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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
62/331,996	05/05/2016		130	18460.0014P1		

27890
STEPTOE & JOHNSON LLP
1330 CONNECTICUT AVENUE, N.W.
WASHINGTON, DC 20036

CONFIRMATION NO. 3115
FILING RECEIPT



Date Mailed: 05/23/2016

Receipt is acknowledged of this provisional patent application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. 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)

Alexander M. Schobel, Whitehouse Station, NJ;
Stephanie M. Varjan, Oradell, NJ;
Stephen P. Wargacki, Somerset, NJ;

Applicant(s)

MONOSOL RX, LLC, Warren, NJ;

Power of Attorney:

Harold Fox--41498

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: 05/20/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 62/331,996**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS

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.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier

license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

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 U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.

SCORE Placeholder Sheet for IFW Content

Application Number: 62331996

Document Date: 05/05/2016

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Drawing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

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

PROVISIONAL APPLICATION FOR PATENT COVER SHEET – Page 1 of 2

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. _____

INVENTOR(S)		
Given Name (first and middle (if any))	Family Name or Surname	Residence (City and either State or Foreign Country)
Alexander M.	Schobel	Whitehouse Station, NJ
Stephanie M.	Varjan	Oradell, NJ
Stephen P.	Wargacki	Somerset, NJ

Additional inventors are being named on the _____ separately numbered sheets attached hereto.

TITLE OF THE INVENTION (500 characters max):

ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☒ The address corresponding to Customer Number: 27890

OR

☐ Firm or Individual Name _____

Address _____

City _____	State _____	Zip _____
Country _____	Telephone _____	Email _____

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Application Data Sheet. See 37 CFR 1.76. ☐ CD(s), Number of CDs _____

☒ Drawing(s) Number of Sheets 12 ☐ Other (specify) _____

☒ Specification (e.g., description of the invention) Number of Pages 39

Fees Due: Filing Fee of \$260 (\$130 for small entity) (\$65 for micro entity). If the specification and drawings exceed 100 sheets of paper, an application size fee is also due, which is \$400 (\$200 for small entity) (\$100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

METHOD OF PAYMENT OF THE FILING FEE AND APPLICATION SIZE FEE FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Applicant must attach form PTO/SB/15A or B or equivalent.

☐ A check or money order made payable to the *Director of the United States Patