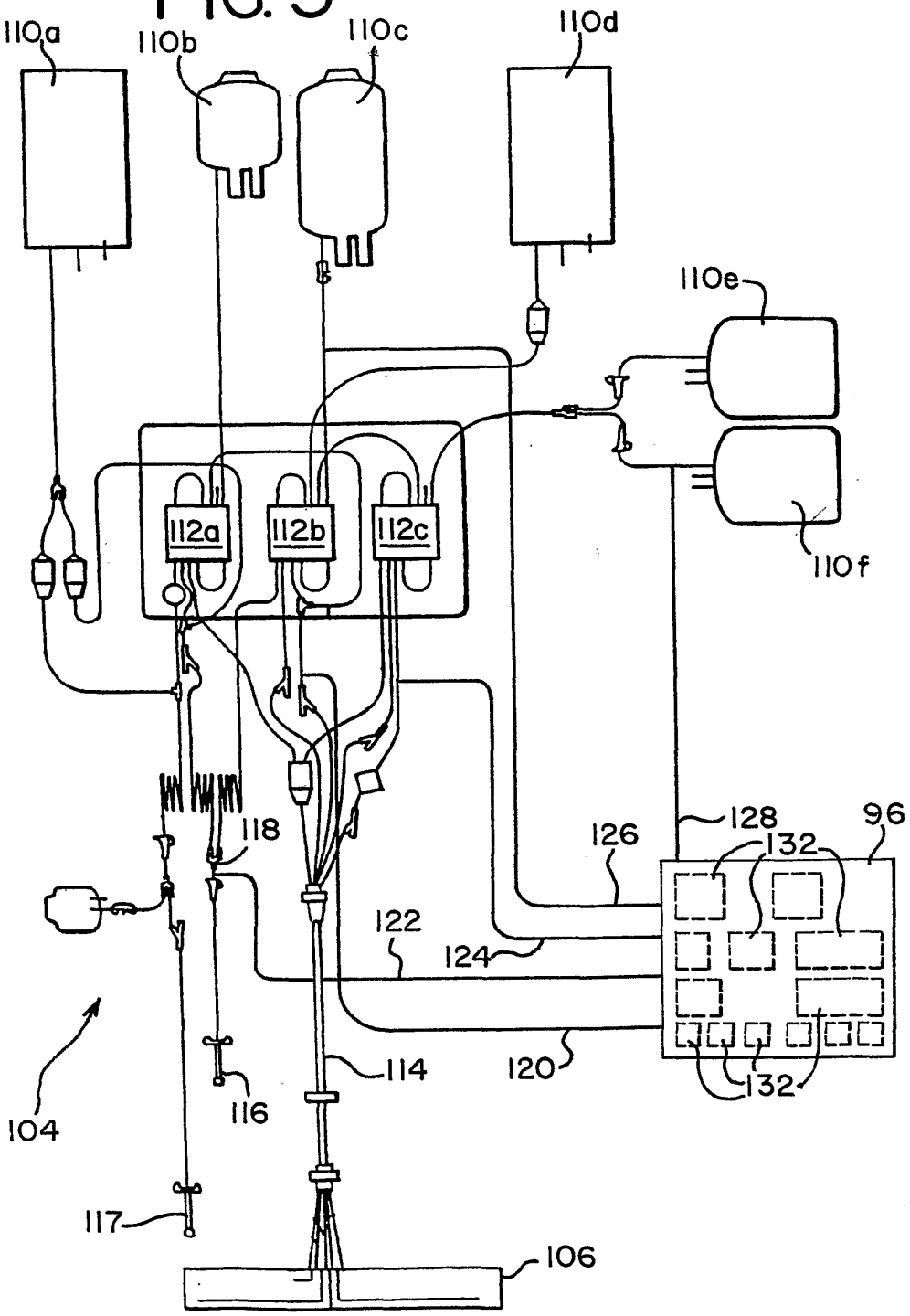
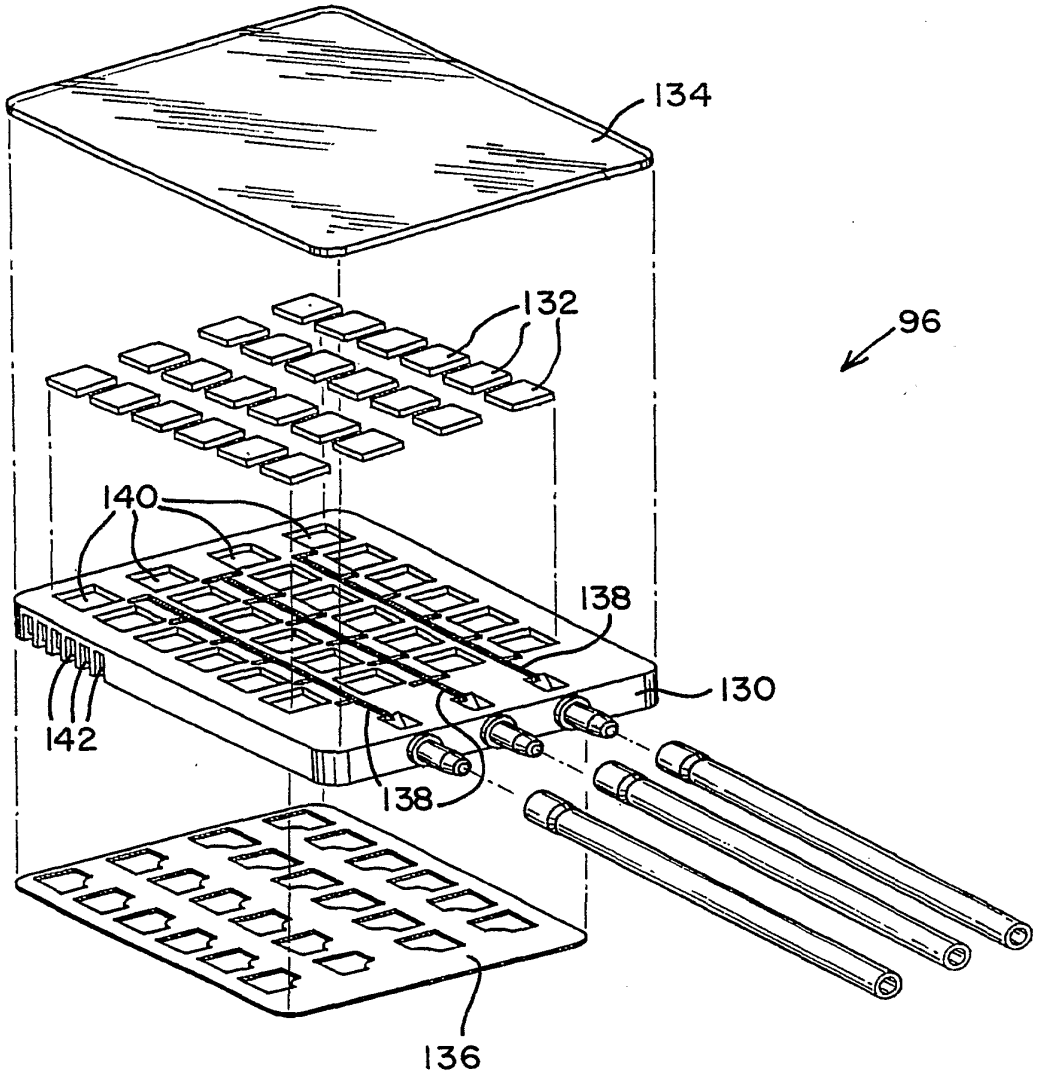

110a
110b
110c
110d
110e
110f
112a
112b
112c
118
126
128
96
132
122
124
104
114
120
116
117
106

FIG. 6



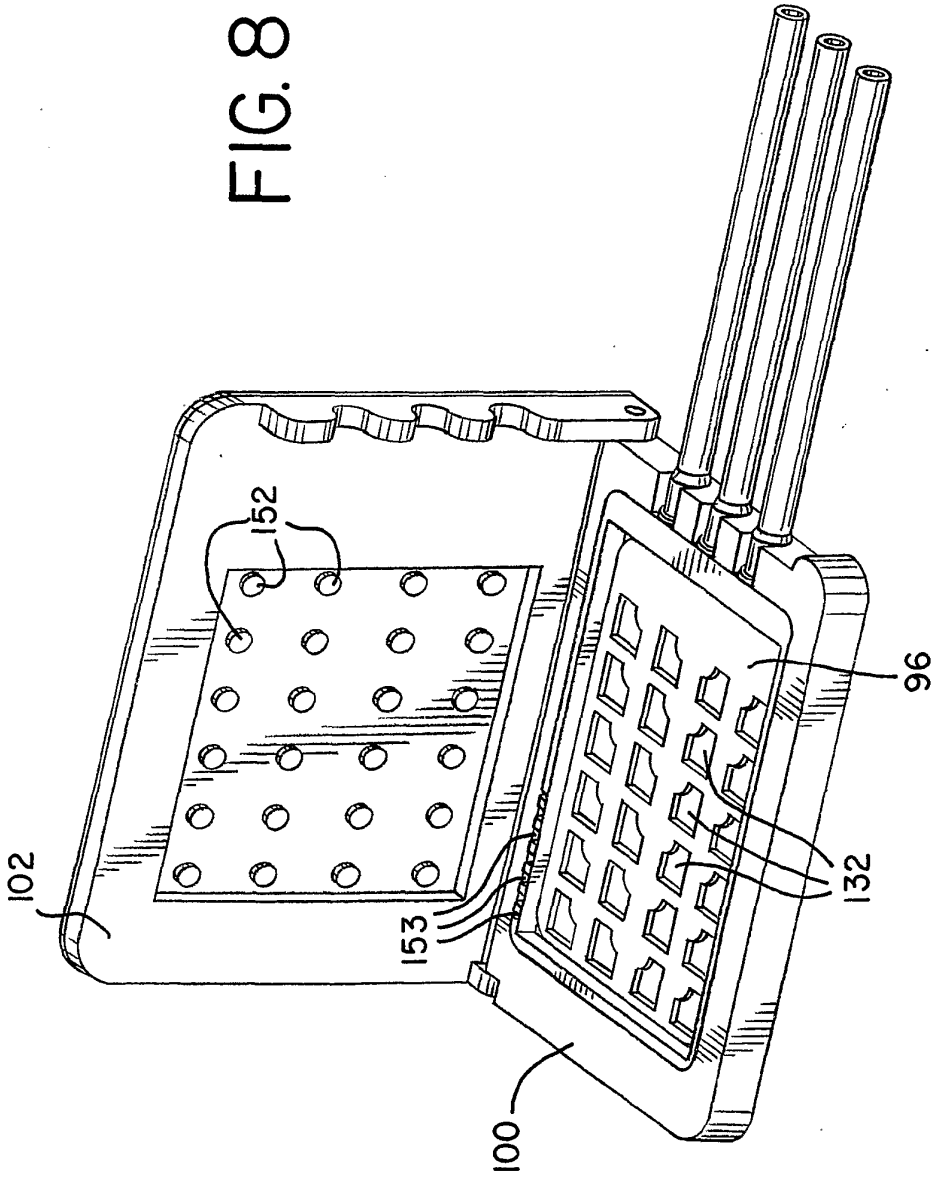
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FIG. 7A

FIG. 7B

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FIG. 8

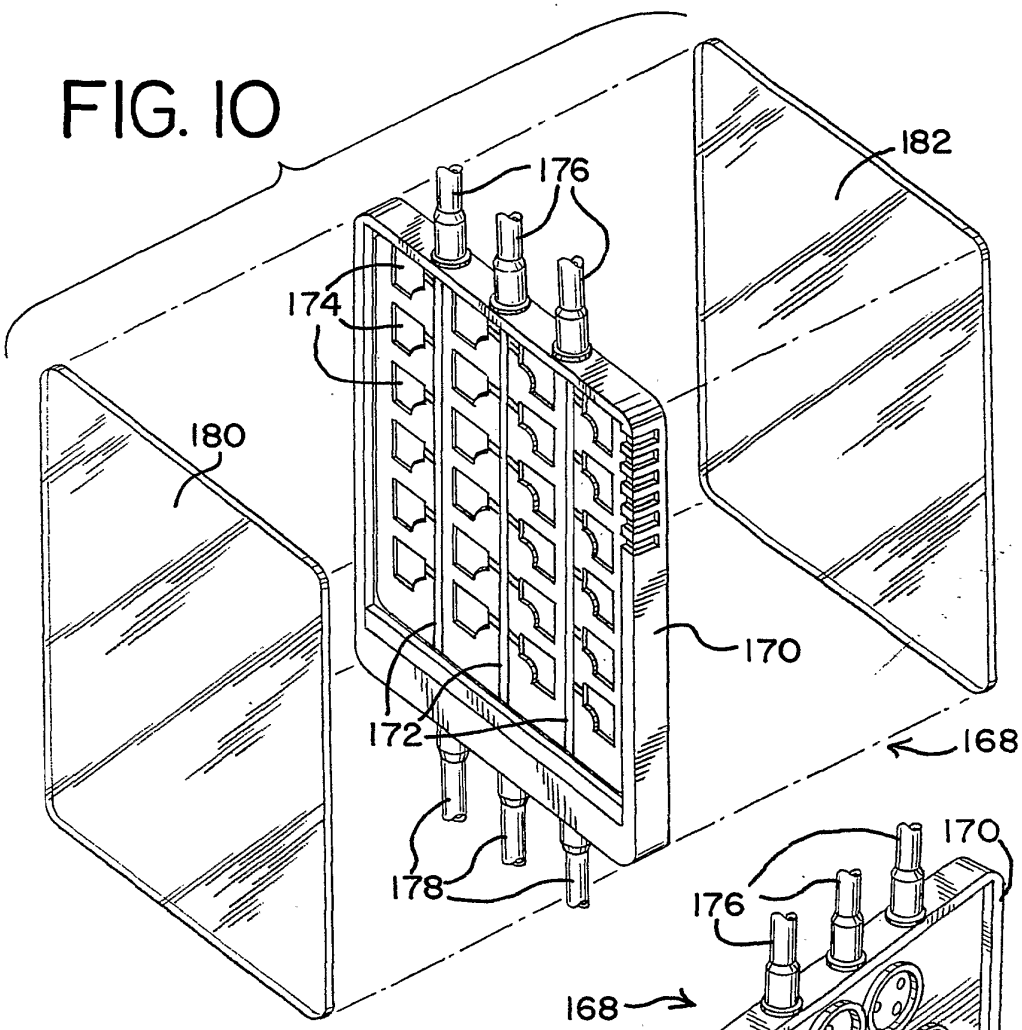


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FIG. 9

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FIG. 10



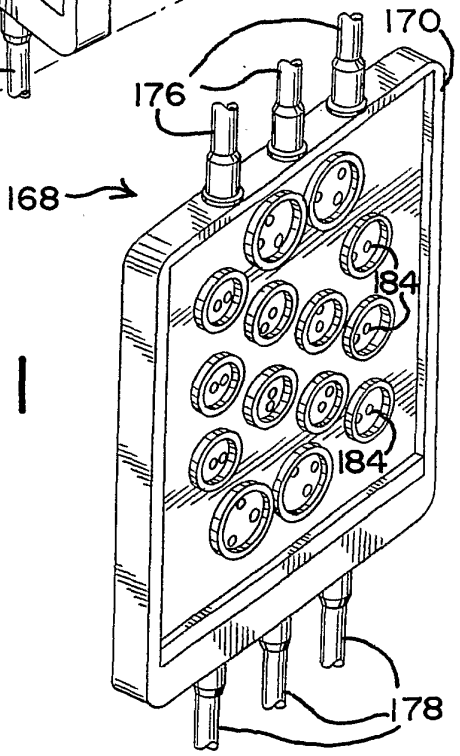


FIG. 11

FIG. 12

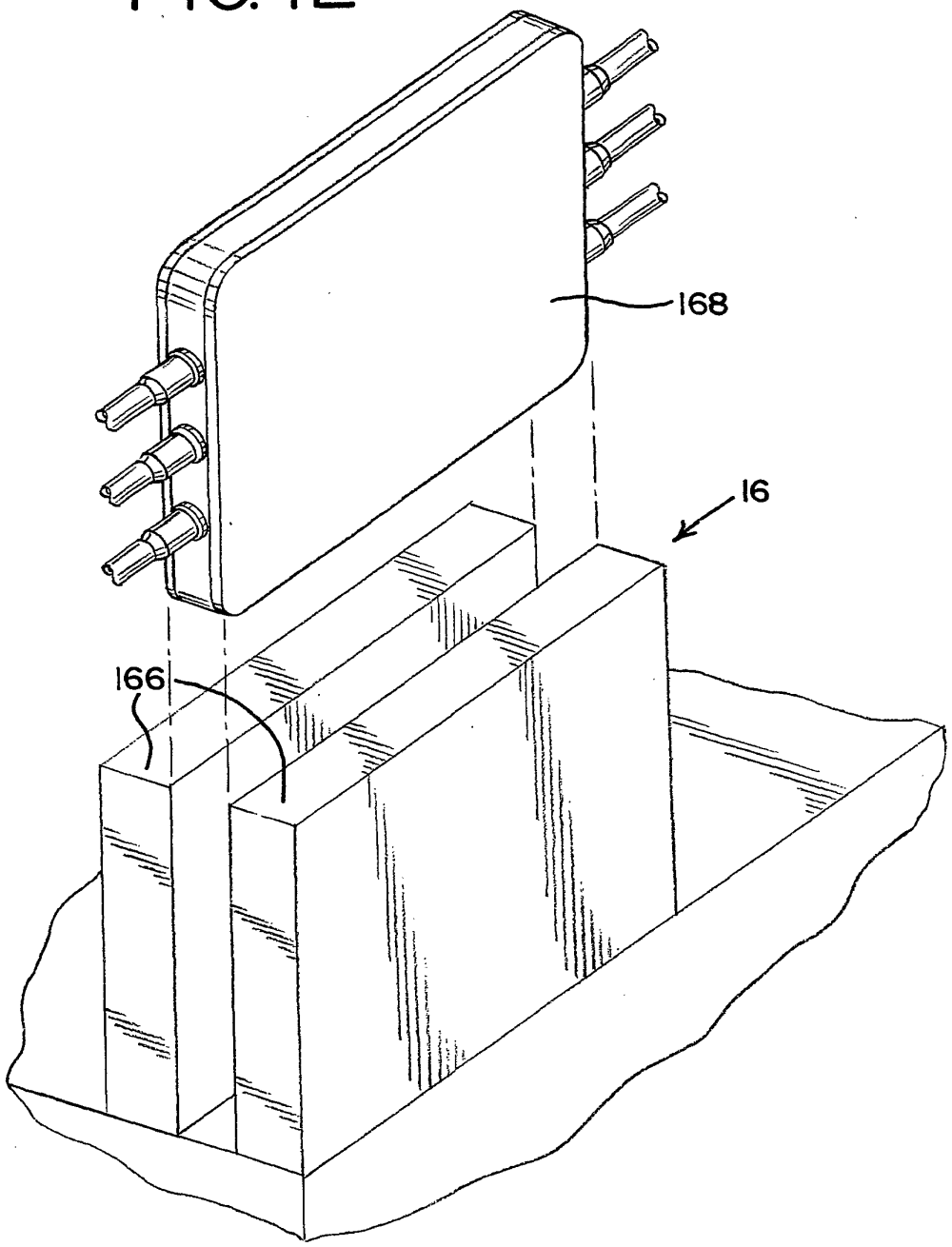


FIG. 13

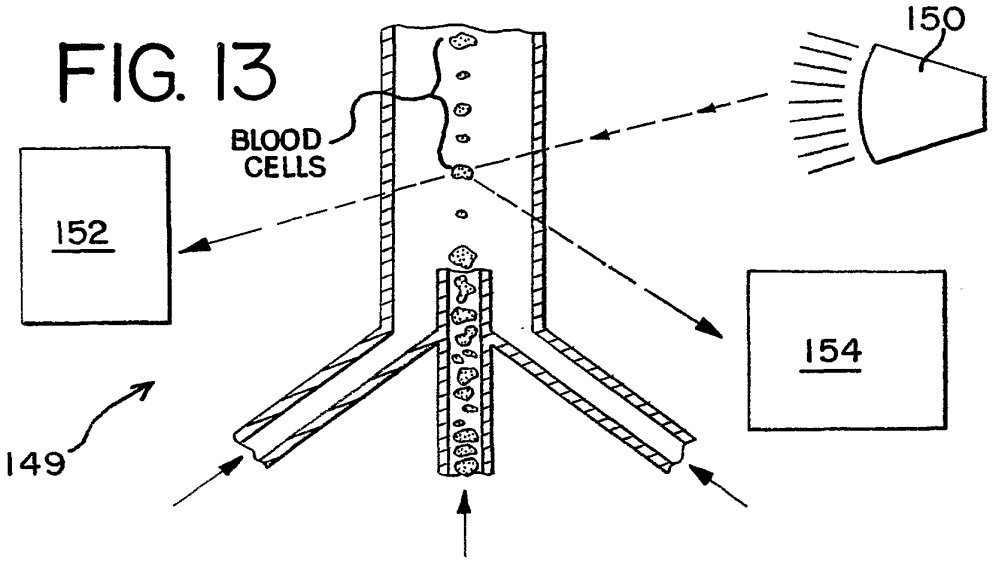


FIG. 14

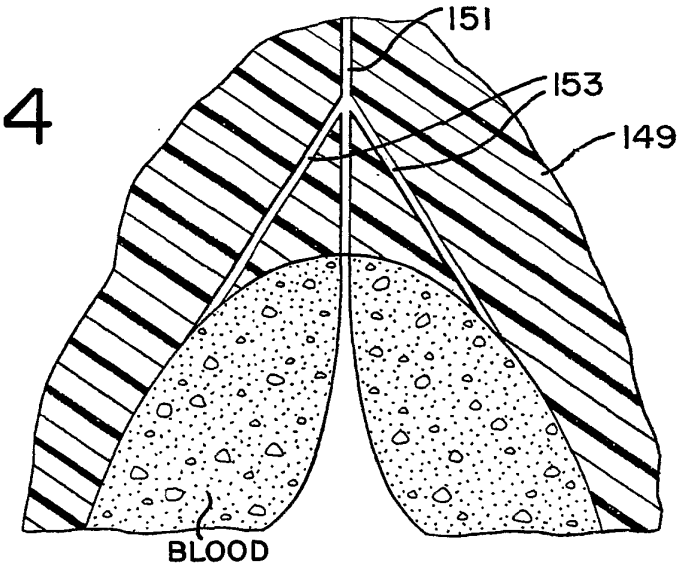


FIG. 15A

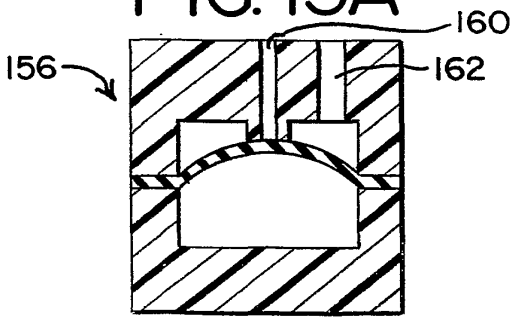


FIG. 15B

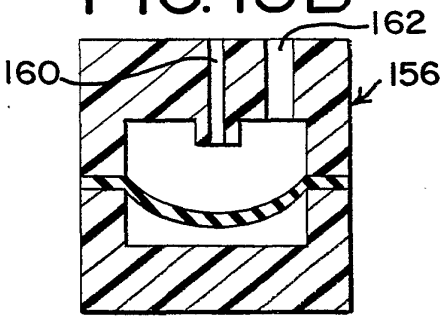


FIG. 16

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FIG. 17a

FIG. 17b

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FIG. 18A

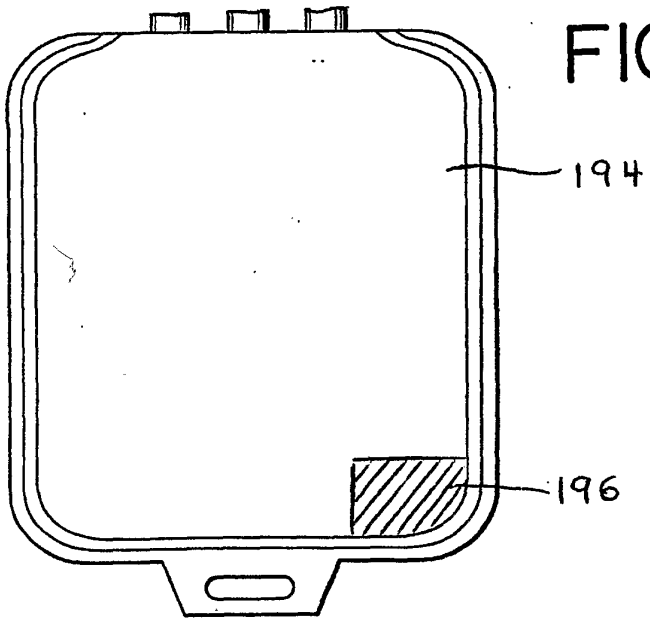
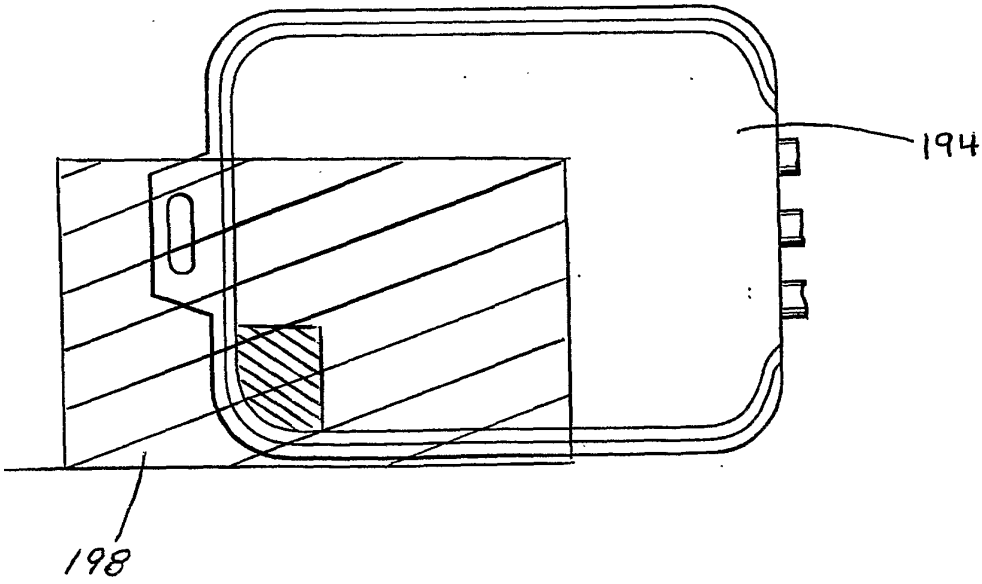


FIG. 18B



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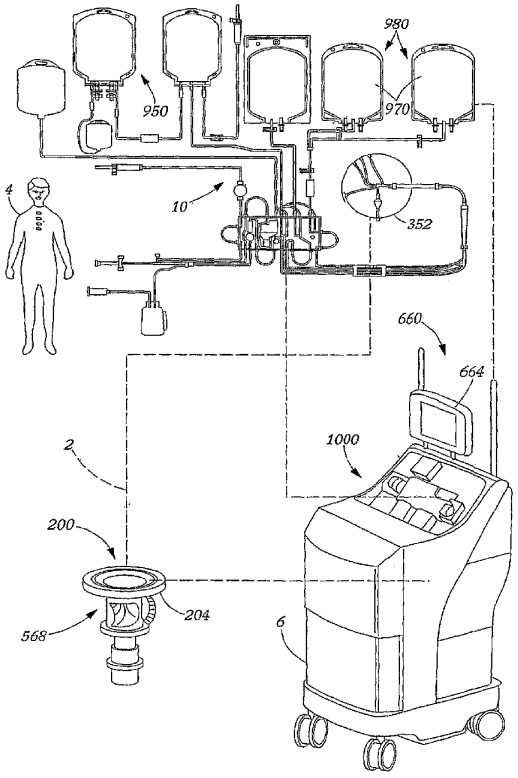
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[Continued on next page]

(54) Title: METHOD AND APPARATUS FOR LEUKOREDUCTION OF RED BLOOD CELLS



(57) Abstract: This invention relates to a method for the continuous separation of red blood cells from whole blood which includes the steps of removing the whole blood from a donor, continuously separating the whole blood into blood component layers within a separation vessel including at least a plasma layer, a buffy coat layer and a red blood cell layer, removing the plasma layer from the separation vessel, removing the buffy coat layer from the separation vessel, and removing red blood cells from the red blood cell layer which partially overlaps with the buffy coat layer to create a mononuclear cell (MNC)-reduced red blood cell layer in the separation vessel.

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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METHODS AND APPARATUS FOR LEUKOREDUCTION OF RED BLOOD CELLS

PRIORITY CLAIM

This invention claims the benefit of United States provisional application number 60/596,591 filed October 5, 2005.

FIELD OF INVENTION

The present invention relates generally to the field of extracorporeal blood processing methods which are particularly useful in blood component collection, and more particularly, the present invention relates to methods for the leukoreduction of red blood cells collected with an apheresis system.

BACKGROUND OF THE INVENTION

One well-known type of extracorporeal blood processing involves an apheresis system and/or procedure in which blood is removed from a donor or a patient (hereafter cumulatively referred to as a donor), directed to a blood component separation device (*e.g.*, centrifuge), and separated into various blood component types (*e.g.*, red blood cells, white blood cells, platelets, plasma) for collection or therapeutic purposes. One or more or all of these blood component types may be collected, and/or treated for therapeutic purposes before storage or return to a patient, while the remainder may simply be returned to the donor or patient.

A number of factors may affect the commercial viability of an apheresis system. One factor relates to the time and/or expertise required of an individual to prepare and operate the apheresis system. For instance, reducing the time required by the operator to complete an entire collection procedure, as well as reducing the complexity of these actions, can increase productivity and/or lower the potential for operator error. Moreover, reducing the dependency of the system on the operator may further lead to reductions in the credentials desired/required for the operators of these systems.

Donor-related factors may also impact the commercial viability of an apheresis system and include, for example, donor convenience and donor comfort. For instance, donors/patients may have a limited amount of time which may be committed to a donation or therapeutic procedure. Consequently, once at the collection or treatment facility, the amount of time which is actually spent collecting and/or treating blood components is an important consideration. This also relates to donor comfort as the actual collection procedure may be

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somewhat discomforting because at least one and sometimes two access needles are disposed in the donor throughout the procedure.

Performance-related factors also affect the commercial viability of an apheresis system. Performance may be judged in terms of the collection efficiency of the apheresis system, which may impact or improve product quality and/or may in turn reduce the amount of processing time and thus decrease operator burden and increase donor convenience. The collection efficiency of a system may be gauged in a variety of ways, such as by the amount of a particular blood component type which is collected in relation to the quantity of this blood component type which passes through the apheresis system. Individual characteristics of the donor also contribute to the performance of apheresis systems, for example, some donors have greater percentages of certain blood cell types than other donors.

Performance may also be evaluated based upon the effect which the apheresis procedure has on the various blood component types. For instance, it is desirable to minimize the adverse effects on the blood component types as a result of the apheresis procedure (*e.g.*, reduce platelet activation).

Another performance-related factor is the end quality of the collected blood component. For example, if red blood cells are the component to be collected, it is generally desirable that such red blood cells be leukoreduced by the removal of white blood cells or leukocytes. Contaminating white blood cells can present problems to the ultimate recipient of the collected blood component, by provoking immunogenic reactions and viral diseases.

Conventionally, filters have been used to remove leukocytes from collected blood products or components. For example, U.S. Patent No. 5,954,971 discloses the use of a filter with an apheresis system for filtering a diluted blood component prior to collection. Other distinctive methods have also been used, and these have generally dictated special preliminary steps such as pre-chilling and/or overnight storage of collected components prior to filtration. Another distinct conventional filtration step is the venting or air handling/re-circulation or by-passing at the end of the filtration procedure which had been deemed important for substantial recovery of a remainder portion of the blood component to be processed through a red blood cell filter.

Leukocytes are made up of mononuclear cells and polymorphonuclear cells. Mononuclear cells consist of lymphocytes, monocytes and stem cells. Polymorphonuclear cells consist of granulocytes, eosinophils and basophils. As discussed above, a performance related factor, which may affect apheresis efficiency, is the amount of a particular cell component a donor has. For example, it has been observed that if a donor has a high

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percentage of lymphocytes as compared to other white blood cell subtypes, (or has a high lymphocyte load), leukofiltration is not as effective as in donors who do not have such high lymphocyte loads. There is often a high residual population of lymphocytes which are not removed via filtration and which contaminate the separated red blood cell component.

The present invention is directed towards removing mononuclear cells in an apheresis procedure before leukoreducing the separated blood components.

SUMMARY OF THE INVENTION

The present invention relates to the extracorporeal separation and collection of red blood cells using an apheresis blood processing system. More particularly, this invention relates to a method for the continuous separation of red blood cells from whole blood wherein the portion of the red blood cells which are closest to the layer containing lymphocytes are collected within the blood processing vessel and are returned to the donor, along with the lymphocytes in the buffy coat, leaving the mononuclear cell reduced red blood cells within the separation vessel.

According to the present invention, before the ultimate collection of the red blood cells in the collection container, the MNC-reduced red blood cells are filtered through a filtration device. This filtration preferably occurs during the overall separation procedure, although it could be initiated soon after and as part of the commencement of the collection procedure. Nevertheless, the separation procedure may be a continuous or batch process, and in either case, the filtration occurs upon or soon after removal of the separated high hematocrit MNC-reduced red blood cells from the processing vessel, yet preferably concurrently with or soon after the overall separation process.

These and still further aspects of the present invention are more particularly described in the following description of the preferred embodiments presented in conjunction with the attached drawings which are described briefly below.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic view of one embodiment of an apheresis system which can be used in or with the present invention.

Fig. 2 is a partial cross-sectional view of a portion of the separation vessel.

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Fig. 3 illustrates a tubing and bag set including an extracorporeal tubing circuit, a cassette assembly, and a filter and collection bag assembly for use in or with the system of Fig. 1 pursuant to the present invention.

Fig. 4 illustrates a cassette assembly similar to that shown in the set of Fig. 3.

Fig. 5 illustrates a filter and collection bag assembly similar to that shown in the set of Fig. 3.

Figs. 6A and 6B illustrate alternative filter and collection bag assemblies also usable in a tubing and bag set like that shown in Fig. 3.

Fig. 7 is a schematic view of an apheresis system according to the present invention.

Fig. 8 is a schematic view of an alternative apheresis system also according to the present invention.

Fig. 9 is a schematic view of an alternative apheresis system according to the present invention.

DETAILED DESCRIPTION

The present invention will be described in relation to the accompanying drawings which assist in illustrating the pertinent features hereof. Generally, the primary aspects of the present invention relate to both procedural and structural improvements in or a sub-assembly for use with a blood apheresis system. However, certain of these improvements may be applicable to other extracorporeal blood processing applications whether any blood components are returned directly to the donor or otherwise; and such are within the scope of the present invention as well.

It should be noted that like elements are depicted by like numbers.

A preferred blood apheresis system **2** for use in and/or with the present invention is schematically illustrated in Fig. 1. System **2** provides for a continuous blood component separation process. Generally, whole blood is withdrawn from a donor **4** and is substantially continuously provided to a blood component separation device **6** where the blood is continuously separated into various component types according to density and at least one of these blood component types is preferably continuously collected from the device **6**. One or more of the separated blood components may then either be provided for collection and subsequent use by another through transfusion or may be returned to the donor **4**.

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Therapeutic treatment and near immediate return of certain separated blood components is a viable alternative use hereof as well. It is also understood that for therapeutic treatment the blood may be separated into components with filtration using the principles of the instant invention and as described below at a patient's bedside for return to such patient.

In the blood apheresis system **2**, blood is withdrawn from the donor **4** and directed through a preconnected extracorporeal tubing circuit **10** and, in one embodiment, a blood processing vessel **352** which together define a closed, sterile and disposable system. The set **10** is preferably disposable and is adapted to be mounted on and/or in the blood component separation device **6**. The separation device **6** preferably includes a pump/valve/sensor assembly **1000** for interfacing with the extracorporeal tubing circuit **10**, and a channel assembly **200** for interfacing with the disposable blood processing vessel **352**.

The channel assembly **200** may include a channel housing **204** which is rotatably interconnected with a rotatable centrifuge rotor assembly **568** which provides the centrifugal forces required to separate blood into its various blood component types by centrifugation. The blood processing vessel **352** may then be interfitted within the channel housing **204**. When connected as described, blood can then be flowed substantially continuously from the donor **4**, through the extracorporeal tubing circuit **10**, and into the rotating blood processing vessel **352**. The blood within the blood processing vessel **352** may then be continuously separated into various blood component types and at least one of these blood component types (platelets, plasma, lymphocytes or red blood cells) is preferably continually removed from the blood processing vessel **352**. Blood components which are not being retained for collection or for therapeutic treatment are preferably also removed from the blood processing vessel **352** and returned to the donor **4** via the extracorporeal tubing circuit **10**. Note, various alternative apheresis systems (not shown) may also make use of the present invention; including batch processing systems (non-continuous inflow of whole blood and/or non-continuous outflow of separated blood components) or smaller scale batch or continuous RBC/plasma separation systems, whether or even if no blood components may be returned to the donor.

Operation of the blood component separation device **6** is preferably controlled by one or more processors included therein, and may advantageously comprise a plurality of embedded computer processors to accommodate interface with ever-increasing PC user facilities (e.g., CD ROM, modem, audio, networking and other capabilities). Relatedly, in order to assist the operator of the apheresis system **2** with various aspects of its operation, the blood component separation device **6** preferably includes a graphical interface **660** with an interactive touch screen **664**.

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Further details concerning the operation of a preferred apheresis system, such as the Gambro Trima® System and the Trima Accel® System (available from Gambro BCT, Inc., Lakewood, Colorado) may be found in a plurality of publications, including, for example, WO99/11305 and U.S. Patents No. 5,653,887; No. 5,676,644; No. 5,702,357; No. 5,720,716; No. 5,722,946; No. 5,738,644; No. 5,750,025; No. 5,795,317; No. 5,837,150; No. 5,919,154; No. 5,921,950; No. 5,941,842; No. 6,129,656; and No. 6,730,055 among numerous others. The disclosures hereof are incorporated herein as if fully set forth. A plurality of other known apheresis systems may also be useful herewith, as for example, the Baxter CS3000® and/or Amicus® and/or Autopheresis-C® and/or Alyx systems, and/or the Haemonetics MCS® or MCS®+ and/or the Fresenius COM.TEC™ or AS-104™ and/or the system described in Patent No. 6,773,389.

Separation Vessel

Fig. 2 schematically illustrates a portion of the separation vessel **352**. Fig. 2 also illustrates an inflow tube **36** for conveying the whole blood to be separated into the separation vessel **352**; first, second, and third collection lines **64**, **62**, **68** for removing separated substances from the separation vessel **352**; and an interface control line **44** for adjusting the level of an interface between separated substances in the vessel **352**. Preferably, the separation vessel **352** forms what is known as a single stage component separation area rather than forming a plurality of such stages. In other words, each of the components separated in the vessel **352** are collected and removed in only one area of the vessel **352**. In addition, the separation vessel **352** includes a substantially constant radius except in the outlet portion **51** where the outer wall of the outlet portion is preferably positioned further away from the axis of rotation to allow for the ports **56**, **58**, **60**, and **61** be positioned at different radial distances and to create a collection pool with greater depth for the high density red blood cells.

Although the ports **56**, **58**, and **60** and lines **62**, **64**, and **68** are referred to as being "collection" ports and lines the substances removed through these ports and lines can be either collected or reinfused back into a donor.

The separation vessel **352** has a generally annular flow path **46** and includes an inlet portion **48** and outlet portion **51**. A wall **52** prevents substances from passing directly between the inlet and outlet portions **48** and **51** without first flowing around the generally annular flow path **46** (e.g., counterclock-wise as illustrated by arrows in Fig. 2).

Although Fig. 2 shows the inlet portion **48** as having a wide radial cross-section, the outer wall of the inlet portion **48** can be spaced closer to the inner wall of the inlet portion **48**

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and/or tapered. An inlet port **54** of inflow tube **36** allows for flow of whole blood, into the inlet portion **48** of separation vessel **352**. During a separation procedure, substances entering the inlet portion **48** follow the flow path **46** and stratify according to differences in density in response to rotation of the rotor **568**. Preferably, the flow path **46** between the inlet and outlet portions **48** and **50** is curved and has a substantially constant radius. In addition, the flow path **46** is placed at the maximum distance from the axis of rotation. This shape ensures that components passing through the flow path **46** encounter a relatively constant gravitational field and a maximum possible gravitational field for the rotor **568**.

The separated substances flow into the outlet portion **51** where they are removed via first **56**, second **58**, and third **60** collection ports respectively, of first **62**, second **64**, and third **68** collection lines. Separated substances may also be removed by an interface control port **61** of the interface control line **44**. As shown in Fig. 2, the first **56**, second **58**, and third **60** ports are positioned at varying radial locations on the rotor **568** to remove substances having varying densities. The second collection port **58** is farther from the axis of rotation than the first and third ports **56** and **60** to remove the most dense substances separated in the separation vessel **352**, such as red blood cells. The third port **60** is located closer to the axis of rotation than the first and second ports **56** and **58** to remove the least dense substances separated in the separation vessel **352**, such as plasma. If desired, the first collection port **56** may be used to remove substances having a medium density such as platelets.

The outlet portion **51** includes a barrier **38** for substantially blocking flow of the intermediate density substances, such as the buffy coat, which as discussed above, consists of white blood cells and platelets. Preferably, the barrier **38** extends completely across the outlet portion **51** in a direction generally parallel to the axis of rotation. The first collection port **56** is positioned immediately upstream of barrier **38**, downstream of the inlet portion **48**, to collect the intermediate density substances blocked by the barrier **38**.

Radially inner and outer edges of the barrier **38** are spaced from radially inner and outer walls of the separation vessel **352** to form a first passage **40** for collection of lower density substances if desired, such as plasma, at a radially inner position in the outlet portion **51** and a second passage **66** for higher density substances, such as red blood cells, at a radially outer position in the outlet portion **51**. The second and third collection ports **58** and **60** are positioned downstream of the barrier **38** to collect the respective low and high density substances passing through the first and second passages **40** and **66**.

The interface port **61** is also positioned downstream of the barrier **38**. During a separation procedure, the interface port **61** removes the least dense of the most dense

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substances in the outlet portion **51** to thereby control the radial position of the interface between the buffy coat layer **82** and the red blood cell layer **86** and plasma layer **84** in the outlet portion **51**.

First port **56** may be used to remove platelets if desired, or may be used to remove the buffy coat layer **82** and a portion of the red blood cell layer next to the buffy coat layer which may contain some contaminating white blood cells. Although the second and third collection ports **58** and **60** and the interface control port **61** are shown downstream of the barrier **38**, one or more of these elements may be upstream of the barrier **38**. In addition, the order of the collection ports **56, 58, 60**, and the interface port **61** along the length of the outlet portion **51** could be changed. Further details concerning the structure and operation of the separation vessel **352** is described in U.S. Patent No. 6053856 to Hlavinka, which has been incorporated herein by reference.

~~Disposable Set: Extracorporeal Tubing Circuit~~

As illustrated in Figs. 3 and 4, a preconnected extracorporeal tubing circuit **10** is shown which may include a cassette assembly **110** and a number of tubing/collection assemblies **20, 50, 60, 100, 90, 950** and **980** interconnected therewith. Preferably, a blood removal/return tubing assembly **20** provides a single needle interface between a donor **4** (see Fig. 1) and the remainder of the tubing circuit **10** (although a two-needle set-up may also be used, not shown). At least two lines **22, 24** are preferably provided in assembly **20** (see Fig. 4) for removal of blood from and return of components to the donor. This embodiment includes a cassette assembly **110**, which is interconnected between the tubing assembly **20** which connects the donor **4** thereto, and blood inlet/blood component tubing line sub-assembly **60** which provides the interface between cassette assembly **110** and blood processing vessel **352**. Three lines **62, 64** and **68** are shown in Figs. 3 and 4 for transport of blood and components to and from the processing vessel **352**. An anticoagulant tubing assembly **50**, a plasma collection tubing and bag assembly **90**, a red blood cell collection assembly **950**, a vent bag tubing line sub-assembly **100**, and an additive solution assembly **980** are also interconnected with cassette assembly **110** in this embodiment. As will be appreciated, the extracorporeal tubing circuit **10** and blood processing vessel **352** are pre-interconnected to combinatively yield a closed, pre-sterilized disposable assembly for a single use.

The disclosures of the above-listed patents include numerous further details of an apheresis system for use with the present invention. Such details are not repeated here except generally for certain of those which may relate particularly to red blood cell (hereafter, RBC) collection and/or other RBC processes. Other blood component separation and collection

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processes are discussed at various points herein where they may be involved in or somewhat related to features of the present disclosure.

For a particular example, emanating from vessel **352** is an RBC outlet tubing line **64** of the blood inlet/blood component tubing assembly **60** which is interconnected with integral RBC passageway **170** of cassette **115** of cassette assembly **110** (see Figs. 3 and 4). The integral RBC passageway **170** includes first and second spurs **170a** and **170b**, respectively. The first spur **170a** is interconnected with RBC return tubing loop **172** to return separated RBCs to a donor **4** as well as the buffy coat and the red blood cells located next to the buffy coat which contain at least some white blood cells. For such purpose, the RBC return tubing loop **172** is preferably interconnected to the top of a blood return reservoir **150** of the cassette assembly **110**. The second spur **170b** may, as preferred herein, be connected with an RBC collection tubing assembly **950** (see Figs. 3 and 4, for example) for collecting RBCs during use. RBC collection tubing and bag assembly **950** preferably includes RBC collector tubing line **951** which communicates with spur **170b**, a second collector tubing line **952** communicating with line **951**, an RBC filtration sub-assembly including an RBC leukoreduction filter **960**, an RBC collection reservoir or bag **954**, and an air removal bag **962**. Bag **954** is connected to the filter **960** by tubing line **965**. An optional clamp **966** (see Fig. 5) may be included on line **965**. The air removal bag **962** is attached to the RBC collection bag **954** by a tubing line **961** which may have an optional clamp **963**, (Figure 5), attached thereto. The RBC collection tubing line, filter and container sub-assembly **950** is a preconnected part of the disposable assembly **10**.

An alternative tubing set filter and collection bag assembly **950a** is shown in Fig. 6A and includes a second collection bag **954a** connected via a Y-type of connection **991** to filter **960**, via the branch tubing line **965a**. A further air bag **962a** is preferably connected to the second bag **954a** via a tubing line **961a**. Slide clamps **966a** and **966b** are used to direct flow to the desired bag. More details particularly as to the use hereof will be set forth below.

A further alternative embodiment is shown in Fig. 6B, which embodiment is an assembly **950b** which also includes a second collection bag **954a** with associated componentry (e.g., air bag **962a**, etc.), and a second filter **960a**, in addition to filter **960** described above. Filter 960a is connected via lines **952a** and **965a** between bag **954a** and incoming line **952**. A branch or Y connector **991a** allows for split flows between branch **952a** and branch **952b** which leads to the first filter **960**. Also slide clamps **966a** and **966b** may again be used to direct the flow to the respective filters.

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The embodiment shown in Fig. 1 includes a connected pair of additive solution bags **970**; however the alternative embodiments of Figs. 3 and 4 preferably have an additive fluid tubing assembly **980** for attachment to and delivery of additive fluid(s) such as sterile saline solution(s), or additive plasma or additive storage solution, for example, to the collected or collecting product in bag system **950** as described in further detail below. As shown in Figs. 3 and 4, the additive fluid assembly **980** includes at least an additive fluid inlet tubing line **982** attached to the cassette **110** in fluid communication with an internal additive fluid passageway **140c** which is in turn connected to an additive fluid tubing loop **142** which is connected back to the cassette **110** and an internal additive fluid passageway **140d**. Two further internal passageways or spurs **144c** and **144d** and tubing **145** and **146** are also shown in the alternative embodiment of Figs. 3 and 4. These passageways **140c**, **140d** and **144c**, **144d** and tubing loops/tubing **142**, **145** and **146** are as shown, preferably similar structurally to the platelet passageways described in various of the above-referenced U.S. Patents, though they may take other forms as well. Indeed, the alternative internal passageway **144d** and tubing **145** of the embodiment of Figs. 3 and 4 may as shown, be blocked off to disallow any fluid flow therein or therethrough. Note, although no outlet tubing line is connected thereto in this embodiment, these flow channels could correspond to a platelet or other blood component collection line as shown in Fig. 2. Though similar structurally in many ways, when referring to the embodiment of Figs. 3 and 4, the component elements thereof will be referred to as additive fluid elements as opposed to platelet assembly components. This alternative naming convention will also be used for other component elements which could be referred to in connection with either the platelet assembly or the additive fluid assembly; for example, the platelet or additive fluid inlet pump (described in the art) will hereafter be referred to as an additive solution pump. Note, one further distinction is the connection of tubing line **146** to tubing lines **951** and **952** via connector **979**.

The additive fluid assembly **980** further preferably includes one or more (as shown) spike assemblies **984a**, **984b** with respective spikes **985a**, **985b** and associated sterile barrier devices **986a**, **986b** and tubing connection lines **988a**, **988b** which may be connected to tubing line **982** via a Y-connector **989** as shown. Note, it may be that only one of one or more of the above devices may be necessary; e.g., perhaps only one sterile barrier device may be used even with more than one bag of solution. One or more slide clamp(s) **990** and/or a level sensing or fluid detection apparatus **995** may also be included.

The cassette assembly **110** further includes a pump-engaging, additive fluid inlet tubing loop **142** interconnecting the first respective integral additive fluid passageway **140c** and a second integral additive fluid passageway **140d**. The second integral or additive fluid passageway **140d** includes first and second spurs **144c**, **144d**, respectively. The second spur

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144d of the second additive fluid passageway **140d** (Figs. 3 and 4) is interconnected with additive fluid tubing **146** to deliver additive fluid through the RBC outlet line **952** for ultimate delivery to the filter **960** and then to the bag **954**. The cassette member **115** also includes an integral frame corner **116** defining a window **118** therethrough. The frame corner **116** includes access openings in window **118** for receiving and orienting the tubing segments including, for example, connector **145** and additive solution tubing **146** in predetermined spaced relationships within window **118** for ultimate engagement with a valve/clamp member on apheresis device **6**. Such a valve/clamp will, when activated, control flow through loop **142**.

In an intervening portion of the cassette **115**, a plasma tubing **68** of blood inlet/blood component tubing assembly **60** (see Figs. 3 and 4) interconnects with a first integral plasma passageway **160a** (see Fig. 4) of cassette assembly **110** (note, this is preferably a plasma collection sub-system; however, other components such as platelets could alternatively be collected here or with a similar arrangement). Cassette assembly **110** further includes a pump-engaging, plasma tubing loop **162** interconnecting the first integral plasma passageway **160a** and a second integral plasma passageway **160b**. The second integral plasma passageway **160b** includes first and second spurs **164a** and **164b**. The first spur **164a** is interconnected to the plasma collection tubing assembly **90** via tubing line **92**. The plasma collection tubing assembly **90** may be employed to collect plasma during use and includes plasma collector tubing **92** and plasma collection bag **94**. A slide clamp **96** (see Fig. 3) may be provided on plasma collector tubing **92**. The second spur **164b** of the second integral plasma passageway **160b** is interconnected to a plasma return tubing loop **166** to return plasma to donor/patient **4**. For such purpose, the plasma return tubing loop **166** is interconnected to the top of the blood return reservoir **150** of the cassette assembly **110**. As is understood, one or more types of uncollected blood components, e.g., plasma and/or platelets, collectively referred to as return blood components, will cyclically accumulate in and be removed from reservoir **150** during use. Here also, valve/clamp access is made through the frame **116** within window **118** of cassette assembly **110** to maintain the plasma collector tubing **92** and plasma return tubing loop **166** in a predetermined spaced relationship within window **118** for flow control therethrough.

Most portions of the tubing assemblies **20, 50, 60, 90, 100, 950, 950a, 950b** and/or **980** and cassette assembly **110** are preferably made from plastic components including, for example, polyvinyl chloride (PVC) tubing lines, that may permit visual observation and monitoring of blood/blood components therewithin during use. It should be noted that thin-walled PVC tubing may be employed for approved, sterile docking (i.e., the direct connection of two pieces of tubing line) for the RBC collector tubing lines **952** and **965**, as may be

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desired and/or for an RBC storage solution spike assembly **980**. In keeping with one aspect of the invention, all tubing lines are preconnected before sterilization of the total disposable assembly to assure that maximum sterility of the system is maintained. Note, a highly desirable advantage to preconnection of all of the elements of the tubing circuit including the filter and collection bag sub-assembly **950** involves the complete pre-assembly and then sterilization hereof after pre-assembly such that no sterile docking is later necessary (spike addition of storage solution excepted). Thus, the costs and risks of sterile docking are eliminated. Alternatively, thicker-walled PVC tubing may be employed for approved, sterile docking RBC collector tubing lines **952** and/or **965**, *inter alia*.

As mentioned, a cassette assembly **110** in the embodiment of Figure 4, may be mounted upon and operatively interface with the pump/valve/sensor assembly **1000** of a blood component separation device **6** during use. Further details of an apheresis system set-up including the loading and interaction of a disposable assembly **8/10** with a blood component separation device **6**, may be found in the above-listed patents, inter alia, and are not exhaustively repeated here.

Operation of Extracorporeal Tubing Circuit and Blood Component Separation Device

Priming and various other operations of the apheresis process are preferably carried out as set forth in the above-listed patents, inter alia. However, certain basic features are also described generally here with particular reference to the schematic diagrams of Figs. 7, 8, and 9, as well as with continuing reference to Figs. 1-6.

For example, during a blood removal submode, whole blood will be passed from a donor **4** into tubing line **22** of blood removal/return tubing assembly **20** and is then transferred to blood component separation device **6** (see generally Fig. 7). At device **6**, the blood is flowed, preferably pumped via loop **132** (see Fig. 4), to the processing vessel **352** (schematically shown in dashed lines in Fig. 7 or in Fig. 2) via the cassette assembly **110** and line **62** of the blood inlet/blood component tubing assembly **60** (Figs. 3 and 4). Separation processing then occurs preferably on a substantially continuous basis in vessel **352**; i.e., blood substantially continuously flows therein, is continuously separated and continuously flows as separated components therefrom. After separation processing in vessel **352** (though separation is continuously occurring), blood components which are not going to be collected are transferred from the processing vessel **352** to and through cassette assembly **110**, into and may then accumulate in reservoir **150** (Figs. 3 and 4) of cassette **110** up to a predetermined level at which the blood component separation device **6**, in a single needle operation, may (though in a continuous system, need not) pause the blood removal submode and initiate a blood return submode wherein these uncollected and/or treated components may be returned

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to the donor **4**. As such, these accumulated components may be transferred into the blood return tubing line **24** of blood removal/return tubing assembly **20** and back into the donor **4**. During the single needle blood return mode, when the accumulated return blood components in reservoir **150** are removed down to a predetermined level, blood component separation device **6** will then automatically end the blood return submode. This preferably will also automatically serve to reinitiate or continue the blood removal submode. The cycle between blood removal and blood return submodes will then continue until a predetermined amount of RBCs or other collected blood components have been harvested. In an alternative dual needle scheme, as is known in the art, blood may be continually removed from and blood components continually returned to a donor **4**. Note, the detailed mechanisms for such operations, including controlling the pumps, for example, are not shown or described in detail herein, particularly not in the schematic views of Figs. 7 and 8.

Note also that certain components may be collected simultaneously or consecutively one after the other. In one example, platelets and plasma may be collected prior to collection of RBCs. In the primary example shown in Figs. 1 and 3-4 and 7, 8 and 9, only two components are shown being collected, RBCs in the RBC sub-assembly **950** and plasma (or platelets) in the other collection assembly **90**. When a sufficient quantity of one or the other is collected, further separated portions of such a component are preferably returned to the donor with any other uncollected components, until a sufficient quantity of all components are collected. It is further understood that only RBCs can be collected with all other components including plasma being returned to the donor.

With specific reference to Figs. 3 and 4, in normal operation, whole blood will pass from the donor **4** through the needle and blood removal tubing assembly **20**, cassette assembly **110** and blood inlet tubing line **62** to processing vessel **352**. The whole blood will then be separated in vessel **352**. As shown in Fig. 2, a buffy coat stream containing MNCs (or a stream containing plasma or platelets) may be separated herein and be either collected in a collector assembly (not shown), or diverted to reservoir **150** for ultimate return to the donor. Further, some red blood cells including the red blood cells located at the buffy coat- RBC interface may be separated in and passed, preferably pushed from vessel **352** through RBC outlet tubing line **64**, through cassette assembly **110** and, in return mode, into reservoir **150**. These RBCs containing contaminating MNCs may be returned to the donor **4**, leaving MNC-reduced RBCs in the vessel. In an alternative, during an RBC collection procedure described below, separated MNC-reduced RBCs will be delivered to RBC collector tubing, bag and filter assembly **950** through tubing lines **951** and **952** for collection. The RBC collection protocol may also include a MNC-reduced RBC filtration process using the preconnected

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leukoreduction filter **960** in line with and prior to RBC collection bag **954**. This procedure will be described further below.

Apheresis Protocol

One protocol, which may be followed for performing an apheresis procedure relative to a donor **4** utilizing the described system **2**, will now be summarized. Initially, an operator loads the disposable plastic assembly **8** in and/or onto the blood component separation device **6**. According hereto, the operator hangs the various bags (e.g., collection bag **954** (and **94**, if used); see Fig. 7, described further below) on the respective hooks (see hook **996** of Fig. 7, e.g.) of the blood component separation device **6**. If one is used, the operator then also loads the cassette assembly **110** on the machine **6** and/or the blood processing vessel **352** within the channel housing **204** as mounted on the centrifuge rotor assembly **568** in the machine **6**.

With the extracorporeal tubing circuit **10** and the blood processing vessel **352** loaded in the described manner, the donor **4** may then be fluidly interconnected with the extracorporeal tubing circuit **10** by inserting an access needle of the needle/tubing assembly **20** into the donor **4** (see, e.g., Fig. 7). In addition, the anticoagulant tubing assembly **50** (see Fig. 3) is primed and the blood removal/return tubing assembly **20** is primed preferably with blood from the donor **4** as described in one or more of the above-listed patents. The blood processing vessel **352** is also primed for the apheresis procedure, preferably also according to processes such as those described in the same above-listed patents. In one embodiment, a blood prime may be used in that blood will be the first liquid introduced into the blood processing vessel **352**. During the priming procedure, as well as throughout the remainder of the apheresis procedure, blood may be continuously flowed into the vessel **352**, blood component types are preferably continuously being separated from each other and one or more of these is also preferably continuously removed from the blood processing vessel **352**, on a blood component type basis. Preferably, at all times during the apheresis procedure, from priming onward, a flow of blood is substantially continuously provided to the blood processing vessel **352** and at least one type of separated component is continuously removed.

It should be noted that when the centrifuge rotor is spinning (as it preferably will be whenever blood is disposed within the blood processing vessel) it will impart centrifugal forces on the blood which will then separate into three primary component layers around the blood processing vessel: a first innermost layer containing at least plasma, a second intermediate layer of "buffy coat" which contains at least platelets and mononuclear cells (MNCs) and a third outermost layer containing primarily red blood cells. It should be noted however, that due to the close sizes of red blood cells and leukocytes, the RBC layer closest

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to the buffy coat layer interface (at the outermost layer) will contain at least a portion of WBCs. This red blood cell layer partially overlaps with the buffy coat layer.

The buffy coat layer is generally found on the interface between the red blood cell layer and the plasma layer (see element **82** of Fig. 2). Because centrifugal separation will less effectively separate the white blood cells from the red blood cells due to their close size as mentioned above, there is likely to be white blood cell contamination of at least a portion of the the red blood cells closest to the buffy coat layer. As discussed above, this fraction or layer is called the red blood cell layer which partially overlaps with the buffy coat layer (see element **83** of Fig. 2).

Although separation and collection of various components may be performed, RBCs are the component of the most interest in the current invention, and thus the separation and collection protocol will continue with a description of the collection and filtration hereof. It is understood that RBCs may also be the only component collected with all other components being returned to the donor.

In turn, such separated blood components may be selectively collected in corresponding storage reservoirs (not shown) or immediately or after a minor delay returned to the donor **4** during respective blood return submodes (or substantially constantly in a two-needle setup). In this regard, and in one approach where more than one blood component is to be collected, such as plasma and/or platelets, blood apheresis system **2** may be used to collect other components during a time period(s) separate from the collection of red blood cells. These components may also be collected simultaneously. Note, if other components are collected prior to RBCs, then RBCs separated during any such other component phase may be diverted back to the donor and not filtered. Preferably, only collected MNC-reduced RBCs will be filtered in the current embodiment (though therapeutic filtration for a particular donor/patient may also be performed). By removing the other component layers, especially the buffy coat layer and the red blood cell layer which partially overlaps with the buffy coat layer, the remaining MNC-reduced red blood cells will be less contaminated with lymphocytes, and will be able to be filtered more efficiently to remove any remaining white blood cells. The buffy coat layer and the RBC layer containing the at least a portion of MNCs can either be returned to the donor, or collected into a storage reservoir or collection bag and further processed.

In any event, the RBC collection procedure is preferably controlled via control signals provided by blood collection device **6**. Such an RBC collection procedure may include a setup phase and a collection phase. During such a setup phase, the blood apheresis system **2** may be adjusted automatically to establish a predetermined hematocrit in those portions of the

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blood processing vessel **352** and extracorporeal tubing circuit **10** through which separated RBCs will pass for collection during the RBC collection phase. A desirable resulting hematocrit for RBC collection may be between about 70 and about 90 or even up to 95+, and may be established at about 80. The term high hematocrit refers to those separated, undiluted RBCs leaving the separation vessel **352**. Dilution with storage solution to a different (generally lower) collected hematocrit may follow.

Additionally, blood component device **6** may, during the set-up phase, divert the flow of separated RBCs flowing through RBC tubing line **64** through return tubing loop **172** and into blood return reservoir **150** for return to the donor **4** until the desired hematocrit is established in the separation vessel **352**.

Also during the set up phase, the blood component separation device may divert the flow of the buffy coat layer **82** and the portion of the red blood cells **83** which are closest to the buffy coat layer either back to the donor or into a collection bag for further processing. By removing this portion of the red blood cells and the buffy coat layer from the blood processing vessel, the majority of the mononuclear cells will be removed. The red blood cells remaining in the separation vessel **352** are known as mononuclear cell reduced red blood cells.

The increased efficiency of removing the buffy coat layer and the layer of RBCs next to the buffy coat layer is shown in the table below.

N (= 22)	Contaminating cell count after leukoreduction without removal of buffy coat laver and the RBCs next to buffy coat laver	Contaminating cell count after leukoreduction of MNC-reduced RBCs
1	4.9	0.31
2	2.4	0.02
3	7.8	0.04
4	0.3	0.22
5	0.2	0.05
6	5.9	0.02
7	3.2	0.05
8	0.1	0.09
9	3.0	0.06
10	4.7	0.01
11	2.0	0.04
12	11.3	1.22
13	1.1	.022
14	15.3	4.03
15	1.3	0.37
16	0.4	0.07
17	14.7	0.44
18	0.5	0.03
19	0.3	0.06
20	2.6	0.16

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21	3.1	2.37
22	2.3	0.04

As can be seen in the table above, the step of removing the buffy coat layer and the RBCs located next to the buffy coat layer produced a final RBC product with much lower WBC contamination as compared to the final RBC product produced without the removal step.

In order to establish the desired packing factor and/or hematocrit for the separated MNC-reduced RBCs, the operating speed of centrifuge rotor assembly **568** (see Fig. 1) may be selectively established via control signals from blood component separation device **6**, and the blood inlet flow rate to vessel **352** may be selectively controlled by blood component separation device **6** controlling the speeds of the respective pump assemblies (not shown or described in detail here). More particularly, increasing the rpms of centrifuge rotor assembly **568** and/or decreasing the inlet flow rate will tend to increase the packing factor and/or hematocrit, while decreasing the rpms and/or increasing the flow rate will tend to decrease the packing factor and/or hematocrit. As can be appreciated, the blood inlet flow rate to vessel **352** may effectively be limited by the desired packing factor or hematocrit.

To establish a desired anticoagulant (AC) ratio, blood component separation device **6** provides appropriate control signals to the anticoagulant pump so as to introduce anticoagulant into the blood inlet flow at a predetermined rate. Relatedly, it should be noted that the inlet flow rate of anticoagulated blood to blood processing vessel **352** may be limited by a predetermined, maximum acceptable anticoagulant infusion rate (ACIR) to the donor **4**. As will be appreciated by those skilled in the art, the predetermined ACIR may be established on a donor-specific basis (e.g. to account for the particular total blood volume of the donor **4**). To establish the desired total uncollected plasma flow rate out of blood processing vessel **352**, blood collection device **6** provides appropriate control signals to the plasma (and platelet) pump assembly(ies). This may also serve to increase the hematocrit in the separated RBCs.

In one embodiment, the desired high hematocrit for the separated RBCs will be between about or approximately 75 and about 85 and will preferably be about or approximately 80; although, again higher hematocrits may be available as well. Then, where a centrifuge rotor assembly **568** may present a defined rotor diameter of about 10 inches, and where a blood processing vessel **352** is utilized, as described hereinabove, it has been determined that in one preferred embodiment channel housing **204** can be typically driven at a rotational velocity of about 3000 rpms to achieve the desired RBC hematocrit during the setup and red blood cell collection phases. Correspondingly, the blood inlet flow rate provided by pumping through loop **132** to vessel **352** may preferably be established at below

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about 65 ml/min. The desired hematocrit can be reliably stabilized by passing about two whole blood volumes of vessel **352** through vessel **352** before the RBC collection phase is initiated.

To initiate the MNC-reduced RBC collection phase, blood component separation device **6** provides an appropriate control signal to the RBC divert valve assembly (not shown) so as to direct the continuous outflow of the separated MNC-reduced high hematocrit RBCs removed from blood processing vessel **352** via line **64** into the RBC collection system **950** through tubing lines **951** and **952**, and filter **960** into collection container **954** via line **965**.

As may be appreciated, the MNC- reduced, separated RBCs are not pumped out of vessel **352** for collection, but instead are flowed out vessel **352** and through extracorporeal tubing circuit **10** by the pressure of the blood inlet flow to vessel **352**. The inlet blood is pumped into vessel **352** via loop **132** of cassette **110**. The separated MNC-reduced RBCs are pushed or pressed out of the vessel **352**.

During the RBC collection phase, the inlet flow into vessel **352** will likely be limited by the above-noted maximum acceptable ACIR to the donor **4**. The desired inlet flow rate may also be limited by that necessary to maintain the desired packing factor and/or hematocrit, as also discussed. In this regard, it will be appreciated that relative to the setup phase, the inlet flow rate may be adjusted slightly upwards during the RBC collection phase since not all anticoagulant is being returned to the donor **4**. That is, a small portion of the AC may remain with the small amount of plasma that is collected with the high hematocrit RBCs in RBC reservoir **954**.

According to the present invention, the relatively high hematocrit (high-crit) MNC-reduced RBCs optionally may be diluted and then filtered as soon as the blood is separated or very soon after having been separated within vessel **352**. Alternatively, the MNC-reduced RBCs may be filtered without dilution in a high-crit state. The phrase high-crit refers to the state of the separated MNC-reduced RBCs as they emerge from the separation vessel **352**. In the substantially continuous centrifugal separation process as described here, a freshly separated stream of MNC-reduced RBCs is substantially continually flowing out of the vessel **352**, first through tubing line **64**, to and through cassette assembly **110** and then through lines **951** and **952** (where they optionally may be joined by diluting storage solution) to the filter **960** and then through line **965** to bag **954** (see Fig. 7). Preferably, these freshly separated MNC-reduced RBCs will be continuously flowing from vessel **352** through filter **960** and then into collection bag **954** (or also into bag **954a**, see Figs. 6A and 6B). Thus, in the described embodiment, white cell/leukocyte filtration will have begun and is continued

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simultaneously with or during the overall continuous separation process, prior to collection. More description of this will be set forth in further detail below.

Note, the phrase freshly-separated is intended to describe the newly-separated blood components in and as they emerge from the mechanical separation system such as device **6** and separation vessel **352**. It also includes the state of these same separated components for a reasonable length of time after removal from the mechanical separation device such as from vessel **352**. Thus, for example, a reasonable length of time may include the entire apheresis procedure which may last up to (and perhaps exceed) two (2) or more hours during which filtration may be substantially continuously performed. Two further terms used herein have similar distinctions, namely, "recently removed" and "soon after." Recently removed is referred to herein primarily relative to that blood taken from the donor which may be immediately taken and processed in a mechanical separation system, or which may have been taken and held subject to a reasonable non-long-term-storage type of delay prior to separation processing in a device such as device **6**. Similarly, "soon after" is used in like manners relative to both of these circumstances as well, as, for example, when separated blood components may be removed from the separation vessel, e.g. soon after separation (whether in continuous or batch mode).

In any event, from the standpoint of the donor **4** and machine **6**, following the separation, filtration and collection processes of the desired quantity of red blood cells, blood separation device **6** may then provide a control signal to the RBC divert assembly so as to divert any further RBC flow back to the donor **4** via loop **172**, reservoir **150** and return line **24**. Additionally, if further blood processing, by apheresis centrifugation here, is not desired, rinseback procedures may be completed. Additionally, once the minimum desired RBCs have been diverted into filtration/collection assembly **950** and after filtration completion, the red blood cell collection reservoir **954** (and/or the entire sub-assembly **950**) may then be disconnected from the extracorporeal tubing circuit **10**. Filter **960** may also be removed herewith or separately or remain attached and disposed of with the cassette **110** and other remaining bags or tubes. However, according to the present invention, a storage solution will be, perhaps during and/or after filtration of the RBCs, added to the RBC flow in tubing line **952** to the filter **960** ultimately to the red blood cell reservoir or bag **954**. Preferably, a spike connection to one or more storage solution bag(s) **970** (see Figs. 1 and 7) through a spike **985** is used. This process will also be described further below. Such storage solutions or additive solutions may advantageously facilitate storage of the RBCs for up to about forty-two days at a temperature of about 1 – 6 °C. In this regard, acceptable storage solutions include a storage solution generically referred to in the United States as Additive Solution 3 (AS-3), available from Medsep Corp. located in Covina, California; and/or a storage solution generically

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referred to in Europe as SAG-M, available from MacoPharma located in Tourcoing, France. It is also possible to use saline before, after or during the filtering process described below which, prior to storage, could be replaced with the desired storage solution. Alternatively saline could be used to flow through the filter **960** to the cassette assembly **110**.

The storage additive solution may be and preferably is contained in a discrete storage solution bag **970** that can be pre-connected, or is separate and may selectively be later interconnected to the tubing circuit **10** via line **982**, preferably through a spike connection **985**. In an alternative embodiment, such selective interconnection may be provided via sterile-docking to tubing line **982** as an example (process not shown) utilizing a sterile connecting device (not shown). By way of example, one such sterile connecting device to interconnect a tubing line **982** to such a storage solution container **970**, is that offered under the trade name "TSCD" or "SCD™ 312" by Terumo Medical Corporation located in Somerset, New Jersey. In the alternative above, the selective interconnection may be established utilizing a sterile barrier filter/spike assembly **980**. The use of such a sterile barrier filter/spike assembly **980** facilitates the maintenance of a closed system, thereby effectively avoiding bacterial contamination. By way of example, the mechanical, sterile barrier filter **986** (Figure 7) or **986a** or **986b** in such an assembly **980** may include a porous membrane having 0.2 micron pores. Pumping via a tubing loop **142** may then provide for selectively flowing solution through tubing line **982** and connecting tubing line **146** for introduction of the storage solution into the RBC line **952** and filter system **950**.

In order to ensure the maintenance of RBC quality, the collection RBC bag **954**, and the storage solution and the anticoagulant used during blood processing should be compatible. For example, the collection RBC reservoir **954** may be a standard PVC DEHP reservoir (i.e. polyvinyl chloride-diethylhexylphthallate) such as those offered by the Medsep Corporation. Alternatively, other PVC reservoirs may be employed. Such a reservoir may utilize a plasticizer offered under the trade name "CITRIFLEX-B6" by Moreflex located in Commerce, California. Further, the anticoagulant utilized in connection with the above-described red blood cell collection procedures may be an acid citrate dextrose-formula A (ACD-A).

Nevertheless, according to an embodiment of the present invention as introduced above, the storage solution may be flowed after and/or added to the flow of separated MNC-reduced red blood cells flowing in lines **951** and **952**, and flow therewith to and through the filter **960.** Filter **960** will remove the majority of the remainder of white blood cells which are left in the MNC-reduced red blood cells. More particularly leukoreduction filtering is desired to establish a white blood cell count of $< 5 \times 10^6$ white blood cells/unit (e.g. about

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250 ml.) to reduce any likelihood of febrile non-hemolytic transfusion reactions. Moreover, such filtering will more desirably achieve a white blood cell count of $< 1 \times 10^6$ white blood cells/unit to reduce any risk of HLA (i.e. human leukocyte A) sensitization and/or other serious side reactions. Studies have also shown positive effects for pre-storage leukocyte reduction in improving the functional quality of erythrocytes during storage and in decreasing the occurrence of alloimmunization in patients receiving multiple transfusions, as well as being favorable in metabolism reactions such as intra-erythrocyte ATP and/or extracellular potassium levels declining more slowly in filtered products. Perhaps more important is the reduction of transfusion transmitted disease, especially cytomegalovirus (CMV) and/or HIV, *inter alia*.

Accordingly, the red blood cell collection container **954** receives, in one embodiment, RBCs and additive solution from the red cell filter **960** such that high hematocrit (preferably Hct between 70 and 90 and/or approximately equal to 80), freshly separated MNC-reduced red blood cells alone or together with additive solution are preferably pushed through filter **960** and into the ultimate RBC collection bag **954**. Such pushed filtration is shown in Figs. 7, 8 and 9, as will be described further below. The red cell filter **960** and collection bag sub-assembly **950** is preferably preconnected to the tubing circuit **8** as part of the disposable assembly **10** (to avoid the costs and risks of sterile docking) as shown in Figs. 1, 3 and 4 in accordance with the teachings of this invention. The red blood cell filter 960 may also be added to the previously existing disposable systems to form a post-manufacturing-connectable disposable assembly using special new kits or commercially available filter/bag kits such as those available under the trade name "Sepacell" from Asahi Corp and/or Baxter, Inc. and/or "RC100", "RC50" and "BPF4", etc., from Pall Corp., located in Glencove, New York, inter alia. In either event, the red cell filter/bag sub-assembly is preferably connected (pre- or post-) to the tubing circuit **8** through a tubing line **951** and/or **952** as shown.

Referring now primarily to Figs. 3, 4 and 5, the procedure for the filtration of MNC-reduced RBCs freshly separated and collected from the apheresis process is as follows. These freshly separated MNC-reduced RBCs are either in an undiluted, high-hematocrit state (Hct approximately 80) during the preferred filtration process, followed by additive solution or storage solution, or are filtered in a mixed state with additive solution added to the RBC flow in line **952** at the connection **979**. Moreover, storage solution may be flowed through the filter **960** prior to any MNC-reduced RBCs (this may enhance the filtration efficacy) and, as noted above, may optionally be flowed through the filter after leukoreduction of the RBCs to be added to the collected RBCs in bag **954**. In an embodiment, no matter when the additive or storage solution initially flows through the filter, it is preferable to run a sufficient amount

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of solution through the filter **960** after MNC-reduced RBC filtration to attempt to displace any RBCs remaining in the volume of the filter **960** for collection.

Either simultaneously with the substantially continuous separation and collection process (i.e., as soon as high hematocrit (high-crit) MNC-reduced RBCs are separated from other components and pushed out of vessel **352** to cassette **110** and not diverted back to the donor), or soon after a desired minimum quantity of other blood components have been collected, if desired, the RBC collection/filtration system **950** is activated to filter the MNC-reduced RBCs. This collection process is activated by switching the clamp/valve of device **6** to stop diversion flow through loop **172** and allow flow through line **951** to line **952** and filter **960**.

In either case; simultaneously with the continuous collection in bag **954** from the separation vessel **352**, or soon after completion of any other non-RBC collection process(es), the MNC-reduced RBCs are flowed preferably by intrinsic pressure pushing (non-active pumping) through filter **960**. As such, collection bag **954** may be hung at a level above both the separation vessel **352** and the filter **960** (see Figs. 5-8) so that the continuously flowing MNC-reduced RBCs are allowed to move upwardly from vessel **352** through the filter **960** and into the collection bag **954**. One embodiment of this is shown in Fig. 7, where the collection bag **954** is hung from a hook **996** of the machine **6** in known fashion. Tubing line **965** depends downwardly therefrom and is shown as connected to the filter **960**, out of the top of which extends the next tubing line **952** which ultimately connects downwardly to the cassette **110** via line **951**.

Any air from bag **954**, or air caught between the incoming filtered RBCs and bag **954** is ultimately removed to air removal bag **962** through tubing line connection **961**. The air is evacuated to air removal bag **962** prior to the flow of the incoming RBCs or is evacuated by the flow of the incoming RBCs. It is also understood that air can also be vented prior to even the separation process by initially running the return pump, (not shown) of the apheresis system. It is also understood that removal of air may also be achieved by other known methods, including, for example, hydrophobic vents and/or by-pass lines. It is desirable to perform the filtering of the MNC-reduced RBCs according to the present invention directly on the machine **6** during the apheresis separation process and without pre-cooling or pre-storing the RBCs. In such a case, these procedures are thus performed without the previously conventional steps of intermediate separation/collection and cooling and storing overnight at 4 °C.

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Then, either after completion of or during and/or even before the filtration in either of these embodiments, namely, the simultaneous collection and filtering, or in the filtering and collection soon after any other component collection processes, storage solution is flowed to and through the filter and/or added to the MNC-reduced RBCs. Again, this may be performed either before and/or during and/or after completion of the filtration of the otherwise high hematocrit MNC-reduced RBCs through filter **960**, although it is preferred that an amount of additional additive or storage solution displace the volume of the filter to recover any residual RBCs therefrom. In particular, a storage solution bag **970** has been connected (by pre-connection or by spike or sterile welding) as depicted in Figs. 1, 7, 8 and 9, the clamp **990** is opened (if any such optional flow-stopping member is used; see Figs. 3 and 4) to allow the introduction of the storage solution into tubing line **982** and pumped via tubing loop **142** through additive solution tubing **146** and into tubing line **952** via connector **979**. The storage solution thus will be pumped from bag **970** through filter **960** and into collection bag **954**. If pumped during collection, the solution may be metered into and mix with and dilute the high-crit MNC-reduced RBCs in line **952** prior to filtration. The rate of mixing can be controlled by pumping via loop **142**. However, the storage solution may be pumped through the filter **960** also before and/or after all of the undiluted MNC-reduced RBCs have been filtered therethrough to assist in the filtration and/or to chase the MNC-reduced RBCs and move any MNC-reduced RBCs caught in the filter out of the filter to the collection bag **954**. Such a storage solution chase may be used also after the metering of storage solution into a pre-filtration MNC-reduced RBC flow (as described above) as well. Again, all of the steps in operating the MNC-reduced RBC filtration system **950** may be performed during the overall apheresis component separation procedure and thus need not be subjected to a cooled, time-delayed environment.

It should be noted that storage solution does not need to be pumped through the filter. Storage solution may also be flushed through the filter manually, using gravity.

One embodiment of the storage solution addition step is shown in Figs. 7, 8 and 9. Note, other component collection processes are not shown here (i.e., whether simultaneous or consecutive collection processes for other components (e.g., plasma and/or platelets) are used is not depicted or described here). In Figs. 7, 8 and 9, the collection bag **954** is shown attached to the upper hook **996** and the air bag **962** hung on another hook **998** (note, air bag **962** may not need to be hung from a hook but could have air bled thereto after the other steps in the process as suggested below). Then, a storage solution bag **970** can be hung from yet another hook **997** so that when connected and hung as shown in Figs. 7 and 8, storage solution can flow down through tubing line **982** and through sterile barrier **986** through pump loop **142**, connecting lines **146** and **952** and then through filter **960** and ultimately into

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collection bag **954**. Although flow of both storage solution and MNC-reduced RBCs is shown entering the filter **960** in the downward direction in Figs. 7 and 8 and the upward direction in Fig. 9, it is also understood that flow to the filter **960** can be in any direction desired, including, but not limited to sideways. This flow against gravity is possible because the MNC-reduced RBCs are pushed through the filter.

Alternatively, the embodiment shown in Fig. 8 also includes a depiction of the placement of the filter **960** in a substantially fixed position on device **6**. In this embodiment flow will remain in a downward direction to aid in priming the filter **960**. Clips or other restraining devices **901** are shown holding filter **960** in place. The further steps of having collected or simultaneously collecting components other than the RBCs in bag **954** and/or the alternatives of simultaneously pumping solution into the flow of MNC-reduced RBCs and/or having completed filtration thereof through filter **960** prior to the addition of storage solution to filter **960** and bag **954** are not easily separately shown in the Figs.; however, flow control over the storage solution will preferably be made by a pump on device **6** engaging loop **142**.

The embodiment shown in Figure 9 depicts the filter **960** hanging from bag **954** without attachment to device **8**. This embodiment allows flow of both storage solution and MNC-reduced RBCs in the upward direction to and through the filter **960**. Although not shown in Fig. 9, a bracket or clip or other restraining device like that shown as element **901** in Fig. 8 may be used to surround filter **960** to provide mechanical support and to insure the filter is placed in the correct orientation.

In either event, upon completion of filtration and/or chasing with additive solution, the collection bag **954** may be separated from the rest of the set **8**. Optional clamp **966** may be closed prior to such a separation. The separation may be made by RF sealing the tubing line **965** above the filter **960** or line **952** below the filter **960** and then separating in accordance with U.S. Patent Nos. 5,345,070 and 5,520,218, inter alia, along the RF-sealed portion of the tubing line. Other well known methods can also be used to close the tubing line and then also separate the RBC collection system **950** from the remainder of the disposable assembly **8**. An RBC collection system **950** which would be remaining after one such severing, e.g., below the filter **960**, is shown schematically in Figs. 5 and/or 6A or 6B (see below).

With respect to Figure 5 it is noted that tubing line **965** may be a segmented tubing line that is further sealed to provide sample segments as is well known. It is also understood that tubing line **961** in addition to tubing line **965** or alternatively to tubing line **965** may also be segmented to again provide the desired samples for blood tying and other optional purposes.

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Several advantages can be realized utilizing the preconnected disposable assembly and the above-described procedure for high-crit MNC-reduced red blood cell collection and filtration. Such advantages include: consistency in final RBC product volume and hematocrit; reduced exposure of a recipient if multiple units of blood products are collected from a single donor and transfused to a single recipient; reduced time requirements for RBC collection and filtration, including collection of double units of red blood cells if desired, and reduced risks of leukocyte contamination of the final RBC product due to the filter becoming clogged with MNCs which get pushed through the filter into the previously filtered RBCs, thus causing recontamination of the previously filtered RBCs. Further advantages include a system which is less complicated and requires less human interaction. Less human interaction is advantageous because it decreases the possibilities of human contamination.

In order to assist an operator in performing the various steps of the protocol being used in an apheresis procedure with the apheresis system **2**, the apheresis system **2** preferably includes a computer graphical interface **660** as illustrated generally in Fig. 1. The graphical interface **660** may preferably include a computer display **664** which has "touch screen" capabilities; however, other appropriate input devices (e.g., keyboard) may also be utilized alone or in combination with the touch screen. The graphics interface **660** may provide a number of advantages, but may preferably, at least, assist the operator by providing pictorials of how and/or when the operator may accomplish at least certain steps of the apheresis and/or filtration procedures.

For example, the display screen optionally may sequentially display a number of pictorials to the operator to convey the steps which should be completed to accomplish the filtering procedure described here. More particularly, a pictorial image optionally may be shown on the screen to pictorially convey to the operator when and/or how to hang the respective RBC and solution bags **954** and/or **970** on the machine **6**, initially and/or during use with a storage solution dilution and/or flush (see Figs. 7 and 8, for example). One or more pictorials may also be provided to instruct the operator when to open or close clamps to begin the filtration process, and/or to visually ensure that the filtration process has appropriately begun simultaneously or during RBC collection. One or more pictorials may also be used to instruct the operator when to connect the spike assembly **980** to a storage solution container **970** and/or when to open a clamp or break a frangible connector (if included) after and/or during the MNC-reduced RBCs flow through filter **960**, to thus initiate the flow of the storage solution through the filter **960** and flush any residual MNC-reduced RBCs therethrough. One or more pictorials may also be used to instruct the operator when the tube line **965** leading to the RBC collection bag **954** should be sealed such that the RBC

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collect bag **954**, and the remaining elements of RBC storage assembly **950** may be separated and/or removed from the disposable assembly **10** and/or from the device **6**. A similar pictorial can instruct when to seal the air tube **961** to isolate the RBC collection bag **954** from the air bag **962** and the rest of the system after the filtration and flushing and air handling procedures may be completed.

Note, a further advantage of the presently described system includes the manner of handling air. More specifically, the present invention eliminates the prior need for the vents and/or by-pass methods and/or apparatuses of conventional red blood cell filters. Moreover, the present invention is capable of delivering this advantage with no reduction in and/or perhaps an increase in the recovery of RBCs that historically have been trapped inside the filtration device.

A means used by the present invention to deliver this advantage is through the provision of a storage solution flush through the filter **960** after the MNC-reduced RBCs have finished filtering therethrough. The storage solution may then be able to wash MNC-reduced RBCs caught therein out of the filter and then into the collection bag **954**. Prior devices relied upon vents or by-pass mechanisms to assist in pushing out any RBCs disposed in the filter. Note, though not preferred or needed, vents or by-passes could still be used with the current pushed filtration process, and also with and/or in lieu of the storage solution flush after filtration. Thus such vents or by-passes may be optional features to the described system if it is desired to purge the filter **960** with air or with a combination of air and fluid.

In any event, elimination of the need for vents or by-passes also reduces other prior difficulties such as inadvertent allowances of excess air into the system. Extra air in the present system will not stop or slow the flow of blood or storage solution through the filter in the present invention. The extra air will then be caught within the collection bag **954** and may thus be removed at the end of the overall process to the air bag **962** (air moved thereto by bag positioning or squeezing, etc.). Then, also, because neither vents nor by-passes are required in this embodiment, failures with respect to the operation of such vents are not of concern since the subsequent storage solution flush recovers the RBCs from the filter without the previously desired use of a vent or by-pass. Consequently, also, the filter may be disposed at any of a plurality of alternative vertical dispositions above or below the vessel **352** and/or the collection bag **954**. Operation of the present invention should not be hindered by such alternative placements. It is understood, however, that air could also be used to chase either the RBCs or additive solution through filter **960** as described above.

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Although the instant invention eliminates the need for by-passes it is understood that one could be provided in the extracorporeal tubing circuit to by-pass the filter **960** in the event the leukoreduction is terminated or is not desired. Similarly it is understood that an optional pressure relief valve or vent could be added to prevent pressure build up in parts of the system including the filter.

The volume of storage solution to be used may, however, be modified depending upon the relative lengths of tubing lines used and/or the air that gets into the system. For example, if 100 ml of storage solution is desired to be mixed with the end product RBCs in collection bag **954** then some certain volume more than 100 ml of storage solution would preferably be fed into the system to compensate for the tubing lengths and the volume of the filter. The amount of solution may be chosen such that 100 ml would go into the collection bag **954** with the additional amount remaining in the tubing line and filter between the cassette **110** and the collection bag **954**.

Note, a storage solution dilution during RBC filtration and/or flush after filtration completion are the primary alternatives taught here. However it is possible that storage solution flow into bag **954** may be begun at other times as well as, for example, prior to starting the high-crit or diluted MNC-reduced RBC pushed filtration. Pulsed and/or intermittent flows may also be desirable to assist in removing final volumes of RBCs from the filter **960**.

Another alternative introduced hereinabove involves the use of other extracorporeal blood processing systems. Although the preference is for a continuous flow apheresis system, as described here, which includes returning some components back to the donor, batch flow and non-return systems are also useable herewith. For example, a batch mode processor takes in a certain quantity of whole blood which was previously collected from a donor at some point before the separation process is begun. The batch mode processor separates the blood into components (in a centrifuge bowl, e.g.) and then passes the separated components to collection containers. The separated components may also be given back to the donor. The filtration process of the present invention could foreseeably nevertheless operate in substantially the same manner such that the separated MNC-reduced RBCs would nonetheless exist in a substantially high hematocrit state as they are flowed from the separation mechanism, at which point these high-crit separated MNC-reduced RBCs could be flowed to a junction with a storage solution tubing line and from there be passed directly or soon thereafter to and through a filter **960** to be collected ultimately in a collection bag **954**. Though continuity may be reduced (or substantially removed), the principles of firstly removing the buffy coat layer and the RBCs located next to the buffy coat layer before pushed

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filtration (high-crit or diluted) during or soon after the overall separation and collection remain the same. Note, even if flow through the filter **960** stops at any point, or a plurality of points, this does not appear problematic here where any air entry therein is handled by ultimate capture in the air bag **962**.

Smaller scale separation and collection devices are also envisioned to be useful herewith. For example, various separation devices (whether centrifugal or membrane or other types) are designed to separate only RBCs and plasma (with the remainder usually remaining in the RBC product), and these can take on smaller scale mechanizations. Nevertheless, the present invention is useful herewith as well in that MNC-reduced RBCs separated hereby may also be freshly push-filtered at high and/or diluted hematocrits. The principle of push-filtering such MNC-reduced RBCs during or soon after the overall separation and collection process remains the same here as well. Thus, whether continuous or in batch mode, a flow of high-crit or diluted, freshly-separated MNC-reduced RBCs can be push-flowed from the separation device immediately or soon after previous processing therein, to and through filter **960** to a collection bag **954**.

The foregoing description of the present invention has been presented for purposes of illustration and description. Furthermore, the description is not intended to limit the invention to the form disclosed herein. Consequently, variations and modifications commensurate with the above teachings, and skill and knowledge of the relevant art, are within the scope of the present invention. The embodiments described hereinabove are further intended to explain best modes known of practicing the invention and to enable others skilled in the art to utilize the invention in such, or other embodiments and with various modifications required by the particular application(s) or use(s) of the present invention. It is intended that the appended claims be construed to include alternative embodiments to the extent permitted by the prior art.

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CLAIMS

1. A method for providing red blood cells from whole blood using an apheresis system comprising the steps of:

separating the whole blood into blood component layers within a separation vessel wherein the blood component layers comprise at least a plasma layer, a buffy coat layer and a red blood cell layer;

removing the plasma layer from the separation vessel;

removing the buffy coat layer from the separation vessel; and

removing a portion of the red blood cell layer closest to the buffy coat layer to provide a mononuclear cell-reduced red blood cell layer in the separation vessel.

2. The method of claim 1 wherein the whole blood is recently removed from a donor.

3. The method of claim 1 wherein the separating step comprises separating in a continuous manner.

4. The method of claim 1 wherein the separating step comprises separating in a batch wise manner.

5. The method of claim 1 further comprising removing the mononuclear cell-reduced red blood cell layer from the separation vessel.

6. The method of claim 1 further comprising leukoreducing the mononuclear cell-reduced red blood cell layer to create leukoreduced red blood cells.

7. The method of claim 6 wherein the leukoreduced red blood cells are at a high hematocrit.

8. The method of claim 5 wherein the step of removing the mononuclear cell-reduced red blood cell layer further comprises removing the mononuclear cell-reduced red blood cell layer from the separation vessel to a preconnected red blood cell collection bag.

9. The method of claim 8 wherein the step of removing the mononuclear cell-reduced red blood cells from the separation vessel to a preconnected red blood cell collection bag occurs after the mononuclear cell-reduced red blood cells have been leukoreduced.

10. The method of claim 6 wherein the step of leukoreducing the mononuclear cell-reduced red blood cells further comprises pushing the mononuclear cell-reduced red blood cells through a leukoreduction filter preconnected to the separation vessel.

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11. The method of claim 10 wherein the step of pushing the mononuclear cell-reduced red blood cells through the leukoreduction filter further comprises pushing by non-gravity forces.

12. The method of claim 10 wherein the step of pushing the mononuclear cell-reduced red blood cells through the leukoreduction filter further comprises pushing by indirect pumping forces.

13. The method of claim 2 wherein the step of removing the buffy coat layer further comprises returning the buffy coat layer to the donor.

14. The method of claim 1 wherein the step of removing the buffy coat layer further comprises collecting the buffy coat layer in a preconnected collection container for further processing.

15. The method of claim 2 wherein the step of removing a portion of the red blood cell layer closest to the buffy coat layer further comprises returning the portion of the red blood cell layer closest to the buffy coat layer to the donor.

16. The method of claim 1 wherein the step of removing a portion of the red blood cell layer closest to the buffy coat layer further comprises collecting the portion of the red blood cell layer closest to the buffy coat layer in a preconnected collection container for further processing.

17. The method of claim 10 further comprising flowing a solution through the preconnected leukoreduction filter after the pushing step to displace high hematocrit mononuclear cell-reduced red blood cells from the filter.

18. The method of claim 17 wherein the flowing step comprises flowing a storage solution.

19. The method of claim 6 wherein the separating step comprises separating in a continuous manner and wherein the step of leukoreducing the mononuclear-reduced red blood cells occurs at least partially during the step of separating in a continuous manner.

20. A method for increasing the performance of a leukoreduction filter for leukoreducing cells collected during an apheresis procedure comprising the steps of:

separating in a blood separation vessel whole blood into

an innermost layer containing at least plasma;

an intermediate layer containing at least buffy coat; and

an outermost layer containing at least red blood cells;

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removing the innermost layer from the blood separation vessel;

removing the intermediate layer from the blood separation vessel; and

removing a portion of the outermost layer closest to the intermediate layer to create a mononuclear cell-reduced red blood cell layer in the blood separation vessel to be further leukoreduced using the leukoreduction filter.

21. The method of claim 20 wherein the step of removing a portion of the outermost layer closest to the intermediate layer increases the performance of the leukoreduction filter by removing mononuclear cells which may clog the leukoreduction filter.

22. The method of claim 20 wherein the step of removing a portion of the outermost layer closest to the intermediate layer increases the performance of the leukoreduction filter by removing mononuclear cells which may be too numerous to be effectively removed by the leukoreduction filter.

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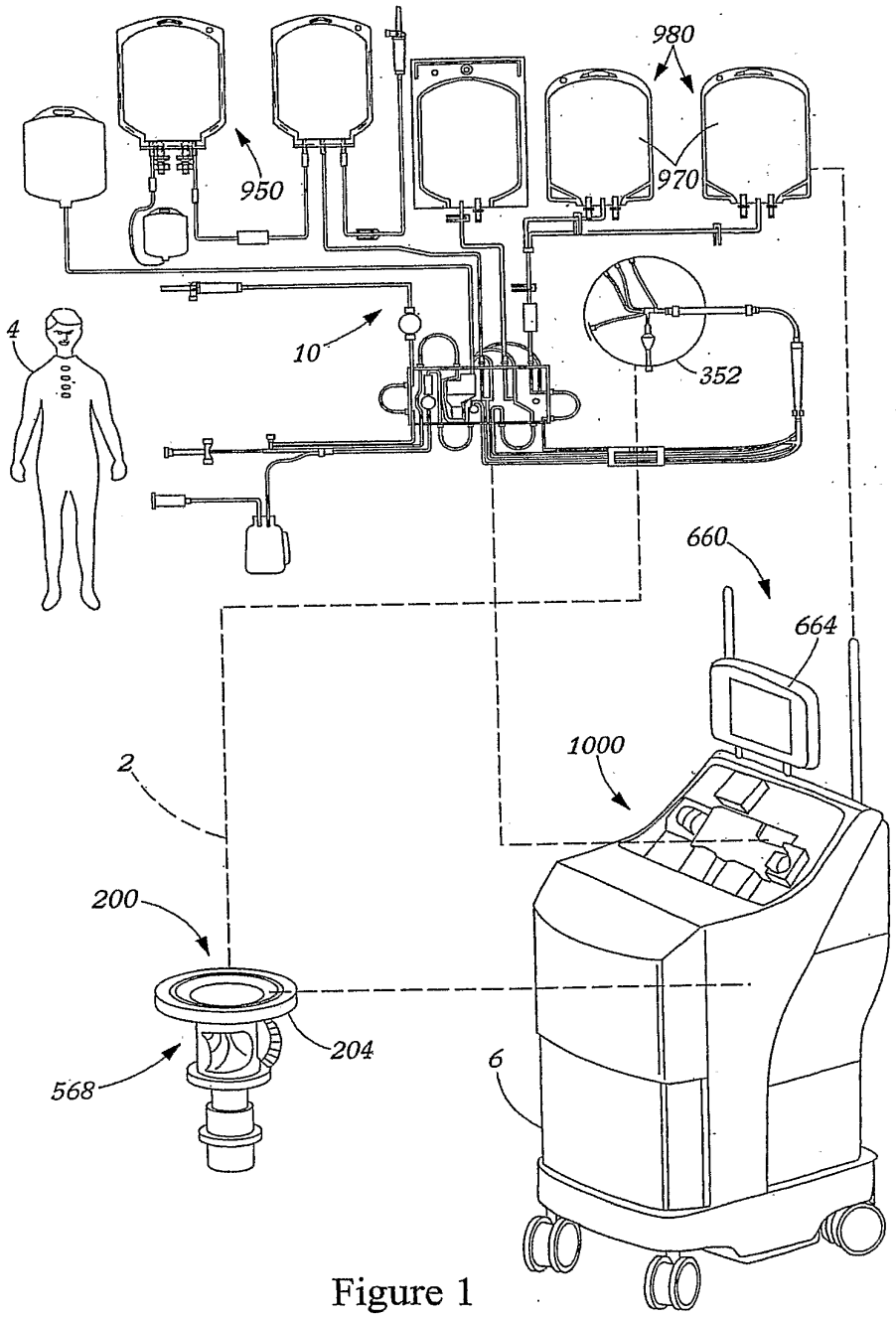


Figure 1

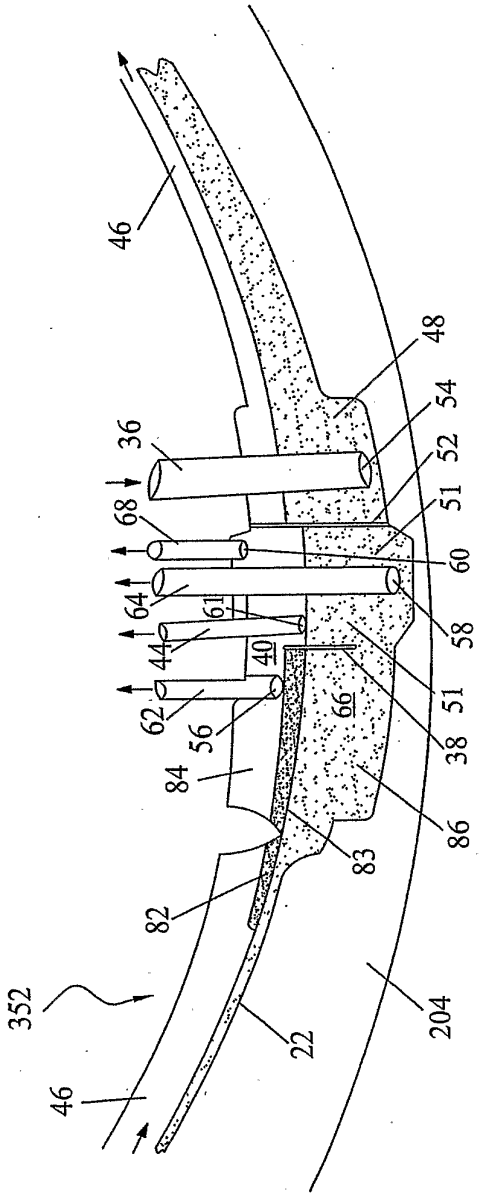

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Figure 2

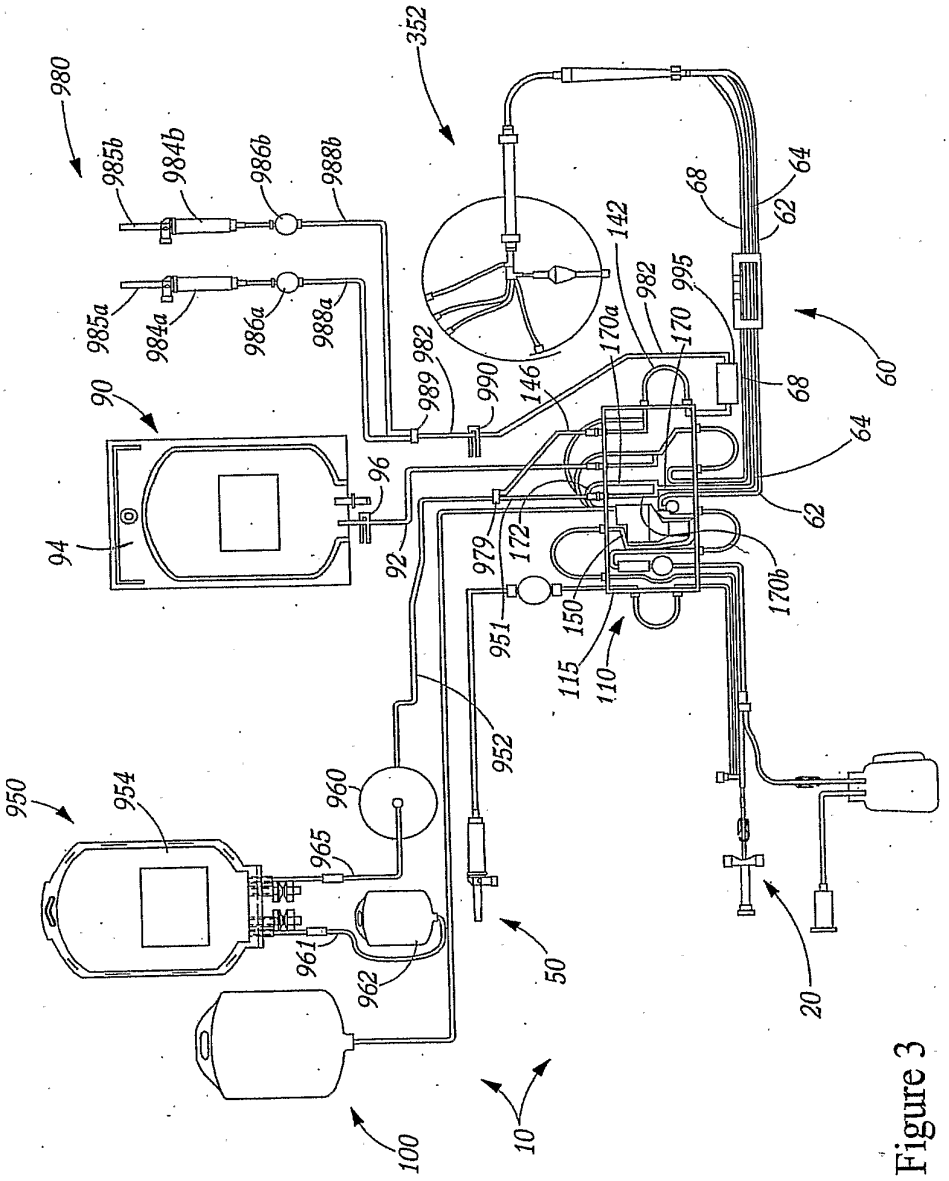

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Figure 3

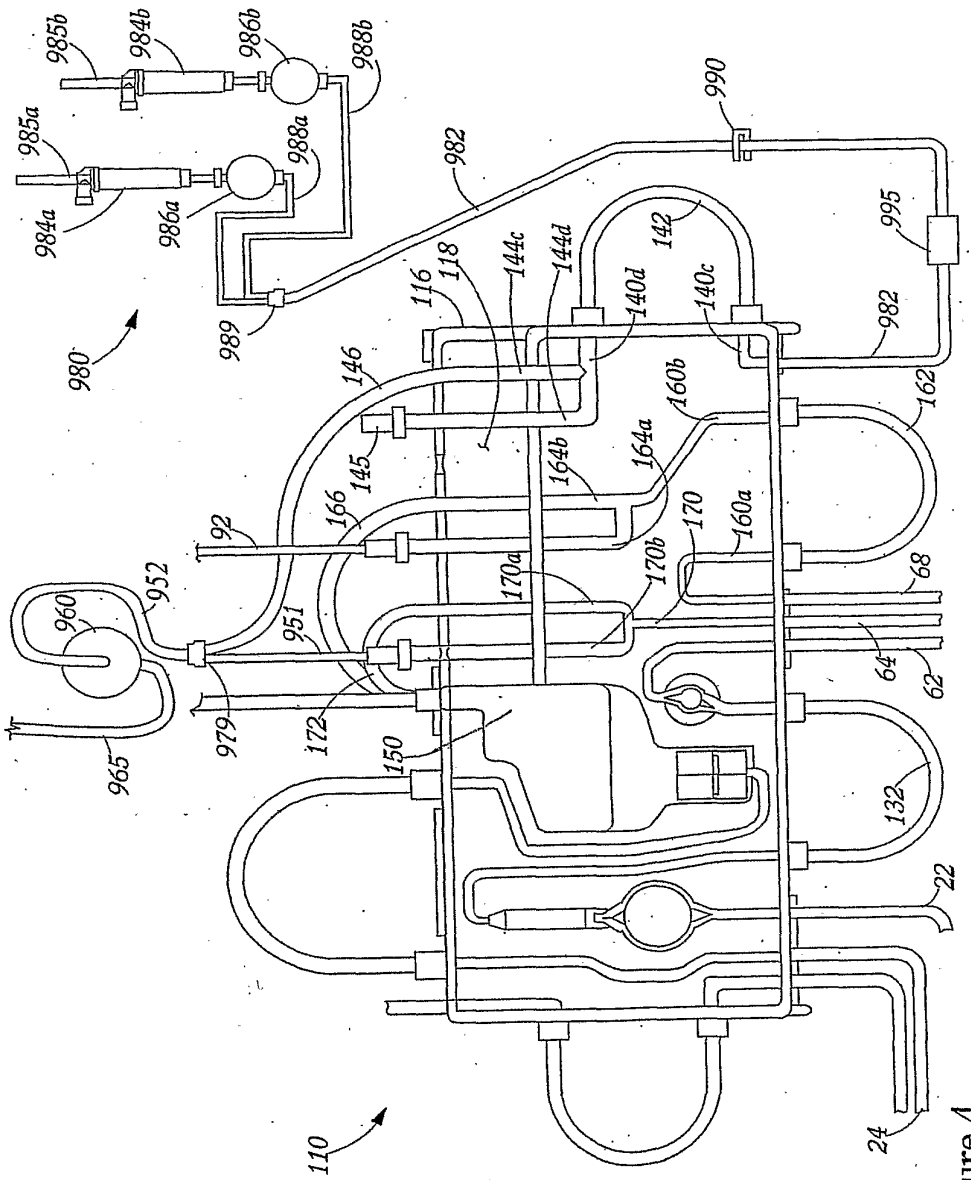

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Figure 4

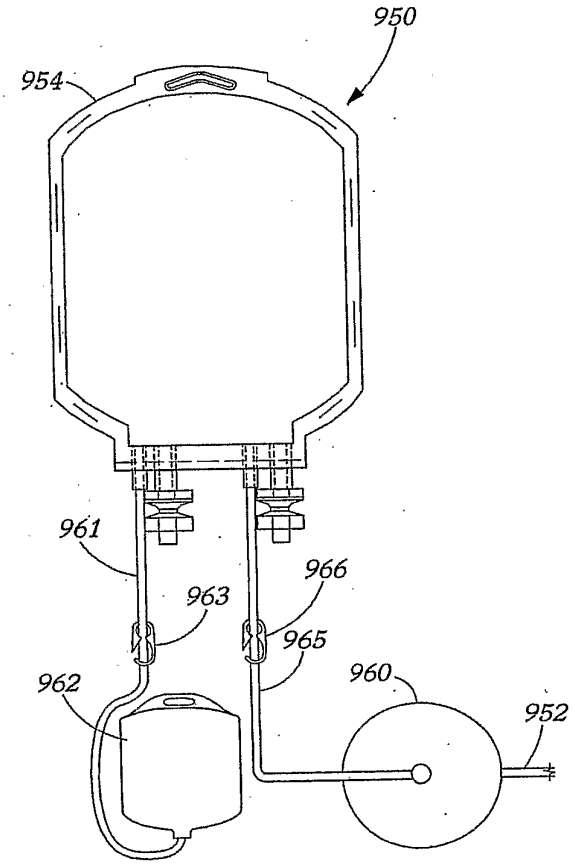


Figure 5

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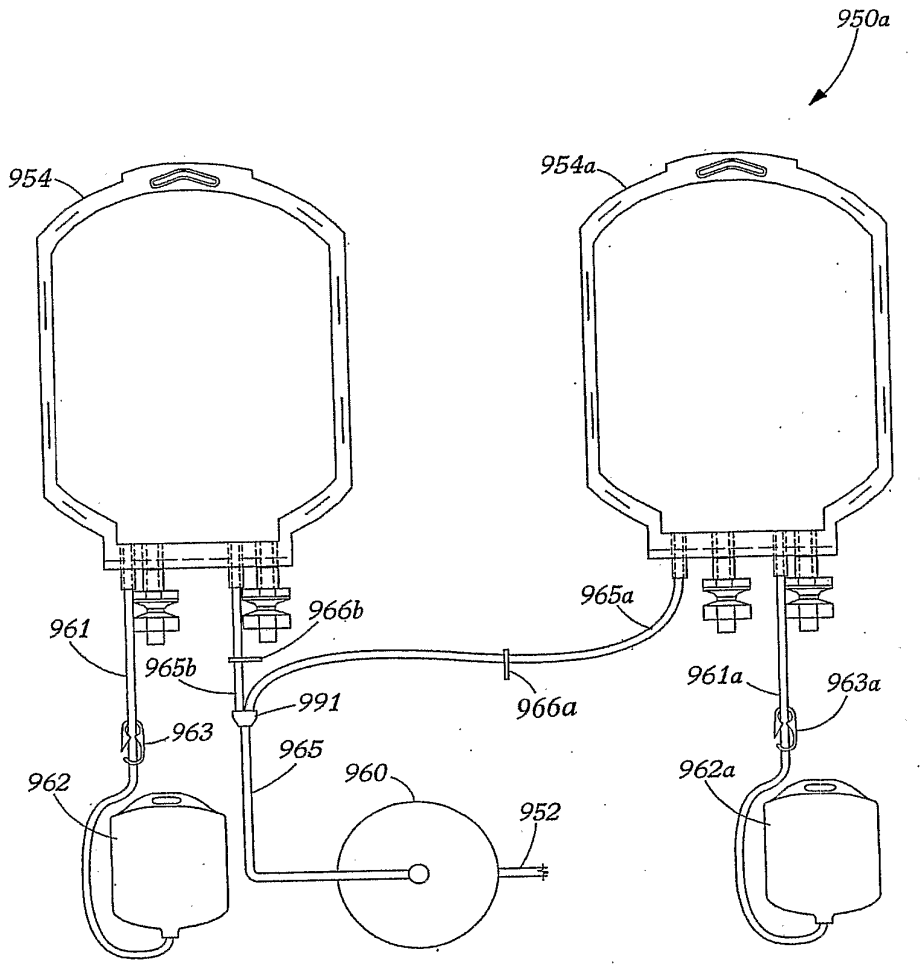

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Figure 6A

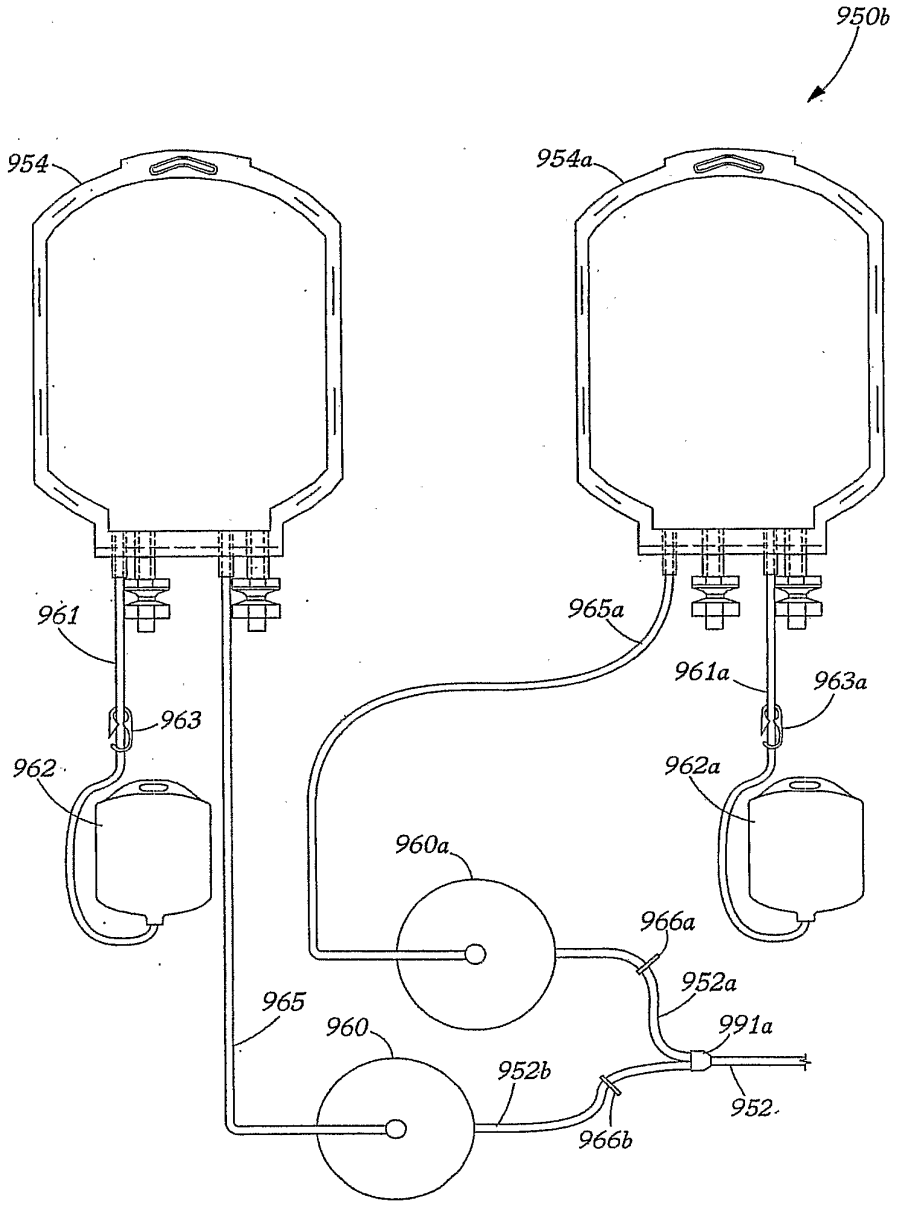

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Figure 6B

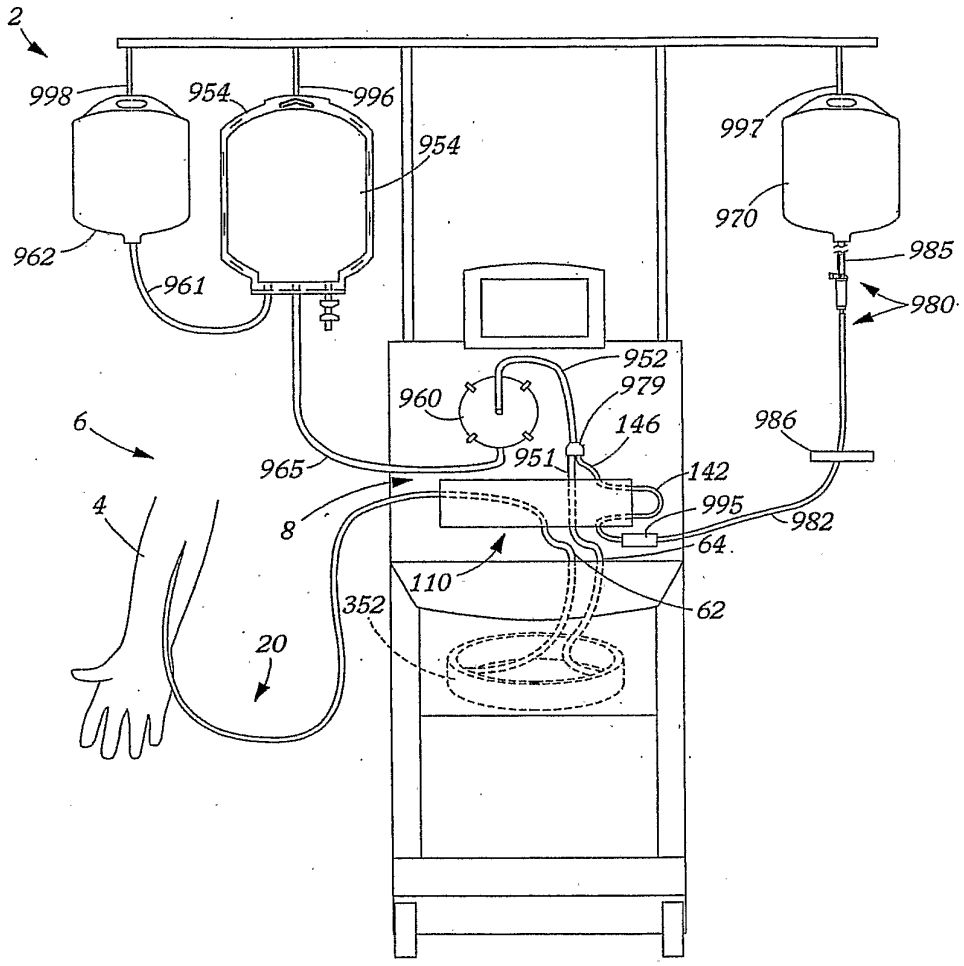

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Figure 7

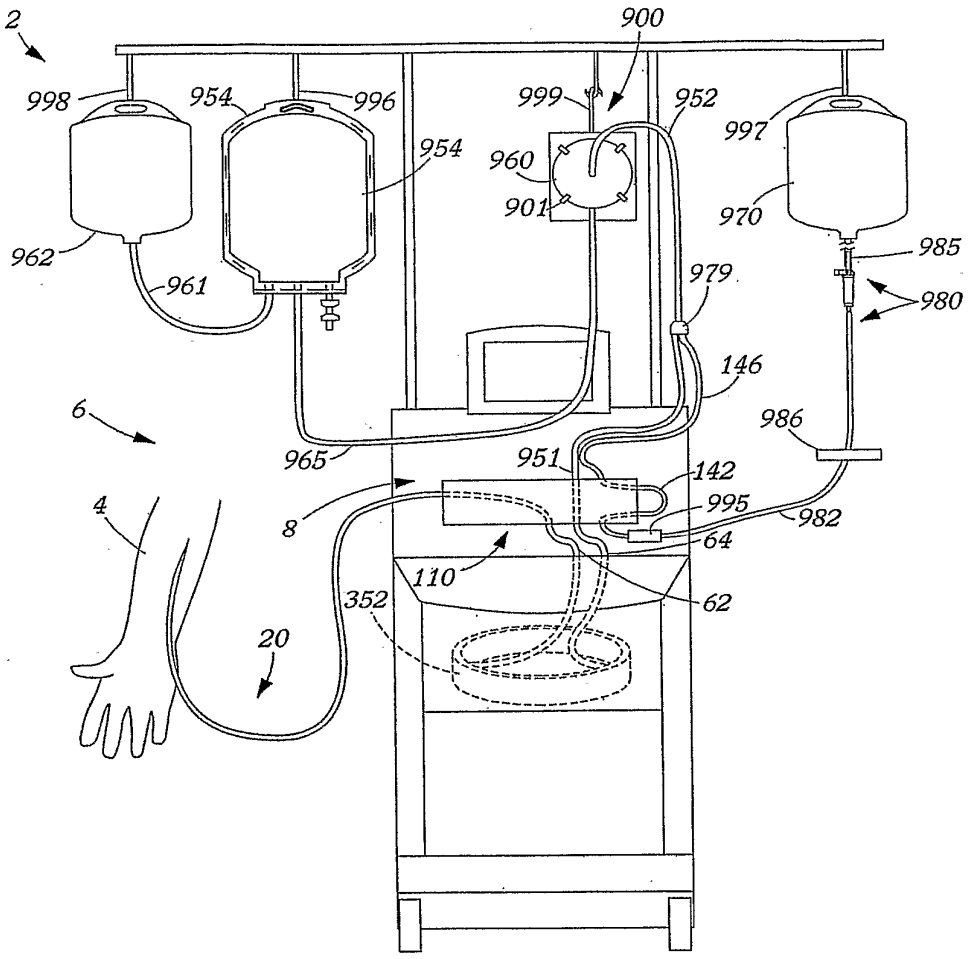

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Figure 8

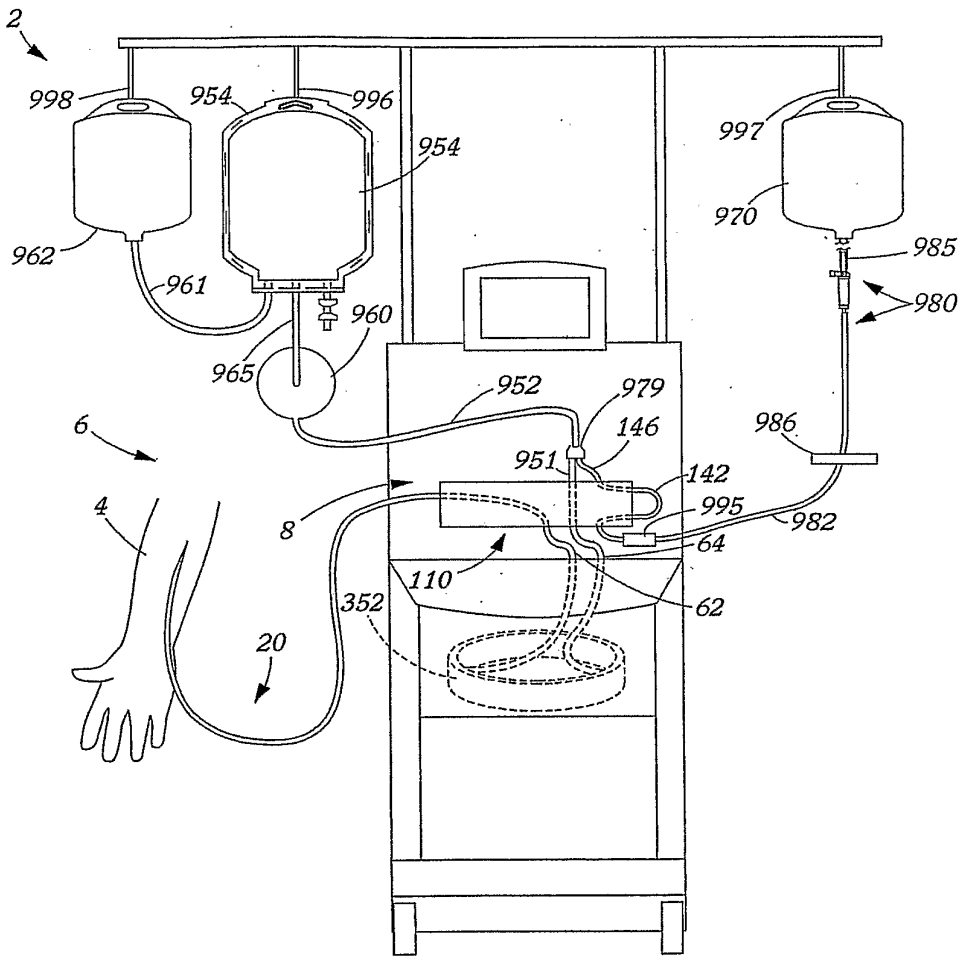

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Figure 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/039153

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M1/36 A61M1/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/106861 A1 (GIBBS BRUCE M [US] ET AL) 12 June 2003 (2003-06-12) paragraphs [0048] - [0057] paragraph [0071] figures 1-8,10-13	20-22
A	US 6 053 856 A (HLAVINKA DENNIS [US]) 25 April 2000 (2000-04-25) column 6, line 56 - column 8, line 67 column 16, line 49 - column 17, line 37 figure 2	20-22
A	US 2004/079707 A1 (SMITH KELLY B [US] ET AL) 29 April 2004 (2004-04-29) paragraphs [0104] - [0110]	20-22

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2007	01/02/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	BICHLMAYER, K

Form PCT/ISA/210 (second sheet) (April 2005)

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1126

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/039153

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 464 167 A (SCHOENDORFER DONALD W [US] ET AL) 7 August 1984 (1984-08-07) figure 3	20-22
A	WO 98/46362 A (OMEGA MEDICINTEKNIK AB [SE]; UNGER PETER [SE]; WESTBERG ERIC [SE]) 22 October 1998 (1998-10-22) page 7, lines 4-35	20-22

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1127

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/039153

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-19
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1128

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/039153

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003106861 A1	12-06-2003	US 2006184086 A1	17-08-2006
US 6053856 A	25-04-2000	AU 702151 B2	18-02-1999
		AU 5560896 A	07-11-1996
		BR 9608031 A	30-11-1999
		DE 69618453 D1	14-02-2002
		DE 69618453 T2	07-11-2002
		DE 69634860 D1	21-07-2005
		DE 69634860 T2	11-05-2006
		EP 0824380 A1	25-02-1998
		JP 11503966 T	06-04-1999
		WO 9633023 A1	24-10-1996
		US 5939319 A	17-08-1999
US 2004079707 A1	29-04-2004	NONE	
US 4464167 A	07-08-1984	NONE	
WO 9846362 A	22-10-1998	AT 261776 T	15-04-2004
		AU 720556 B2	01-06-2000
		AU 7093098 A	11-11-1998
		DE 69822481 D1	22-04-2004
		EP 1011871 A1	28-06-2000
		JP 2001520570 T	30-10-2001
		US 6261217 B1	17-07-2001

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1129

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1611-C80WO	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2018/033826	International filing date *(day/month/year)* 22 May 2018	(Earliest) Priority Date *(day/month/year)* 30 May 2017
Applicant HAEMONETICS CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      ☒ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1130

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/033826

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61M 1/02; A61M 1/30; A61M 1/34; A61M 1/36; A61M 1/38 (2018.01)

CPC - A61M 1/382; A61M 1/0213; A61M 1/024; A61M 1/304; A61M 1/3424; A61M 1/3441; A61M 1/3609; A61M 1/385 (2018.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 435/4; 435/7.25; 435/13; 604/4.01; 604/5.01; 604/6.01; 604/6.04; 604/6.09; 604/6.11; 702/19; 702/45 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/0125881 A1 (RYAN) 03 July 2003 (03.07.2003) entire document	1, 3, 5, 6, 8, 10-12, 14, 16, 17, 19
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Y		2, 4, 7, 9, 13, 18, 20
Y	US 2012/0175313 A1 (BARRY, JR. et al) 12 July 2012 (12.07.2012) entire document	2, 4, 13
Y	US 2014/0039373 A1 (HAEMONETICS CORPORATION) 06 February 2014 (06.02.2014) entire document	7, 18
Y	US 2014/0356851 A1 (HAEMONETICS CORPORATION) 04 December 2014 (04.12.2014) entire document	9, 20
A	US 5,970,432 A (ISHIMOTO et al) 19 October 1999 (19.10.1999) entire document	1-20
A	US 7,270,645 B2 (LANGLEY et al) 18 September 2007 (18.09.2007) entire document	1-20
A	US 8,759,094 B2 (RÄNBY) 24 June 2014 (24.06.2014) entire document	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 July 2018	03 AUG 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: JONATHAN C. LOVELY
SUNSTEIN KANN MURPHY & TIMBERS LLP
125 SUMMER STREET
BOSTON, MA 02110-1618

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	03 AUG 2018
Applicant's or agent's file reference 1611-C80WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2018/033826	22 May 2018	30 May 2017

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61M 1/02; A61M 1/30; A61M 1/34; A61M 1/36; A61M 1/38 (2018.01)
CPC - A61M 1/382; A61M 1/0213; A61M 1/024; A61M 1/304; A61M 1/3424; A61M 1/3441; A61M 1/3609; A61M 1/385 (2018.05)

Applicant HAEMONETICS CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	09 July 2018	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2018/033826

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
   - [X] the international application in the language in which it was filed.
   - [ ] a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. [ ] This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).

3. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
   - a. [ ] forming part of the international application as filed:
     - [ ] in the form of an Annex C/ST.25 text file.
     - [ ] on paper or in the form of an image file.
   - b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
   - c. [ ] furnished subsequent to the international filing date for the purposes of international search only:
     - [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
     - [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1133

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2018/033826

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2, 4, 7, 9, 13, 15, 18, 20	YES
	Claims	1, 3, 5, 6, 8, 10-12, 14, 16, 17, 19	NO
Inventive step (IS)	Claims	15	YES
	Claims	1-14, 16-20	NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1, 3, 5, 6, 8, 10-12, 14, 16, 17, and 19 lack novelty under PCT Article 33(2) as being anticipated by Ryan.

Regarding Claim 1, Ryan discloses a method for collecting plasma (abstract) comprising: (a) determining a weight of a donor (determination of the amount of plasma which can be derived from an individual donor 11 is calculated based on the donor's body weight, hematocrit and the amount of anticoagulant used in the procedure, para. 0014; paras. 0014-0018 regarding the equation); (b) determining a hematocrit of the donor (determination of the amount of plasma which can be derived from an individual donor 11 is calculated based on the donor's body weight, hematocrit and the amount of anticoagulant used in the procedure, para. 0014; paras. 0014-0018 regarding the equation); (c) inserting a venous-access device into the donor (extract whole blood from a donor 11 via an intravenous needle 12 which has been positioned in the vein of the donor by a technician, para. 0011, fig. 1); (d) withdrawing whole blood from the donor through the venous-access device and a draw line, the draw line connected to a blood component separation device (typical plasmapheresis system operating in the collection mode to pump or extract whole blood from a donor 11 via an intravenous needle 12 which has been positioned in the vein of the donor by a technician. The whole blood leaves donor 11 via needle 12 and moved through tube 13, para. 0011; Separator 26 is a conventional plasma separation membrane device, para. 0012, fig. 1); (e) introducing anticoagulant into the withdrawn whole blood through an anticoagulant line (In system 10, an anticoagulant, such as sodium citrate is contained in reservoir 18 and is pumped through anticoagulant line 20 by anticoagulant pump 22 to intravenous needle 12 where anticoagulant line 20 is joined with tube 13 by one-way valve 24, mixing of the anticoagulant with the whole blood prior to movement of the whole blood through tube 13, para. 0011, fig. 1); (f) separating the withdrawn whole blood into a plasma component and at least a second blood component using the blood component separation device (Separator 26 is a conventional plasma separation membrane device which comprises a membrane that allows the passage of the plasma component of whole blood therethrough while preventing passage of the cellular components of whole blood through the membrane, separation of the plasma component of blood from the cellular components of blood. After separation, the plasma component passes through plasma tube 28 and through plasma valve 30 and is deposited in plasma reservoir 32. The cellular component of whole blood leaves separator 26 along cellular output line 34, para. 0012); (g) collecting the plasma component from the blood component separation device and into a plasma collection container (After separation, the plasma component passes through plasma tube 28 and through plasma valve 30 and is deposited in plasma reservoir 32, para. 0012); (h) calculating a percentage of anticoagulant in the collected plasma component (paras .0038-0043 regarding the equation for calculation; paras. 0014-0019); calculating a volume of pure plasma collected within the plasma collection container based, at least in part, on the calculated percentage of anticoagulant in the collected plasma component (After processor 48 has calculated the volume of plasma which may be removed from donor 11 and has calculated the expected blood volume from which will be obtained from that volume of plasma, controller 46 will operate to initiate the functioning of pump 14 by communicating with pump 14 through communication line 50. The course of pumping by pump 14, rate of actual pumping can be compared with the intended volume of blood that is to be extracted from donor 11. The comparison of expected blood volume to be extracted from donor 11, and the blood volume that is actually extracted from donor 11, is a matter of a continuing calculation based upon the number of revolutions of pump 14 and the amount of blood that is pumped with each revolution of pump 14. This calculation is then continually compared with the volume of blood to be removed from donor 11 as determined by processor 48 at the beginning of the operation. Upon obtaining that goal, controller 46 can shut down pump 14 or notify the operator that the desired volume of blood has been pumped from donor 11, para. 0038; paras .0038-0043 regarding the equation for calculation; paras. 0014-0019); and continuing steps (d) through (i) until a target volume of pure plasma is collected within the plasma collection container (comparison of expected blood volume to be extracted from donor 11, and the blood volume that is actually extracted from donor 11, is a matter of a continuing calculation based upon the number of revolutions of pump 14 and the amount of blood that is pumped with each revolution of pump 14. This calculation is then continually compared with the volume of blood to be removed from donor 11 as determined by processor 48 at the beginning of the operation. Upon obtaining that goal, controller 46 can shut down pump 14 or notify the operator that the desired volume of blood has been pumped from donor 11, para. 0038; paras .0038-0043 regarding the equation for calculation; paras. 0014-0019).

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1134

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2018/033826

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Regarding Claim 3, Ryan discloses a method according claim 1, further comprising: determining a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump (After processor 48 has calculated the volume of plasma which may be removed from donor 11 and has calculated the expected blood volume from which will be obtained from that volume of plasma, controller 46 will operate to initiate the functioning of pump 14 by communicating with pump 14 through communication line 50. The course of pumping by pump 14, rate of actual pumping can be compared with the intended volume of blood that is to be extracted from donor 11. The comparison of expected blood volume to be extracted from donor 11, and the blood volume that is actually extracted from donor 11, is a matter of a continuing calculation based upon the number of revolutions of pump 14 and the amount of blood that is pumped with each revolution of pump 14. This calculation is then continually compared with the volume of blood to be removed from donor 11 as determined by processor 48 at the beginning of the operation. Upon obtaining that goal, controller 46 can shut down pump 14 or notify the operator that the desired volume of blood has been pumped from donor 11, para. 0038; paras .0038-0043 regarding the equation for calculation; paras. 0014-0019).

Regarding Claim 5, Ryan discloses a method according to claim 1, further comprising: monitoring a volume of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component (volume of plasma in reservoir 32 can be determined by weight or by volume using optical sensors which respond to the change in light transmission through plasma reservoir 32, data from the scale or from the optical sensor is transmitted to controller 46 and to processor 48 which monitor the amount of plasma collected. Controller 46 is responsive to processor 48 which can be any type of conventional microprocessor available for use in calculation and control functions, para. 0031).

Regarding Claim 6, Ryan discloses a method according to claim 1, further comprising: monitoring a weight of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component (control of system 10 is provided by communications link 52 which provides controller 46 with data on the volume of plasma that has arrived in plasma reservoir 32 as a result of the functioning of separator 26 on whole blood received by the pumping of pump 14. It will be appreciated by those skilled in the art that the volume of plasma in reservoir 32 can be determined by weight or by volume using optical sensors which respond to the change in light transmission through plasma reservoir 32 as various portions of plasma reservoir 32 fill with plasma, para. 0031, fig. 1).

Regarding Claim 8, Ryan discloses a method according to claim 1, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor (determination of the amount of plasma which can be derived from an individual donor 11 is calculated based on the donor's body weight, hematocrit and the amount of anticoagulant used in the procedure, para. 0014; paras. 0014-0018 regarding the equation).

Regarding Claim 10, Ryan discloses a method according to claim 1, further comprising: returning, after collecting at least a portion of the target volume of pure plasma, the second blood component to the donor through a return line (cellular component of whole blood leaves separator 26 along cellular output line 34, movement of the whole blood cellular component from separator 26 is assisted by cellular component pump 36 whereupon the whole blood cellular component is passed along line 38 until it is deposited in cellular component holding reservoir 40 until it is reinfused into donor 11 along reinfusion line 42 which passes through blood pump 14 and back into donor 11, para. 0012, fig. 1).

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Regarding Claim 11, Ryan discloses a system for collecting plasma (abstract) comprising: a venous-access device for drawing whole blood from a subject and returning blood components to the subject (extract whole blood from a donor 11 via an intravenous needle 12 which has been positioned in the vein of the donor by a technician, para. 0011, fig. 2); a blood component separation device for separating the drawn blood into a plasma component and a second blood component, the blood component separation device having an outlet and being configured to send the plasma component to a plasma container (Separator 26 is a conventional plasma separation membrane device which comprises a membrane that allows the passage of the plasma component of whole blood therethrough while preventing passage of the cellular components of whole blood through the membrane, separation of the plasma component of blood from the cellular components of blood. After separation, the plasma component passes through plasma tube 28 and through plasma valve 30 and is deposited in plasma reservoir 32. The cellular component of whole blood leaves separator 26 along cellular output line 34, para. 0012); a blood draw line fluidly connected to the venous-access device and configured to transport drawn whole blood to the blood component separation device, the flow through the blood draw line being controlled by a blood draw pump (plasmapheresis system operating in the collection mode to pump or extract whole blood from a donor 11 via an intravenous needle 12 which has been positioned in the vein of the donor by a technician, para. 0011; Separator 26 is a conventional plasma separation membrane device, para. 0012, fig. 2; whole blood leaves donor 11 via needle 12 and moves through tube 13 until it contacts whole blood pump 14 which serves to continue to move the whole blood along the preseparator tube 15, para. 0011); an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood (anticoagulant, such as sodium citrate is contained in reservoir 18 and is pumped through anticoagulant line 20 by anticoagulant pump 22 to intravenous needle 12 where anticoagulant line 20 is joined with tube 13, para. 0011); and a controller configured to control the operation of the centrifuge bowl and the blood draw pump, the controller configured to calculate (1) a percentage of anticoagulant in the collected plasma component, and (2) a volume of pure plasma collected within the plasma container based, at least in part, upon the percentage of anticoagulant in the collected plasma component, the controller configured to stop the blood draw pump when a target volume of pure plasma is collected within the plasma container (processor 48 of controller 46 to determine the plasma and anticoagulant volume to be obtained from a donor of a donor-specific body weight, para. 0025, fig. 2; After processor 48 has calculated the volume of plasma which may be removed from donor 11 and has calculated the expected blood volume from which will be obtained from that volume of plasma, controller 46 will operate to initiate the functioning of pump 14 by communicating with pump 14 through communication line 50. The course of pumping by pump 14, rate of actual pumping can be compared with the intended volume of blood that is to be extracted from donor 11. The comparison of expected blood volume to be extracted from donor 11, and the blood volume that is actually extracted from donor 11, is a matter of a continuing calculation based upon the number of revolutions of pump 14 and the amount of blood that is pumped with each revolution of pump 14. This calculation is then continually compared with the volume of blood to be removed from donor 11 as determined by processor 48 at the beginning of the operation. Upon obtaining that goal, controller 46 can shut down pump 14 or notify the operator that the desired volume of blood has been pumped from donor 11, para. 0038; paras .0038-0043 regarding the equation for calculation of received products; paras. 0014-0019).

Regarding Claim 12, Ryan discloses a system according to claim 11, wherein the percentage of anticoagulant in the collected plasma component is based, at least in part, on a volume of anticoagulant added to the drawn whole blood and the subject's hematocrit (processor 48 of controller 46 to determine the plasma and anticoagulant volume to be obtained from a donor of a donor-specific body weight, para. 0025, fig. 2; paras .0038-0043 regarding the equation for calculation of received products, equation includes hematocrit and anticoagulant; paras. 0014-0019).

Regarding Claim 14, Ryan discloses a system according to claim 11, wherein the controller is configured to monitor a number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump (processor 48 of controller 46 to determine the plasma and anticoagulant volume to be obtained from a donor of a donor-specific body weight, para. 0025, fig. 2; After processor 48 has calculated the volume of plasma which may be removed from donor 11 and has calculated the expected blood volume from which will be obtained from that volume of plasma, controller 46 will operate to initiate the functioning of pump 14 by communicating with pump 14 through communication line 50. The course of pumping by pump 14, rate of actual pumping can be compared with the intended volume of blood that is to be extracted from donor 11. The comparison of expected blood volume to be extracted from donor 11, and the blood volume that is actually extracted from donor 11, is a matter of a continuing calculation based upon the number of revolutions of pump 14 and the amount of blood that is pumped with each revolution of pump 14. This calculation is then continually compared with the volume of blood to be removed from donor 11 as determined by processor 48 at the beginning of the operation. Upon obtaining that goal, controller 46 can shut down pump 14 or notify the operator that the desired volume of blood has been pumped from donor 11, para. 0038; paras .0038-0043 regarding the equation for calculation of received products; paras. 0014-0019).

Regarding Claim 16, Ryan discloses a system according to claim 11, further comprising: a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component (control of system 10 is provided by communications link 52 which provides controller 46 with data on the volume of plasma that has arrived in plasma reservoir 32 as a result of the functioning of separator 26 on whole blood received by the pumping of pump 14. It will be appreciated by those skilled in the art that the volume of plasma in reservoir 32 can be determined by weight or by volume using optical sensors which respond to the change in light transmission through plasma reservoir 32 as various portions of plasma reservoir 32 fill with plasma, para. 0031, fig. 1).

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

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Regarding Claim 17, Ryan discloses a system according to claim 11, further comprising: a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component (control of system 10 is provided by communications link 52 which provides controller 46 with data on the volume of plasma that has arrived in plasma reservoir 32 as a result of the functioning of separator 26 on whole blood received by the pumping of pump 14. It will be appreciated by those skilled in the art that the volume of plasma in reservoir 32 can be determined by weight or by volume using optical sensors which respond to the change in light transmission through plasma reservoir 32 as various portions of plasma reservoir 32 fill with plasma, para. 0031, fig. 1).

Regarding Claim 19, Ryan discloses a system according to claim 11, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor (determination of the amount of plasma which can be derived from an individual donor 11 is calculated based on the donor's body weight, hematocrit and the amount of anticoagulant used in the procedure, para. 0014; paras. 0014-0018 regarding the equation).

Claims 2, 4, and 13 lack an inventive step under PCT Article 33(3) as being obvious over Ryan in view of Barry, Jr. et al. (hereinafter Barry).

Regarding Claim 2, Ryan discloses a method according to claim 1, but Ryan fails to explicitly disclose further comprising: determining a change in volume within an anticoagulant container, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant container.
Barry is in the field of automatically adjusting the operational parameters of a blood separation procedure (abstract) and teaches determining a change in volume within an anticoagulant container, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant container (e holding trays 144 comprise molded recesses in the base 20 which accommodate selected containers of the flow set 12. and may also include weight sensors, para. 0056; Using the weight sensors, the controller 16 can continuously determine the actual volume of fluid that is moved per pump stroke and correct for any deviations from commanded flow. The controller 16 can also diagnose exceptional situations, such as leaks and obstructions in the fluid path. This measure of monitoring and control is desirable in an automated apheresis application, where it is desirable for anticoagulant to be accurately metered with the whole blood as it is drawn from the donor, and where product quality, plasma purity, may be influenced by the accuracy of the pump flow rates, para. 0057). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Barry for the purpose of continuously monitoring the source fluid container volumes thereby allowing a control measure for product quality (Barry, para. 0057).

Regarding Claim 4, Ryan discloses a method according to claim 1, but Ryan fails to explicitly disclose further comprising: determining a volume of anticoagulant within the blood component separation device, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.
Barry is in the field of automatically adjusting the operational parameters of a blood separation procedure (abstract) and teaches determining a volume of anticoagulant within the blood component separation device, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device (holding trays 144 comprise molded recesses in the base 20 which accommodate selected containers of the flow set 12. and may also include weight sensors, para. 0056; Using the weight sensors, the controller 16 can continuously determine the actual volume of fluid that is moved per pump stroke and correct for any deviations from commanded flow. This measure of monitoring and control is desirable in an automated apheresis application, where it is desirable for anticoagulant to be accurately metered with the whole blood as it is drawn from the donor, and where product quality, plasma purity, may be influenced by the accuracy of the pump flow rates, para. 0057). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Barry for the purpose of continuously monitoring the source fluid container volumes thereby allowing a control measure for product quality (Barry, para. 0057).

Regarding Claim 13, Ryan discloses a system according to claim 11, but Ryan fails to explicitly disclose further comprising: an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant container based on the measured weight of the anticoagulant source, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant source.
Barry is in the field of automatically adjusting the operational parameters of a blood separation procedure (abstract) and teaches an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant container based on the measured weight of the anticoagulant source, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant source (holding trays 144 comprise molded recesses in the base 20 which accommodate selected containers of the flow set 12. and may also include weight sensors, para. 0056; Using the weight sensors, the controller 16 can continuously determine the actual volume of fluid that is moved per pump stroke and correct for any deviations from commanded flow. This measure of monitoring and control is desirable in an automated apheresis application, where it is desirable for anticoagulant to be accurately metered with the whole blood as it is drawn from the donor, and where product quality, plasma purity, may be influenced by the accuracy of the pump flow rates, para. 0057). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Barry for the purpose of continuously monitoring the source fluid container volumes thereby allowing a control measure for product quality (Barry, para. 0057).

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Petitioner Terumo Exhibit 1021-1137

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
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Claims 7 and 18 lack an inventive step under PCT Article 33(3) as being obvious over Ryan in view of US 2014/0039373 A1 to Haemonetics Corporation (hereinafter Haemonetics'373).

Regarding Claim 7, Ryan discloses a method according to claim 1, but Ryan fails to explicitly disclose wherein step (b) includes monitoring a volume of red blood cells collection within the blood separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor.
Haemonetics'373 is in the field of an apparatus for separating whole blood (abstract) and teaches monitoring a volume of red blood cells collection within the blood separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor (controller 190 may also monitor the output signal from the optical sensor 14 to determine when the bowl 120 is full of red blood cells, para. 0038; input device 198 may allow the user to input a target volume of whole blood to withdraw, a target volume of red blood cells to collect, and/or the hematocrit value of the whole blood being drawn into the system 100, controller 190 may control the speed of the centrifuge 110 based, at least in part, upon the hematocrit valve of the whole blood, the controller may increase the speed for high hematocrit donors, controller 190 may also receive outputs from the pressure sensors and a line sensor 14. The line sensor 14 may be an optical sensor that detects the presence of blood components passing through the line sensor 14 from the output port PT2, para. 0031; controller 190 may calculate the total volume of blood drawn from the source based upon the number of revolutions of the draw pump P1, para. 0037, 450, fig. 4). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Haemonetics'373 for the purpose of determining the hematocrit of the patient during removal of blood products thereby allowing greater patient safety and control of the flow through the system (Haemonetics'373, para. 0031).

Regarding Claim 18, Ryan discloses a system according to claim 11, but Ryan fails to explicitly disclose further comprising: an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood separation device, the controller configured to determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor.
Haemonetics'373 is in the field of an apparatus for separating whole blood (abstract) and teaches further comprising: an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood separation device, the controller configured to determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor (controller 190 may also monitor the output signal from the optical sensor 14 to determine when the bowl 120 is full of red blood cells, para. 0038; input device 198 may allow the user to input a target volume of whole blood to withdraw, a target volume of red blood cells to collect, and/or the hematocrit value of the whole blood being drawn into the system 100, controller 190 may control the speed of the centrifuge 110 based, at least in part, upon the hematocrit valve of the whole blood, the controller may increase the speed for high hematocrit donors, controller 190 may also receive outputs from the pressure sensors and a line sensor 14. The line sensor 14 may be an optical sensor that detects the presence of blood components passing through the line sensor 14 from the output port PT2, para. 0031; controller 190 may calculate the total volume of blood drawn from the source based upon the number of revolutions of the draw pump P1, para. 0037, 450, fig. 4). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Haemonetics'373 for the purpose of determining the hematocrit of the patient during removal of blood products thereby allowing greater patient safety and control of the flow through the system (Haemonetics'373, para. 0031).

Claims 9 and 20 lack an inventive step under PCT Article 33(3) as being obvious over Ryan in view of US 2014/0356851 A1 to Haemonetics Corporation (hereinafter Haemonetics'851).

Regarding Claim 9, Ryan discloses a method according to claim 1, but Ryan fails to explicitly disclose wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.
Haemonetics'851 is in the field of apheresis system that includes priming the blood apheresis system with anticoagulant (abstract) and teaches wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step (pumps P1 and P3 are energized to prime the tube 28 of the apparatus 10 with the anticoagulant, After priming, the venous access device 24 may be inserted into the donor and the draw step is ready to be commenced, para. 0030; FIG. 3 is a flowchart depicting a method for collecting blood components from a subject, During draw step 310, whole blood is drawn from the subject, typically at a rate of about 80 ml/min. and mixed with the anticoagulant using the pumps P1 and P3, pump P3 introduces and mixes the anticoagulant with the whole blood drawn from the subject, para. 0031). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Haemonetic'851 for the purpose of monitoring the anticoagulant in the plasma collection system thereby reducng the risk of returning too mush anticoagulant into the patient (Haemonetics'851, para. 0057).

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Petitioner Terumo Exhibit 1021-1138

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2018/033826

Supplemental Box

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Regarding Claim 20, Ryan discloses a system according to claim 11, but Ryan fails to explicitly disclose wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step
Haemonetics'851 is in the field of apheresis system that includes priming the blood apheresis system with anticoagulant (abstract) and teaches wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step (pumps P1 and P3 are energized to prime the tube 28 of the apparatus 10 with the anticoagulant, After priming, the venous access device 24 may be inserted into the donor and the draw step is ready to be commenced, para. 0030; FIG. 3 is a flowchart depicting a method for collecting blood components from a subject, During draw step 310, whole blood is drawn from the subject, typically at a rate of about 80 ml/min. and mixed with the anticoagulant using the pumps P1 and P3, pump P3 introduces and mixes the anticoagulant with the whole blood drawn from the subject, para. 0031). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Haemonetics'851 for the purpose of monitoring the anticoagulant in the plasma collection system thereby reducng the risk of returning too mush anticoagulant into the patient (Haemonetics'851, para. 0057).

Claim 15 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest:

Regarding claim 15, the prior art of record, individually or in combination, does not teach or fairly suggest a system according to claim 11, further comprising: an optical sensor located on the blood component separation device and configured to monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.

Claims 1-20 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/608,183	05/30/2017	Michael Ragusa	1611/C80

CONFIRMATION NO. 7286

86738
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
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PUBLICATION NOTICE

OC000000104263426

Title: System and Method for Collecting Plasma

Publication No.US-2018-0344910-A1
Publication Date:12/06/2018

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/608,183	05/30/2017	Michael Ragusa	1611/C80

CONFIRMATION NO. 7286

86738
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265 Franklin Street
Boston, MA 02110

POA ACCEPTANCE LETTER

OC000000103659714

Date Mailed: 11/08/2018

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/05/2018.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mbeyene/

Terumo v. Haemonetics - PGR2025-00077
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/608,183	05/30/2017	Michael Ragusa	1611/C80

CONFIRMATION NO. 7286

2101
Sunstein Kann Murphy & Timbers LLP
125 SUMMER STREET
BOSTON, MA 02110-1618

POWER OF ATTORNEY NOTICE

OC000000103659686

Date Mailed: 11/08/2018

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/05/2018.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mbeyene/

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1142

PTO/SB/81 (01-09)
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Application Number	
Filing Date	
First Named Inventor	
Title	
Art Unit	
Examiner Name	
Attorney Docket Number	

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

86738

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

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I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature	John F. Perullo	Date	10/23/18
Name	John F. Perullo	Telephone	
Title and Company	Vice President, Associate General Counsel and Chief Intellectual Property Officer, Haemonetics Corporation		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1143

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Haemonetics Corporation

Application No./Patent No.: 15/608,183 Filed/Issue Date: May 30, 2017

Titled: SYSTEM AND METHOD FOR COLLECTING PLASMA

Haemonetics Corporation (Name of Assignee) , a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [x] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [x] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 045684 , Frame 0875 , or for which a copy thereof is attached.

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
   Reel _____ , Frame _____ , or for which a copy thereof is attached.

2. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
   Reel _____ , Frame _____ , or for which a copy thereof is attached.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1145

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

4. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

5. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

6. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Jonathan C. Lovely, Reg. No. 60,821/	November 5, 2018
Signature	Date
Jonathan C. Lovely	60,821
Printed or Typed Name	Title or Registration Number

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1146

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

MAY 2, 2018

PTAS

JONATHAN C. LOVELY
SUNSTEIN KANN MURPHY & TIMBERS LLP
125 SUMMER STREET
BOSTON, MA 02110-1618

504894417

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT RECORDATION BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE ASSIGNMENT RECORDATION BRANCH AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT RECORDATION BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 05/01/2018 REEL/FRAME: 045684/0875
NUMBER OF PAGES: 5

BRIEF: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

DOCKET NUMBER: 1611/C80

ASSIGNOR:
RAGUSA, MICHAEL DOC DATE: 05/01/2018

ASSIGNEE:
HAEMONETICS CORPORATION
400 WOOD ROAD
BRAINTREE, MASSACHUSETTS 02184

APPLICATION NUMBER: 15608183 FILING DATE: 05/30/2017
PATENT NUMBER: ISSUE DATE:
TITLE: SYSTEM AND METHOD FOR COLLECTING PLASMA

ASSIGNMENT RECORDATION BRANCH
PUBLIC RECORDS DIVISION

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1147

504894417 05/01/2018

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

EPAS ID: PAT4941160

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
MICHAEL RAGUSA	05/01/2018

RECEIVING PARTY DATA

Name:	HAEMONETICS CORPORATION
Street Address:	400 WOOD ROAD
City:	BRAINTREE
State/Country:	MASSACHUSETTS
Postal Code:	02184

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	15608183

CORRESPONDENCE DATA

Fax Number: (617)443-0004

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.

Phone: 617-443-9292
Email: rmooney@sunsteinlaw.com
Correspondent Name: JONATHAN C. LOVELY
Address Line 1: SUNSTEIN KANN MURPHY & TIMBERS LLP
Address Line 2: 125 SUMMER STREET
Address Line 4: BOSTON, MASSACHUSETTS 02110-1618

ATTORNEY DOCKET NUMBER:	1611/C80
NAME OF SUBMITTER:	JONATHAN C. LOVELY
SIGNATURE:	/Jonathan C. Lovely, #60,821/
DATE SIGNED:	05/01/2018

Total Attachments: 4
source=ram1611_C80_Assignment#page1.tif
source=ram1611_C80_Assignment#page2.tif
source=ram1611_C80_Assignment#page3.tif
source=ram1611_C80_Assignment#page4.tif

Electronic Acknowledgement Receipt

EFS ID:	34200899
Application Number:	15608183
International Application Number:	
Confirmation Number:	7286
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Customer Number:	2101
Filer:	Jonathan Lovely
Filer Authorized By:	
Attorney Docket Number:	1611/C80
Receipt Date:	05-NOV-2018
Filing Date:	30-MAY-2017
Time Stamp:	14:48:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	102318_Haemonetics_Corporation_-_GPOA_PTO_SB_81.PDF	101461 e045cdd3cac0e73279ae6e112673dc3c3c6b312e	no	2

Warnings:

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1149

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
2	Assignee showing of ownership per 37 CFR 3.73	Statement_Under_37_CFR_3.pdf	24797 01c5ba3894abf12191366afc6028add72e3bc479	no	2
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	2916910_1.PDF	103809 946d57cbe62b4160b0dcadc5fe6418b2ffeb8c9e	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	230067	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Practitioner's Docket No. 1611/C80 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Michael Ragusa
Application No.: 15/608,183 Group No.: 3761
Filed: May 30, 2017 Examiner: Not yet assigned
For: System and Method for Collecting Plasma

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

RESPONSE TO INFORMATIONAL NOTICE TO APPLICANT

I. This replies to the Informational Notice to Applicant mailed on June 8, 2017. A copy of the Informational Notice to Applicant is attached.

DECLARATION OR OATH

II. The inventor's executed declaration is attached.

ADDITIONAL FEES

III. If any fees are required, please charge Deposit Account Number 19-4972.

DATE: August 24, 2017

/Jonathan C. Lovely, #60,821/

Jonathan C. Lovely
Registration No. 60,821
SUNSTEIN KANN MURPHY & TIMBERS LLP
Customer Number 02101
125 Summer Street
Boston, MA 02110-1618

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1151

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/608,183	05/30/2017	Michael Ragusa	1611/C80

CONFIRMATION NO. 7286

2101
Sunstein Kann Murphy & Timbers LLP
125 SUMMER STREET
BOSTON, MA 02110-1618

INFORMAL NOTICE

OC00000091875551

Date Mailed: 06/08/2017

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Michael Ragusa

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/snguyen/

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1152

Attorney Docket No. 1611/C80

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

(For Application filed on or after September 16, 2012)

Title of Invention: System and Method for Collecting Plasma

This declaration is directed to:

[ ] The attached application, or

[X] United States application or PCT international application number 15/608,183
filed on May 30, 2017
as amended on _____(if applicable).

The application was made or was authorized to be made by me.

I have reviewed and understand the contents of the above-identified application.

I believe myself to be the original inventor or an original joint inventor of a claimed invention in the application.

I acknowledge the duty to disclose to the US Patent and Trademark Office all information known to me to be material to patentability.

I hereby acknowledge that any willful false statement made in this Declaration is punishable under 18 U.S.C. § 1001, by fine or imprisonment of not more than five years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Michael Ragusa Date: 6/1/2017

Signature: Michael J Ragusa

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1153

Practitioner's Docket No. 1611/C80 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Michael Ragusa
Application No.: 15/608,183 Group No.: 3761
Filed: May 30, 2017 Examiner: Not yet assigned
For: System and Method for Collecting Plasma

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF REPLACEMENT DRAWINGS

Attached please find:

(a) Four replacement drawing sheets for figures 1-4.

(b) Please publish this application with these replacement drawings.

DATE: August 24, 2017

/Jonathan C. Lovely, #60,821/

Jonathan C. Lovely
Registration No. 60,821
SUNSTEIN KANN MURPHY & TIMBERS LLP
Customer Number 02101
125 Summer Street
Boston, MA 02110-1618

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1154

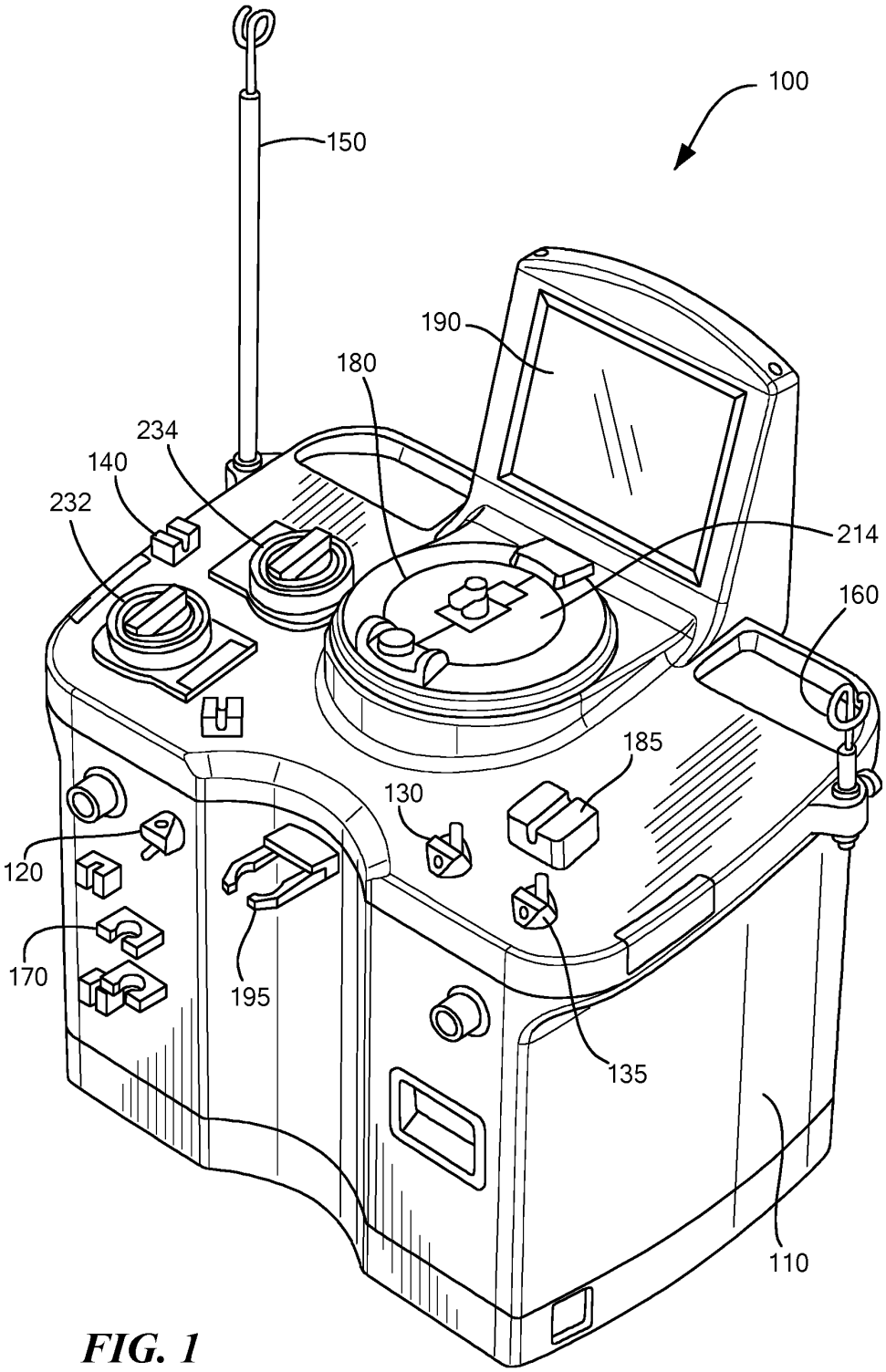


FIG. 1

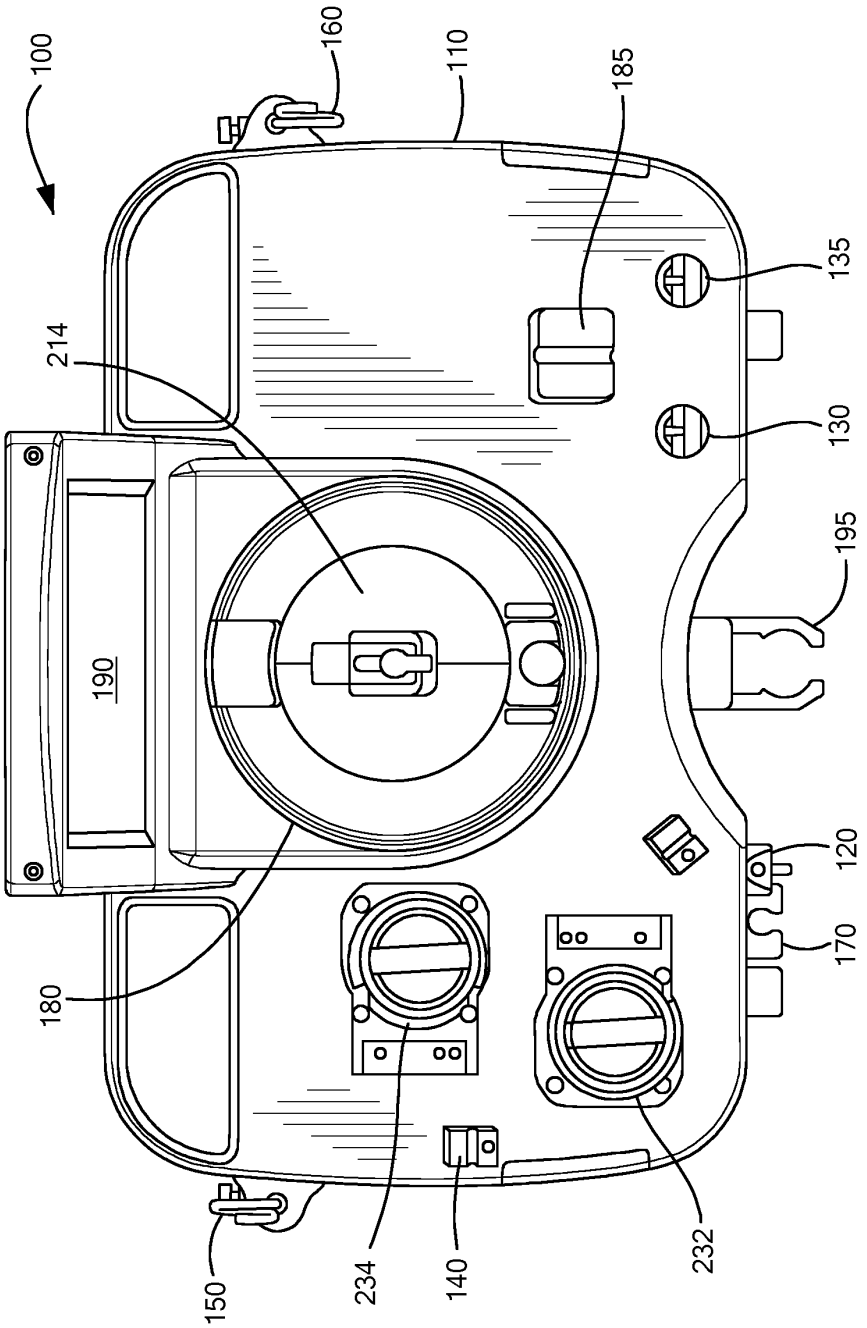


FIG. 2

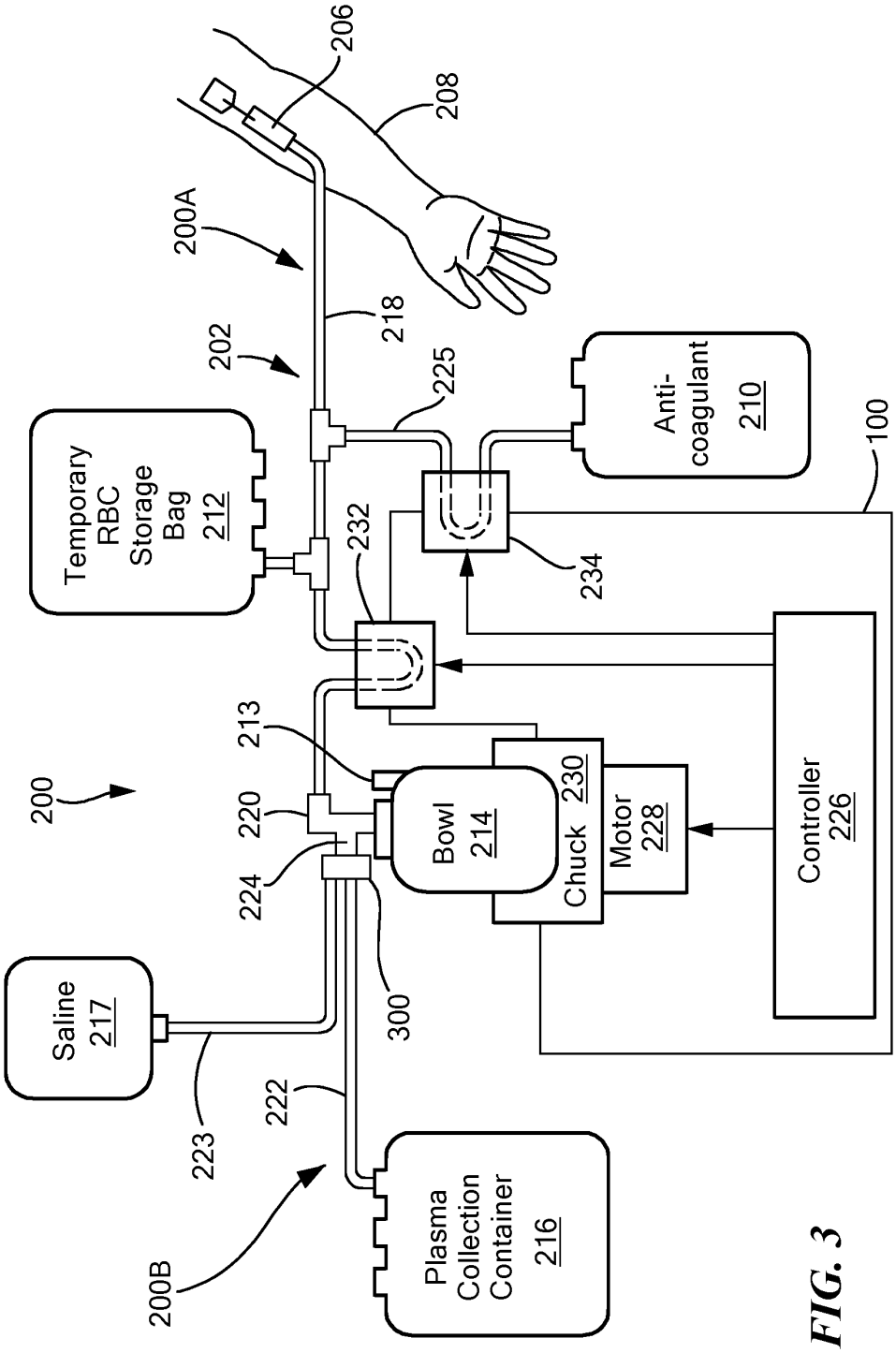

206
208
200A
218
202
225
Anti-coagulant 210
100
Temporary RBC Storage Bag 212
232
234
213
200
220
Bowl 214
Chuck 230
Motor 228
Controller 226
224
300
Saline 217
222
223
200B
Plasma Collection Container 216

FIG. 3

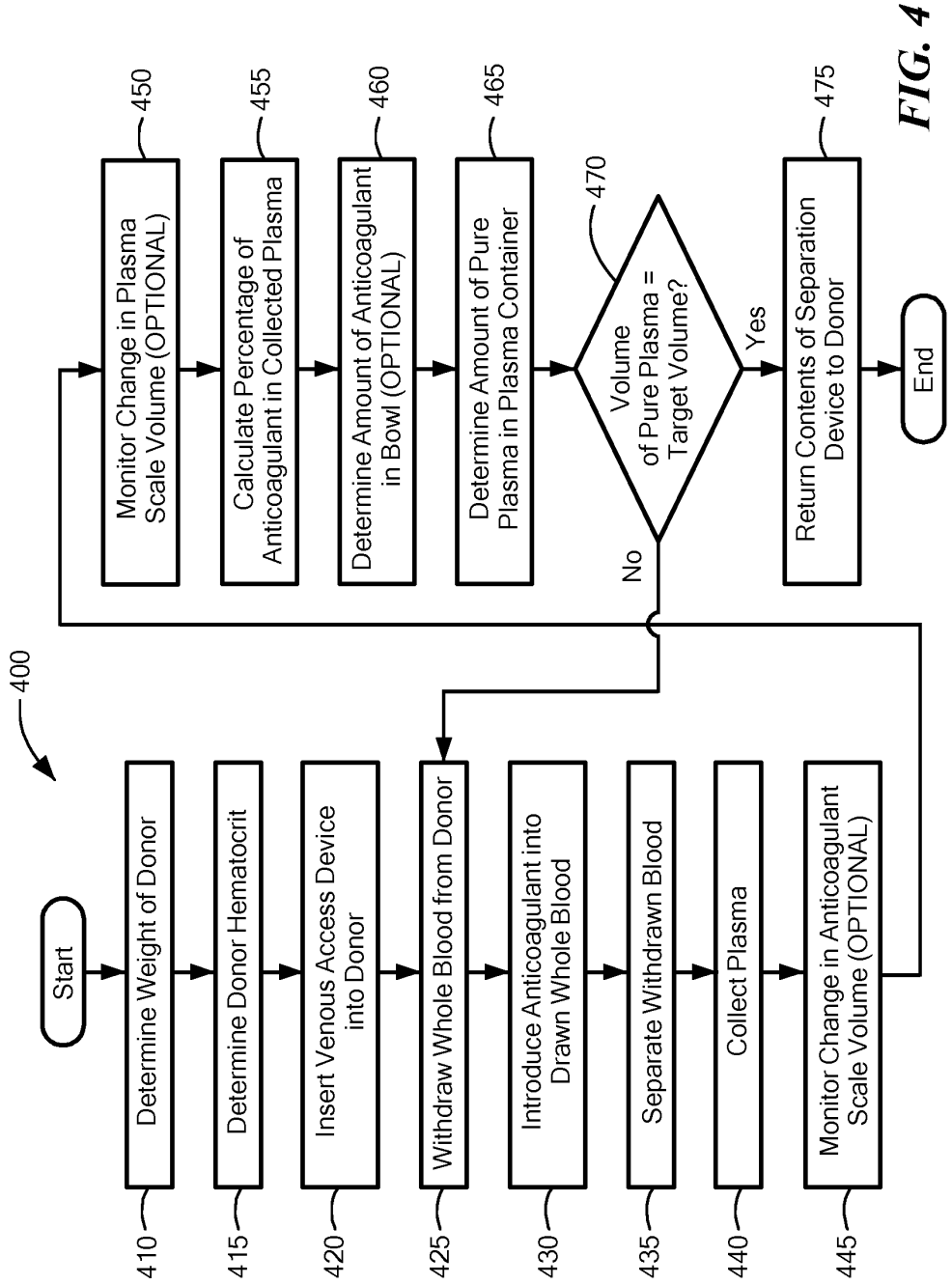

400
Start
Determine Weight of Donor
410
Determine Donor Hematocrit
415
Insert Venous Access Device into Donor
420
Withdraw Whole Blood from Donor
425
Introduce Anticoagulant into Drawn Whole Blood
430
Separate Withdrawn Blood
435
Collect Plasma
440
Monitor Change in Anticoagulant Scale Volume (OPTIONAL)
445
Monitor Change in Plasma Scale Volume (OPTIONAL)
450
Calculate Percentage of Anticoagulant in Collected Plasma
455
Determine Amount of Anticoagulant in Bowl (OPTIONAL)
460
Determine Amount of Pure Plasma in Plasma Container
465
Volume of Pure Plasma = Target Volume?
470
No
Yes
Return Contents of Separation Device to Donor
475
End

FIG. 4

Electronic Acknowledgement Receipt

EFS ID:	30173123
Application Number:	15608183
International Application Number:	
Confirmation Number:	7286
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Customer Number:	2101
Filer:	Jonathan Lovely
Filer Authorized By:	
Attorney Docket Number:	1611/C80
Receipt Date:	24-AUG-2017
Filing Date:	30-MAY-2017
Time Stamp:	15:29:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		ram1611_C80_Declaration.pdf	609558 fa79ebaf9126e0a954169167f1e0e4824830c05b	yes	3

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1159

	Multipart Description/PDF files in .zip description			
	Document Description	**Start**	**End**	
	Applicant Response to Pre-Exam Formalities Notice	1	2	
	Oath or Declaration filed	3	3	
Warnings:				
Information:				
2	ram1611_C80_FormalDrawings.pdf	189314 12eb75e21c16aadfc52eb9171ef61108bb881ab1	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	1
	Drawings-only black and white line drawings	2	5
Warnings:			
Information:			
	Total Files Size (in bytes):	798872	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/608,183	05/30/2017	3761	1740	1611/C80	20	2

CONFIRMATION NO. 7286

2101
Sunstein Kann Murphy & Timbers LLP
125 SUMMER STREET
BOSTON, MA 02110-1618

FILING RECEIPT

OC000000091875350

Date Mailed: 06/08/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Michael Ragusa, Hingham, MA;

Applicant(s)

Haemonetics Corporation, Braintree, MA;

Power of Attorney: The patent practitioners associated with Customer Number 02101

Domestic Applications for which benefit is claimed - None.
A proper domestic benefit claim must be provided in an Application Data Sheet in order to constitute a claim for domestic benefit. See 37 CFR 1.76 and 1.78.

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

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Projected Publication Date: 12/06/2018

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Early Publication Request: No

Title

System and Method for Collecting Plasma

Preliminary Class

604

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/608,183	05/30/2017	Michael Ragusa	1611/C80

CONFIRMATION NO. 7286

2101
Sunstein Kann Murphy & Timbers LLP
125 SUMMER STREET
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INFORMAL NOTICE

OC000000091875551

Date Mailed: 06/08/2017

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Michael Ragusa

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/snguyen/

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/608,183

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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I/we hereby appoint the practitioners associated with the Customer Number: **02101**

with the firm: SUNSTEIN KANN MURPHY & TIMBERS LLP
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Boston, MA 02110-1618
United States

As attorneys to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications where the assignee is named as an applicant or where the applications are assigned to the undersigned according to the USPTO assignment records or assignment documents, in which case the details will be listed on an attached form in accordance with 37 CFR 3.73(c).

Address all correspondence to: **Customer Number: 02101**

Direct all telephone calls to: 617-443-9292
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(a) Full name and registered address of Assignee

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Assignee

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Dated this 12th day of November, 2012

(b) Signature of Assignee: (b) John F. Perullo

By (c) Signatory's name: (c) JOHN F. PERULLO

(d) Signatory's Title: (d) Title: VP, IP LEGAL AFFAIRS

Attorney Docket: 1611/C80

System and Method for Collecting Plasma

Technical Field

[0001] The present invention relates to systems and methods for blood apheresis, and more particularly system and methods for collecting a plasma product.

Background Art

[0002] Apheresis is a procedure in which individual blood components can be separated and collected from whole blood temporarily withdrawn from a subject. Typically, whole blood is withdrawn through a needle inserted into a vein of the subjects arm and into a cell separator, such as a centrifugal bowl. Once the whole blood is separated into its various components, one or more of the components (e.g., plasma) can be removed from the centrifugal bowl. The remaining components can be returned to the subject along with optional compensation fluid to make up for the volume of the removed component. The process of drawing and returning continues until the quantity of the desired component has been collected, at which point the process is stopped. A central feature of apheresis systems is that the processed but unwanted components are returned to the donor. Separated blood components may include, for example, a high density component such as red blood cells, an intermediate density component such as platelets or white blood cells, and a lower density component such as plasma.

[0003] Many jurisdictions have regulations regarding the amount of whole blood and/or blood components that can be removed from a donor. For example, the U.S. Food and Drug Administration ("the FDA") sets both an upper limit on the volume of plasma that may be collected (e.g., 800 ml for an adult weighing more than 175 pounds) as well as an upper limit on the total collection volume (e.g., 880 ml for an adult weighing more than 175 pounds). Prior art plasma collection systems are unable to determine the total volume of plasma that has been collected (e.g., because the product collected is a mixture of plasma and

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anticoagulant) and, therefore collect based on the total collection volume, even if the total volume of plasma that has been collected is below the limit prescribed by the FDA.

Summary of the Invention

[0004] In accordance with some embodiments of the present invention, a method for collecting plasma includes determining the weight and hematocrit of a donor, and inserting a venous-access device into the donor. Once the venous access device is inserted, the method may withdraw whole blood from the donor through the venous-access device and a draw line that is connected to a blood component separation device. The method may then introduce anticoagulant into the withdrawn whole blood through an anticoagulant line and separate, using the blood component separation device, the withdrawn whole blood into a plasma component and at least a second blood component. Once separated, the plasma component may be collected from the blood component separation device and into a plasma collection container. During processing, the method may calculate (1) a percentage of anticoagulant in the collected plasma component, and (2) a volume of pure plasma collected within the plasma collection container. The volume of pure plasma may be based, at least in part, on the calculated percentage of anticoagulant in the collected plasma component. The method may continue the process (e.g., withdrawing whole blood, introducing anticoagulant into the whole blood, separating the blood, collecting the plasma, and calculating the percentage of anticoagulant and volume of pure plasma) until a target volume of pure plasma is collected within the plasma collection container.

[0005] In some embodiments, the method may determine a change in volume within an anticoagulant container, and the calculated percentage of anticoagulant in the collected plasma may be based, at least in part, on the change in volume within the anticoagulant container. Additionally or alternatively, the method may determine a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump. In such embodiments, the calculated percentage of anticoagulant in the collected plasma may be based, at least in part, on the number of rotations of the anticoagulant pump. The method may also determine a volume of anticoagulant within the blood component separation device, and the calculated percentage of anticoagulant in the

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collected plasma may be based, at least in part, on the volume of anticoagulant within the blood component separation device.

[0006] In further embodiments, the method may monitor the volume and/or weight of the plasma component collected within the plasma collection container (e.g., using a weight sensor), and the calculated volume of pure plasma collected within the plasma collection device may be based, at least in part, on the monitored volume and/or weight of the collected plasma component. Additionally or alternatively, determining the hematocrit of the donor may include monitoring a volume of red blood cells collection within the blood separation device. In such embodiments, the determined hematocrit of the donor may be based, at least in part, on the monitored volume of red blood cells collected within the blood separation device and the volume of whole blood withdrawn from the donor.

[0007] The target volume of pure plasma may be based, at least in part, on the weight of the donor. The percentage of anticoagulant in the collected plasma component may include at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant that is added to the system during a priming step. After collecting at least a portion of the target volume of pure plasma, the method may return the second blood component to the donor through a return line.

[0008] In accordance with additional embodiments, a system for collecting plasma includes a venous-access device for drawing whole blood from a subject and returning blood components to the subject, and a blood component separation device for separating the drawn blood into a plasma component and a second blood component. The blood component separation device has an outlet and is configured to send the plasma component to a plasma container. The system may also include a blood draw line fluidly connected to the venous-access device and an anticoagulant line connected to an anticoagulant source. The blood draw line transports drawn whole blood to the blood component separation device, and the flow through the blood draw line may be controlled by a blood draw pump. The anticoagulant line may introduce anticoagulant into the drawn whole blood.

[0009] Additionally, the system may include a controller that controls the operation of the centrifuge bowl. The controller may also calculate (1) a percentage of anticoagulant in the collected plasma component, and (2) a volume of pure plasma collected within the plasma container. The volume of pure plasma may be based, at least in part, upon the

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percentage of anticoagulant in the collected plasma component. The controller may stop the blood draw pump when a target volume of pure plasma (e.g., based, at least in part, on the weight of the donor) is collected within the plasma container. In some embodiments, the percentage of anticoagulant in the collected plasma component may be based, at least in part, on the volume of anticoagulant added to the drawn whole blood and the subject's hematocrit.

[0010] The system may also include an anticoagulant source weight sensor that measures the weight of the anticoagulant source. The controller may monitor the change in volume within the anticoagulant container based on the measured weight of the anticoagulant source, and the calculated percentage of anticoagulant in the collected plasma may be based, at least in part, on the change in volume within the anticoagulant source. Additionally or alternatively, the controller may monitor the number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood. In such embodiments, the calculated percentage of anticoagulant in the collected plasma may be based, at least in part, on the number of rotations of the anticoagulant pump.

[0011] In some embodiments, the system may include an optical sensor located on the blood component separation device. The optical sensor may monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device. The calculated percentage of anticoagulant in the collected plasma may be based, at least in part, on the volume of anticoagulant within the blood component separation device.

[0012] In additional embodiments, the system may also include a plasma container weight sensor that monitors a volume and/or weight of the plasma component collected within the plasma collection container. The calculated volume of pure plasma collected within the plasma collection container may be based, at least in part, on the monitored volume and/or weight of collected plasma component. The system may also have an optical sensor located on the blood component separation device. The optical sensor may monitor the volume of red blood cells collected within the blood separation device. The controller may then determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood separation device and the volume of whole blood withdrawn from the donor. The percentage of anticoagulant in the collected plasma component may include at least a portion of the anticoagulant introduced into the

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withdrawn blood and at least a portion of a volume of anticoagulant added to the system during a priming step.

Brief Description of the Drawings

[0013] The foregoing features of the invention will be more readily understood by reference to the following detailed description, taken with reference to the accompanying drawings, in which:

[0014] Fig. 1 schematically shows a perspective view of a blood processing system in accordance with some embodiments of the present invention.

[0015] Fig. 2 schematically shows a top view of the blood processing system of Figure 1, in accordance with some embodiments of the present invention;

[0016] Fig. 3 schematically shows a disposable set installed within the blood processing system of Figure 1, in accordance with some embodiments of the present invention.

[0017] Fig. 4 is a flowchart depicting a method of collecting plasma, in accordance with embodiments of the present invention.

Detailed Description of Specific Embodiments

[0018] Illustrative embodiments of the present invention provide blood processing systems and methods for collecting a target volume of pure plasma. The system and method calculate a percentage of anticoagulant collected within a plasma collection cotnainer (e.g., in addition to the plasma that is collected within the container) based on the amount of anticoagulant added to the system and the hematocrit of the donor. The system/method may then calculate the volume of pure plasma (e.g., plasma without anticoagulant) that has been collected within the container. Details of the illustrative embodiments are discussed below.

[0019] As shown in Figures 1 and 2, the blood processing system 100 includes a cabinet 110 that houses the main components of the system 100 (e.g., the non-disposable components). Within the cabinet 110, the system 100 may include a first/blood pump 232 that draws whole blood from a subject, and a second/anticoagulant pump 234 that pumps anticoagulant through the system 100 and into the drawn whole blood. Additionally, the

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system 100 may include a number of valves that may be opened and/or closed to control the fluid flow through the system 100. For example, the system 100 may include a donor valve 120 that may open and close to selectively prevent and allow fluid flow through a donor line 218 (e.g., an inlet line; Fig. 3), and a plasma valve 130 that selectively prevents and allows fluid flow through an outlet/plasma line 222 (Fig. 3). Some embodiments may also include a saline valve 135 that selectively prevents and allows saline to flow through a saline line 223.

[0020] To facilitate the connection and installation of a disposable set and to support the corresponding fluid containers, the system 100 may include an anticoagulant pole 150 on which the anticoagulant solution container 210 (Fig. 3) may be hung, and a saline pole 160 on which a saline solution container 217 (Fig. 3) may be hung (e.g., if the procedure being performed requires the use of saline). Additionally, in some applications, it may be necessary and/or desirable to filter the whole blood drawn from the subject for processing. To that end, the system 100 may include blood filter holder 170 in which the blood filter (located on the disposable set) may be placed.

[0021] As discussed in greater detail below, apheresis systems 100 in accordance with embodiments of the present invention withdraw whole blood from a subject through a venous access device 206 (Fig. 3) using the blood pump 232. As the system 100 withdraws the whole blood from the subject, the whole blood enters a blood component separation device 214, such as a Latham type centrifuge (other type of separation chambers and devices may be used, such as, without limitation, an integral blow-molded centrifuge bowl, as described in U.S. Patent Nos. 4,983,158 and 4,943,273, which are hereby incorporated by reference). The blood component separation device 214 separates the whole blood into its constituent components (e.g., red blood cells, white blood cell, plasma, and platelets). Accordingly, to facilitate operation of the separation device 214, the system 100 may also include a well 180 in which the separation device 214 may be placed and in which the separation device 214 rotates (e.g., to generate the centrifugal forces required to separate the whole blood).

[0022] To allow the user/technician to monitor the system operation and control/set the various parameters of the procedure, the system 100 may include a user interface 190 (e.g., a touch screen device) that displays the operation parameters, any alarm messages, and buttons which the user/technician may depress to control the various parameters. Additional

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components of the blood processing system 100 are discussed in greater detail below (e.g., in relation to the system operation).

[0023] FIG. 3 is a schematic block diagram of the blood processing system 100 and a disposable collection set 200 (with an inlet disposable set 200A and an outlet disposable set 200B) that may be loaded onto/into the blood processing system 100, in accordance with the present invention. The collection set 200 includes a venous access device 206 (e.g., a phlebotomy needle) for withdrawing blood from a donor's arm 208, a container of anti-coagulant 210, a centrifugation bowl 214 (e.g., a blood component separation device), a saline container 217, and a final plasma collection bag 216. The blood/inlet line 218 couples the venous access device 206 to an inlet port 220 of the bowl 214, the plasma/outlet line 222 couples an outlet port 224 of the bowl 214 to the plasma collection bag 216, and a saline line 223 connects the outlet port 224 of the bowl 214 to the saline container 217. An anticoagulant line 225 connects the anti-coagulant container 210 to the inlet line 218. In addition to the components mentioned above and as shown in Figure 3, the blood processing system 100 includes a controller 226, a motor 228, and a centrifuge chuck 230. The controller 226 is operably coupled to the two pumps 232 and 234, and to the motor 228, which, in turn, drives the chuck 230. The controller 226 may be operably coupled to and in communication with the user interface 190.

[0024] In operation, the disposable collection set 200 (e.g., the inlet disposable set 200A and the outlet disposable set 200B) may be loaded onto/into the blood processing system 100 prior to blood processing. In particular, the blood/inlet line 218 is routed through the blood/first pump 232 and the anticoagulant line 225 from the anti-coagulant container 210 is routed through the anticoagulant/second pump 234. The centrifugation bowl 214 may then be securely loaded into the chuck 230. Once the bowl 214 is secured in place, the technician may install the outlet disposable set 200B. For example the technician may connect a bowl connector 300 to the outlet 224 of the bowl 214, install the plasma container 216 into the weight senor 195, run the saline line 223 through valve 135, and run the plasma/outlet line 222 through valve 130 and the line sensor 185. Once the disposable set 200 is installed and the anticoagulant and saline containers 210/217 are connected, the system 100 is ready to begin blood processing.

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[0025] Figure 4 is a flowchart depicting an exemplary method of collecting plasma in accordance with various embodiments of the present invention. Prior to connecting the donor to the blood processing device 100, it is beneficial (and perhaps necessary in some instances) to obtain/determine some information regarding the donor, namely, the donor's weight (Step 410) and hematocrit (Step 415). Not only does this information help determine if the individual is a viable donor and the volumes of blood components that may be withdrawn/collected (e.g., per the FDA guidelines), the hematocrit may be used during processing to help collect a target volume of plasma. The technician may obtain/determine the donor's weight by weighing the donor (e.g., on a scale). To obtain/determine the donor's hematocrit, the technician may draw a blood sample from the donor and test the sample of blood. Additionally or alternatively, as discussed in greater detail below, the system may determine the hematocrit during blood processing. For example, the blood processing device 100 may include a hematocrit sensor (not shown) that determines the hematocrit of the blood flowing into the blood processing device 100 and/or the system 100 may determine the hematocrit based on a volume of red blood cells collected within the bowl 214.

[0026] Once the lines 222/223 are in place and the technician has determined the donor's weight and/or hematocrit (if needed), the user/technician may insert the venous access device 206 into the donor's arm 208 (Step 420). Next, the controller 226 activates the two pumps 232, 234 and the motor 228. Operation of the two pumps 232, 234 causes whole blood to be drawn from the donor (step 425), anticoagulant from container 210 to be introduced into the drawn whole blood (step 430), and the now anticoagulated whole blood to be delivered to the inlet port 220 of the bowl 214.

[0027] It should be noted that the anticoagulant line 225 may also include a bacteria filter (not shown) that prevents any bacteria in the anticoagulant source 210, the anticoagulant, or the anticoagulant line 225 from entering the system 100 and/or the subject. Additionally, the anticoagulant line 225 may include an air detector 140 that detects the presence of air within the anticoagulant. The presence of air bubbles within any of the system 100 lines can be problematic for the operation the system 100 and may also be harmful to the subject if the air bubbles enter the blood stream. Therefore, the air detector may be connected to an interlock that stops the flow within the anticoagulant line 225 in the event that an air

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bubble is detected (e.g., by stopping the anticoagulant pump 234), thereby preventing the air bubbles from entering the subject.

[0028] As the anti-coagulated whole blood is withdrawn from the subject and contained within the blood component separation device 214, the blood component separation device 214 separates the whole blood into several blood components (Step 435). For example, the blood component separation device 214 may separate the whole blood into a first, second, third, and, perhaps, fourth blood component. More specifically, the blood component separation device 214 (and the centrifugal forces created by rotation of the separation device 214) can separate the whole blood into plasma, platelets, red blood cells ("RBC"), and, perhaps, white blood cells ("WBC"). The higher density component, i.e., RBC, is forced to the outer wall of the bowl 214 while the lower density plasma lies nearer the core. A buffy coat is formed between the plasma and the RBC. The buffy coat is made up of an inner layer of platelets, a transitional layer of platelets and WBC and an outer layer of WBC. The plasma is the component closest to the outlet port and is the first fluid component displaced from the bowl 214 via the outlet port 224 as additional anticoagulated whole blood enters the bowl 214 through the inlet port 220.

[0029] As shown in Figure 3, the system 100 may also include an optical sensor 213 that may be applied to a shoulder portion of the bowl 214. The optical sensor monitors each layer of the blood components as they gradually and coaxially advance toward the core from the outer wall of the bowl 214. The optical sensor 213 may be mounted in a position (e.g., within the well 180) at which it can detect the buffy coat and/or the red blood cells reaching a particular radius, and the steps of drawing the whole blood from the subject/donor and introducing the whole blood into the bowl 12 may be altered and/or terminated in response to the detection.

[0030] Additionally, in some embodiments, the optical sensor 213 may be used to determine the hematocrit of the donor during processing. For example, as the bowl 214 fills with red blood cells and the optical sensor 213 detects the layer of red blood cells, the system 100 (e.g., the controller) can determine the volume of red blood cells within bowl 214 based on the location of the red blood cell layer and the fixed/known bowl volume. The system 100 may then calculate the donor hematocrit based on the volume of red blood cells within the bowl and the volume of whole blood that has been processed to that point.

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[0031] Once the blood component separation device 214 has separated the blood into the various components, one or more of the components can be removed from the blood component separation device 214. For instance, the plasma may be removed to a plasma container 216 (e.g., a plasma bottle) through line 222 (Step 440). As noted above, some embodiments of the system 100 may include a weight sensor 195 (Fig. 1) that measures the amount of plasma collected. The plasma collection process may continue until the a target volume of pure plasma (discussed in greater detail below) is collected within the plasma collection container 216. Although not shown, if the blood processing system 100 and/or the disposable set 200 include platelet, red blood cell, and/or white blood cell bags, each of the bags/containers may include similar weight sensors (e.g., load cells).

[0032] In some embodiments, the system 100 may also include a line sensor 185 (mentioned above) that can determine the type of fluid (e.g., plasma, platelets, red blood cells etc.) exiting the blood component separation device 214. In particular, the line sensor 185 consists of an LED which emits light through the blood components leaving the bowl 214 and a photo detector which receives the light after it passes through the components. The amount of light received by the photo detector is correlated to the density of the fluid passing through the line. For example, if plasma is exiting the bowl 214, the line sensor 185 will be able to detect when the plasma exiting the bowl 214 becomes cloudy with platelets (e.g., the fluid existing the bowl 214 is changing from plasma to platelets). The system 100 may then use this information to either stop the removal of blood components from the bowl 214, stop drawing whole blood from the subject, or redirect the flow by, for example, closing one valve an opening another.

[0033] It is important to note that during processing, the osmolarity of the red blood cells prevents the anticoagulant introduced into the whole blood from entering/remaining with the red blood cells (e.g., within the bowl 214). Rather, the anticoagulant mixes with the plasma component. Therefore, the anticoagulant exits the bowl 214 with the plasma and is collected within collection container 216 along with the plasma. In other words, the weight of the product measured by the weight senor 195 is the weight of the plasma, as well as any anticoagulant that is mixed with the plasma – the weight provided by the weight sensor 195 is not the weight of pure plasma.

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[0034] Additionally, whole blood contains a variable amount of plasma, as determined by the donor's hematocrit. The hematocrit for typical donors can vary from 38% to 54%, which means that for 100 ml of whole blood, the volume of plasma can vary from 36 to 62 ml. Furthermore, the amount of anticoagulant added to the withdrawn whole blood is fixed (e.g., it does not depend on the hematocrit of the donor), meaning that the percentage of anticoagulant in the collected plasma may vary from 9.7% to 12.7% for donor hematocrits between 38% to 54%, respectively. Therefore, not only does the volume measured by the weight sensor 195 include the volume of anticoagulant, that volume of anticoagulant may vary from donor to donor based on the hematocrit.

[0035] As mentioned above, some embodiments of the present invention continue the blood processing/separation procedure until a target volume of pure plasma (e.g., plasma only – without the volume of any anticoagulant mixed with the plasma included in the target volume) is collected within the plasma collection container 216. To that end, some embodiments of the present invention may calculate the volume of pure plasma within the plasma collection container 216. For example, the technician or the system 100 (e.g., the controller) may calculate the percentage of anticoagulant within the collected plasma (Step 455) (e.g., the plasma contained within the plasma collection container 216) based on the amount of anticoagulant added/metered into the whole blood and the hematocrit of the donor. The technician and/or system can calculate the percentage of anticoagulant according to the following equation, where AC is the amount of anticoagulant added to the system 100. As noted above, because the osmolarity of the red blood cells prevents the anticoagulant from mixing with it, essentially all of the anticoagulant exits the bowl 214 and is collected within the plasma collection container 216 along with the plasma.

$$\%\boldsymbol{AC} = \frac{\mathbf{1}}{\mathbf{1} + (\boldsymbol{AC} - \mathbf{1})(\mathbf{1} - \boldsymbol{Hct_D})}$$

[0036] The amount of anticoagulant that is added to the system 100 can be determined in a number of ways. For example, the system 100 can base the amount of anticoagulant (e.g., the value of "AC" in the above equation) on the predetermined ratio of anticoagulant per unit of anticoagulated whole blood. In some embodiments, the value of "AC" may be the inverse of the predetermined ratio (e.g., "AC" would be 16 if the ratio of

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anticoagulant to anticoagulated whole blood was 1:16). Additionally or alternatively, the technician/system 100 can monitor the volume of anticoagulant added to the system. In such embodiments, the technician/system can monitor the volume of anticoagulant added to the system 100 based on the number of rotations of the anticoagulant pump (e.g., each rotation of the anticoagulant pump introduces a set volume of anticoagulant into the system 100) and/or based on the change in weight of the anticoagulant container 210 as measured by a weight sensor (discussed in greater detail below).

[0037] Once the technician/system 100 has calculated the percentage of anticoagulant within the plasma collection container 216, the technician/system 100 may then use this information to calculate the volume of pure plasma within the plasma collection container 216 (Step 465). For example, the technician/system 100 may determine the volume of anticoagulant within the container (based on the percentage of anticoagulant within the container 216) and subtract this volume from the total volume of fluid within the container 216 as measured by the weight sensor 195. The system 100 may continue to monitor the volume of pure plasma collected within the container 216 and continue processing whole blood (e.g., continue performing Steps 425, 430, 435, 440, 455, 460 and 465) until a target volume of pure plasma is collected within the plasma collection container 216 (Step 470) (e.g., 800 mL for an adult donor weighing more than 175 pounds or other limit prescribed by the FDA or similar governing body).

[0038] Once the system 100 has collected the target volume of pure plasma within the plasma collection container 216, the system 100 can return the remaining components (e.g., the components remaining within the bowl 214) to the subject (Step 475). For example, when all the plasma has been removed and the bowl 214 is full of RBCs (and any other blood component not collected), the controller 226 stops the draw of whole blood from the subject and reverses the direction of the blood/first pump 232 to draw the RBCs (and other components) from the bowl 214 directly back to the subject. Alternatively, if the system 100 is so equipped, the system may return the components to the subject via a dedicated return line.

[0039] In addition to the non-collected blood components (e.g., the components remaining in the bowl 214), the system 100 may also return saline to the patient/subject. The saline may be used as a compensation fluid to make up for the volume of the blood

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component (e.g., plasma) that was removed and collected, and is not being returned to the patient. To that end, during the return step (e.g., Step 475), the saline valve 135 may be opened to allow saline from the saline container 217 to flow through the saline line 223 and into the bowl 214 (via outlet 224), where it can be returned to the patient/donor with or after the remaining blood components.

[0040] It should be noted that some embodiments may perform some additional and optional steps to help determine the volume of pure plasma within the plasma collection container 216. For example, as mentioned above, some embodiments may monitor the change in weight of the anticoagulant container 210 (e.g., as measured by a weight sensor/load cell on the anticoagulant container 210) (step 445). This measurement provides an indication of the volume of anticoagulant that has been added to the system 100, and may be used help determine the percentage of anticoagulant within the plasma collection container 216. Additionally or alternatively, some embodiments may similarly, monitor the change in weight and/or volume of the plasma and anticoagulant collected within the plasma collection container 216 (e.g., via weight sensor 195) (step 450). This measurement may be used to calculate of the total volume of pure plasma collected within the plasma collection container 216 (e.g., to obtain the total weight from which to subtract the calculated volume of anticoagulant).

[0041] Some embodiments may also (optionally) monitor the volume of anticoagulant remaining in the bowl 214 (step 460) (e.g., anticoagulant that did not mix with the plasma and/or otherwise remained in the bowl). For example, the system 100 may utilize the optical sensor on the bowl 214 to determine whether any anticoagulant remains within the bowl 214. If it does, the method 400/system 100 may modify the calculation of the amount of pure plasma collected within the plasma collection container (e.g., either increase the calculated amount or decreased the calculated amount), based on the volume of anticoagulant remaining within the bowl 214.

[0042] Various embodiment of the present invention provide numerous benefits over prior art plasma collection systems. In particular, as noted above, prior art plasmapheresis devices end plasma collection based on a total volume of anticoagulated plasma (e.g., pure plasma plus the added anticoagulant). Although this is the easiest method because it requires only that the product collection container be weighed, the amount of true product – the pure

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plasma – is dependent on the donor's hematocrit. In other words, prior art systems will collect more plasma from low hematocrit donors than from high hematocrit donors because of the variation of the percentage of anticoagulant in the product. Various embodiments of the present invention address the issues of prior art systems by collecting a standard volume (e.g., a target volume) of pure plasma from each donor. As noted above, embodiments of the present invention accomplish this by using knowledge of the donor's hematocrit and the amount of anticoagulant collected within the plasma collection container 216 (e.g., by counting pump rotations and/or using scale/weight sensors, etc.) to determine the percentage of anticoagulant in the product. Additionally, by stopping the plasma collection process based on a volume of pure plasma collected, embodiments of the present invention are able to collect a greater volume of plasma as compared to prior art systems that stop based on a plasma/anticoagulant mixture.

[0043] It is also important to note that, although the various embodiments discussed above are in relation to a blood processing system that collects plasma, the features discussed herein may be applied to any type of blood processing system. For example, the features described herein may be implemented on blood processing systems that collect and/or process red blood cells, platelets and/or white blood cells.

[0044] The embodiments of the invention described above are intended to be merely exemplary; numerous variations and modifications will be apparent to those skilled in the art. All such variations and modifications are intended to be within the scope of the present invention as defined in any appended claims.

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What is claimed is:

1. A method for collecting plasma comprising:

(a) determining a weight of a donor;

(b) determining a hematocrit of the donor;

(c) inserting a venous-access device into the donor;

(d) withdrawing whole blood from the donor through the venous-access device and a draw line, the draw line connected to a blood component separation device;

(e) introducing anticoagulant into the withdrawn whole blood through an anticoagulant line;

(f) separating the withdrawn whole blood into a plasma component and at least a second blood component using the blood component separation device;

(g) collecting the plasma component from the blood component separation device and into a plasma collection container;

(h) calculating a percentage of anticoagulant in the collected plasma component;

(i) calculating a volume of pure plasma collected within the plasma collection container based, at least in part, on the calculated percentage of anticoagulant in the collected plasma component; and

(j) continuing steps (d) through (i) until a target volume of pure plasma is collected within the plasma collection container.

2. A method according to claim 1, further comprising:

determining a change in volume within an anticoagulant container, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant container.

3. A method according claim 1, further comprising:

determining a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump, the calculated percentage of anticoagulant in

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the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump.

4. A method according to claim 1, further comprising:

determining a volume of anticoagulant within the blood component separation device, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.

5. A method according to claim 1, further comprising:

monitoring a volume of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component.

6. A method according to claim 1, further comprising:

monitoring a weight of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component.

7. A method according to claim 1, wherein step (b) includes monitoring a volume of red blood cells collection within the blood separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor.

8. A method according to claim 1, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

9. A method according to claim 1, wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

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10. A method according to claim 1, further comprising:

returning, after collecting at least a portion of the target volume of pure plasma, the second blood component to the donor through a return line.

11. A system for collecting plasma comprising:

a venous-access device for drawing whole blood from a subject and returning blood components to the subject;

a blood component separation device for separating the drawn blood into a plasma component and a second blood component, the blood component separation device having an outlet and being configured to send the plasma component to a plasma container;

a blood draw line fluidly connected to the venous-access device and configured to transport drawn whole blood to the blood component separation device, the flow through the blood draw line being controlled by a blood draw pump;

an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood; and

a controller configured to control the operation of the centrifuge bowl and the blood draw pump, the controller configured to calculate (1) a percentage of anticoagulant in the collected plasma component, and (2) a volume of pure plasma collected within the plasma container based, at least in part, upon the percentage of anticoagulant in the collected plasma component, the controller configured to stop the blood draw pump when a target volume of pure plasma is collected within the plasma container.

12. A system according to claim 11, wherein the percentage of anticoagulant in the collected plasma component is based, at least in part, on a volume of anticoagulant added to the drawn whole blood and the subject's hematocrit.

13. A system according to claim 11, further comprising:

an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant container based on the measured weight of the anticoagulant source, the

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calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant source.

14. A system according to claim 11, wherein the controller is configured to monitor a number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump.

15. A system according to claim 11, further comprising:

an optical sensor located on the blood component separation device and configured to monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.

16. A system according to claim 11, further comprising:

a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component.

17. A system according to claim 11, further comprising:

a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component.

18. A system according to claim 11, further comprising:

an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood separation device, the controller configured to determine the subject's hematocrit based, at least in part, upon on the

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monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor

19. A system according to claim 11, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

20. A system according to claim 11, wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

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Attorney Docket: 1611/C80

System and Method for Collecting Plasma

Abstract

A method for collecting plasma includes determining the weight and hematocrit of a donor, and inserting a venous-access device into the donor. The method then withdraws blood from the donor through a draw line connected to a blood component separation device, and introduces anticoagulant into the withdrawn blood. The blood component separation device separates the blood into a plasma component and a second blood component, and the plasma component is collected from the blood component separation device and into a plasma collection container. The method may then calculate (1) a percentage of anticoagulant in the collected plasma component, and (2) a volume of pure plasma collected within the plasma collection container. The volume of pure plasma may be based, at least in part, on the calculated percentage of anticoagulant. The method may continue until a target volume of pure plasma is collected within the plasma collection container.

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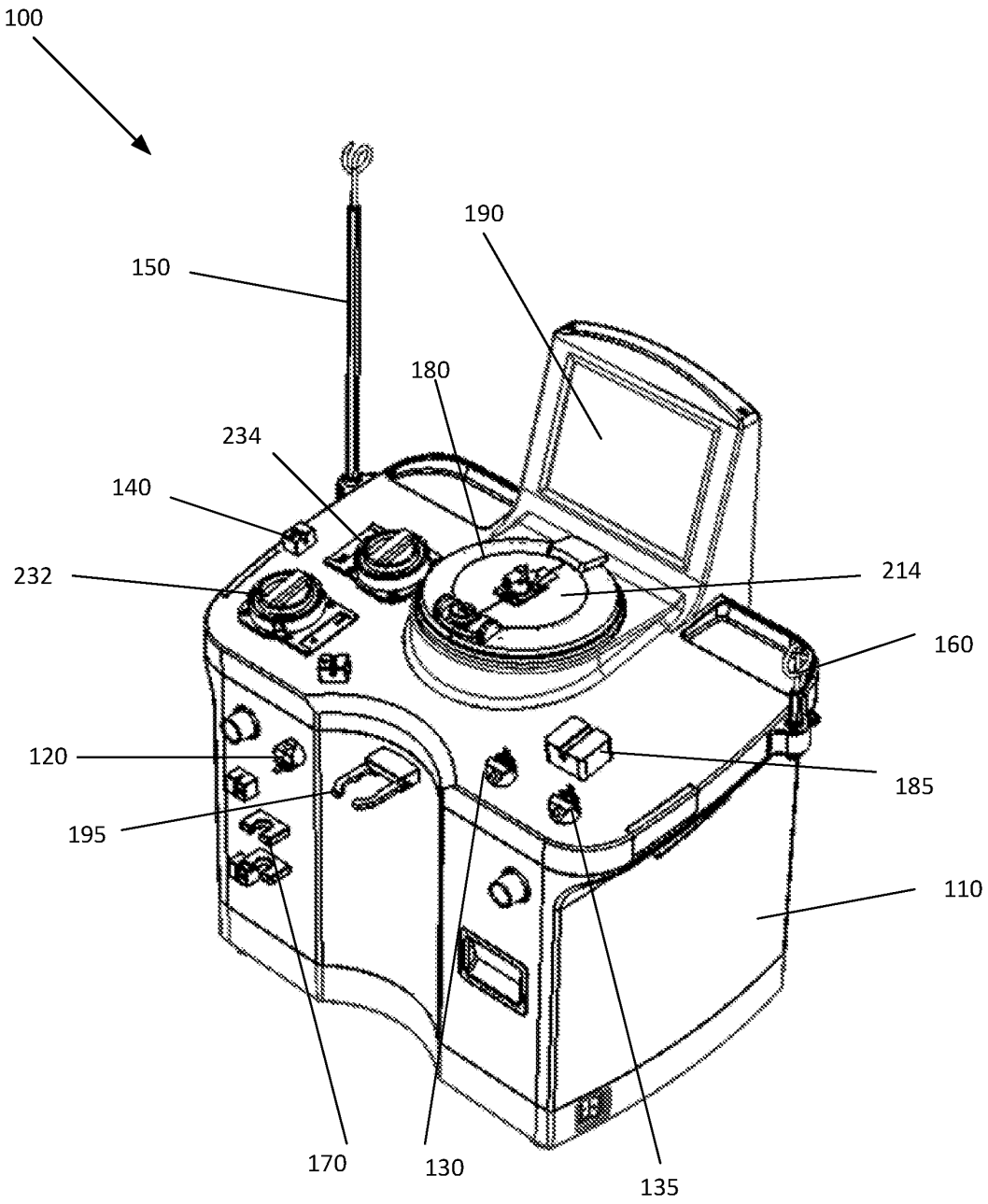


Fig. 1

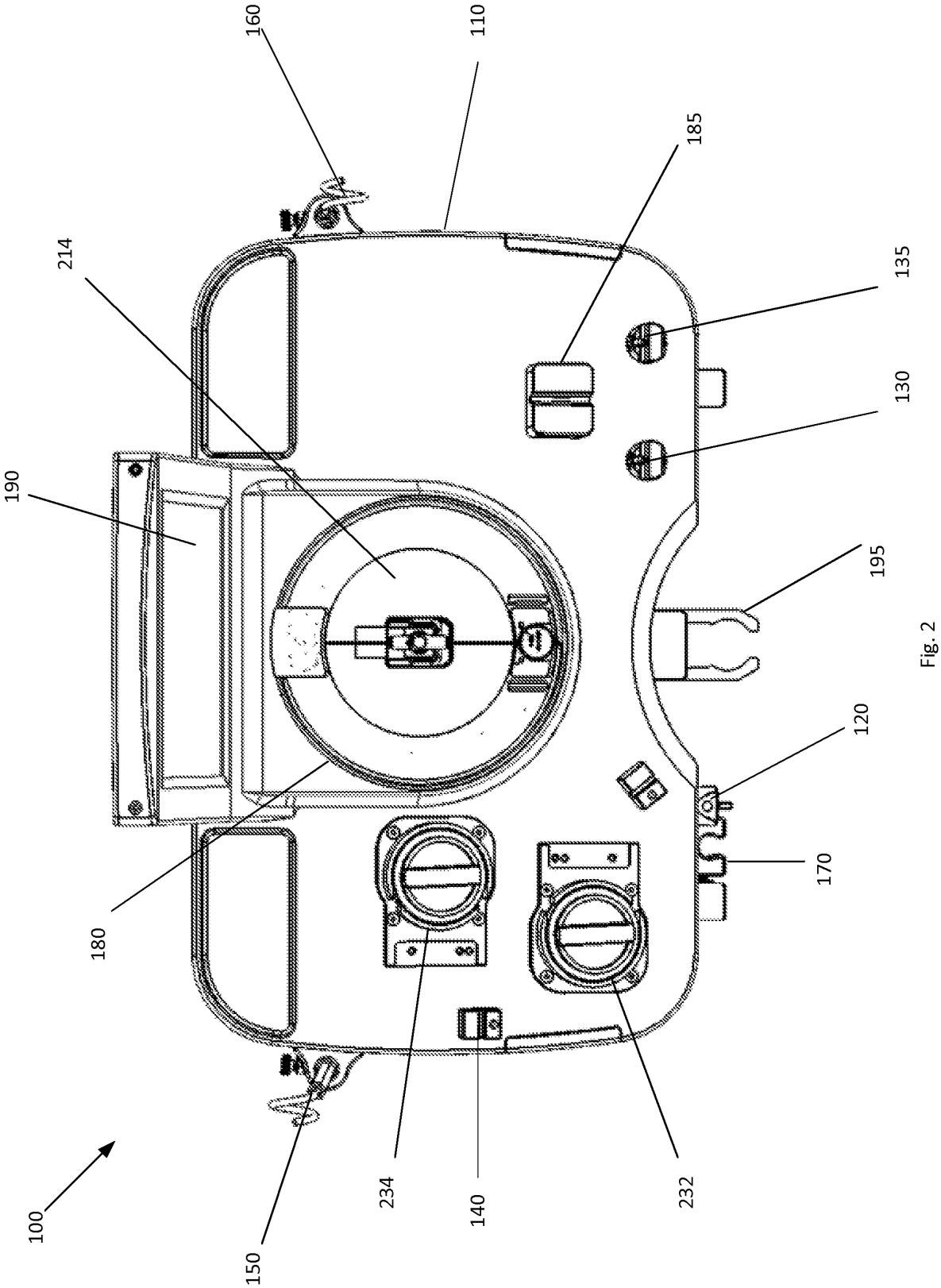


Fig. 2

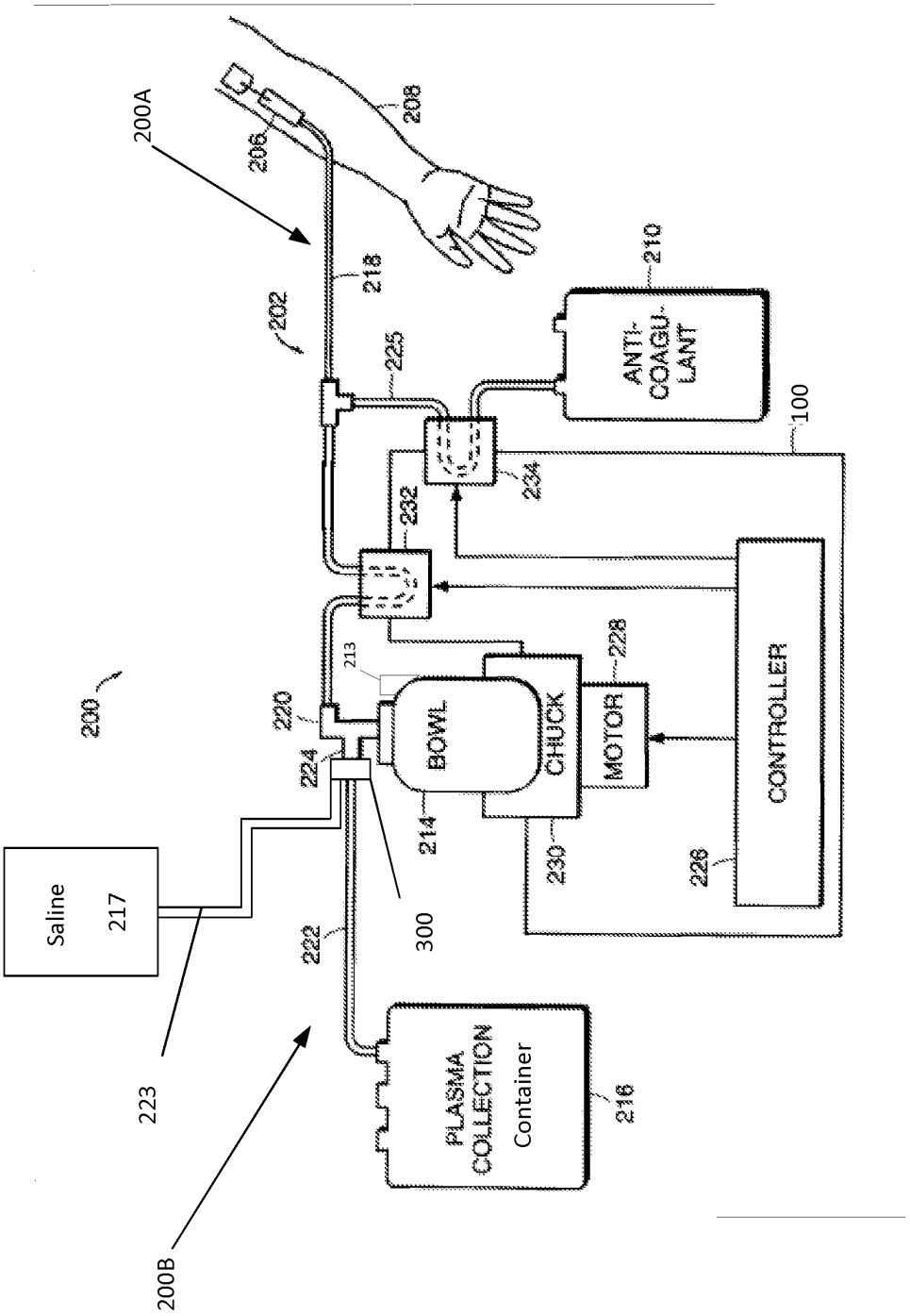

200A
206
208
218
202
225
210
ANTI-COAGU-LANT
100
234
232
213
220
224
200
BOWL
CHUCK
MOTOR
228
CONTROLLER
214
230
226
Saline
217
222
300
223
PLASMA COLLECTION Container
216
200B

Fig. 3

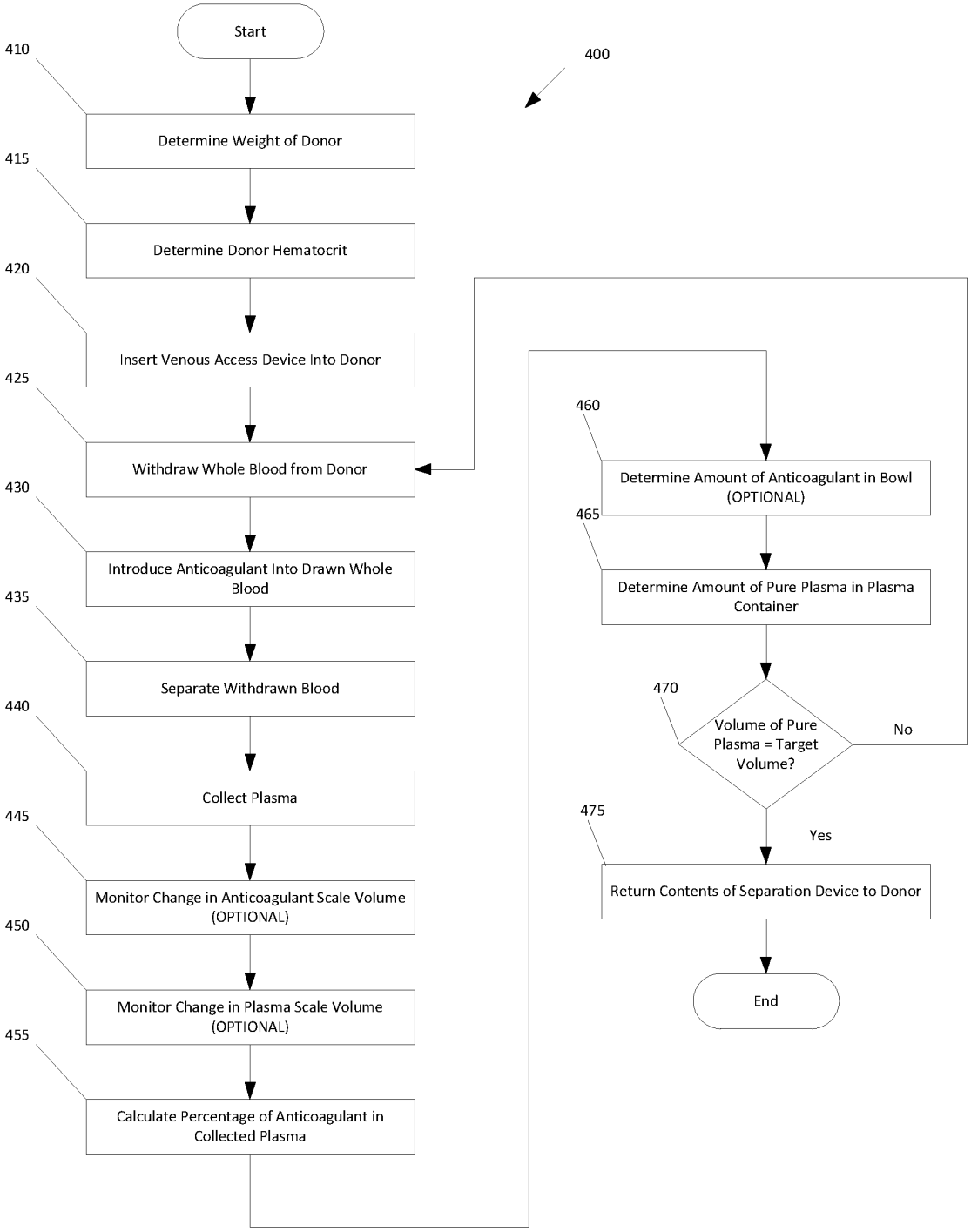

Start
400
410
Determine Weight of Donor
415
Determine Donor Hematocrit
420
Insert Venous Access Device Into Donor
425
Withdraw Whole Blood from Donor
430
Introduce Anticoagulant Into Drawn Whole Blood
435
Separate Withdrawn Blood
440
Collect Plasma
445
Monitor Change in Anticoagulant Scale Volume (OPTIONAL)
450
Monitor Change in Plasma Scale Volume (OPTIONAL)
455
Calculate Percentage of Anticoagulant in Collected Plasma
460
Determine Amount of Anticoagulant in Bowl (OPTIONAL)
465
Determine Amount of Pure Plasma in Plasma Container
470
Volume of Pure Plasma = Target Volume?
No
Yes
475
Return Contents of Separation Device to Donor
End

Fig. 4

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 — Remove

Legal Name

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Postal Code	02043	Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	02101		
Email Address	usptomail@sunsteinlaw.com	Add Email	Remove Email

Application Information:

Title of the Invention	System and Method for Collecting Plasma		
Attorney Docket Number	1611/C80	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	4	Suggested Figure for Publication (if any)	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

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Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	02101		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1194

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Haemonetics Corporation		
Mailing Address Information For Applicant:			
Address 1	400 Wood Road		
Address 2			
City	Braintree	**State/Province**	MA
Country	US	Postal Code	02184
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1195

PTO/AIA/14 (11-15)
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Jonathan C. Lovely, #60,821/			Date (YYYY-MM-DD)	2017-05-30
First Name	Jonathan C.	Last Name	Lovely	Registration Number	60,821

Additional Signature may be generated within this form by selecting the Add button. Add

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1196

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1197

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Terumo v. Haemonetics - PGR2025-00077
Petitioner Terumo Exhibit 1021-1198

Doc Code: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorized/Internet Communications Authorization Withdrawn

PTO/SB/439 (11-15)

AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS

Application No.	Not yet assigned
Filing Date	May 30, 2017
First Named Inventor	Michael Ragusa
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Practitioner Docket No.	1611/C80

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I. To authorize permission for Internet Communications.

☑ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

II. To withdraw authorization for Internet Communications.

☐ The authorization given on _____, to the USPTO to communicate with the undersigned and any practitioner in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via Internet communications such as video conferencing, instant messaging, or electronic mail is hereby withdrawn. I understand that the withdrawal is effective when approved rather than when received.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 60,821.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Jonathan C. Lovely, #60,821/ — Signature

May 30, 2017 — Date

Jonathan C. Lovely — Typed or printed name

617-443-9292 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Juristic entities must be represented by a patent practitioner (see 37 CFR 1.31, which is applicable to any paper filed on or after September 16, 2012, that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below*.

☑ * Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Filer:	Jonathan Lovely
Attorney Docket Number:	1611/C80

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	280	280
UTILITY SEARCH FEE	1111	1	600	600
UTILITY EXAMINATION FEE	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	1051	1	140	140
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1740**

Electronic Acknowledgement Receipt	
EFS ID:	29321375
Application Number:	15608183
International Application Number:	
Confirmation Number:	7286
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Customer Number:	2101
Filer:	Jonathan Lovely
Filer Authorized By:	
Attorney Docket Number:	1611/C80
Receipt Date:	30-MAY-2017
Filing Date:	
Time Stamp:	15:14:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1740
RAM confirmation Number	053117INTEFSW00001906194972
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	1611_Haemonetics_General_POA.pdf	64248 24bd3fac30b34fc3e9b648e967ee3fef31199683	no	1
Warnings:					
Information:					
2		ram1611_C80_Application.pdf	365747 6390c738793044b6e554134fc93e6a94994859a7	yes	24

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	14
Claims	15	19
Abstract	20	20
Drawings-only black and white line drawings	21	24

Warnings:					
Information:					
3	Application Data Sheet	ram1611_C80_ADS.pdf	1822879 dcfaafd33bb3e37630561bfa5958be1b79557fa3	no	8
Warnings:					
Information:					
4	Internet Communications Authorized	ram1611_C80_SB439.pdf	88592 770ecf2a65553479cc38e3d587fa9ea1377e4d0a	no	2
Warnings:					
Information:					

5	Fee Worksheet (SB06)	fee-info.pdf	36650 e3cc832ca90411b46a95599126b1df3e21f134a1	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2378116	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.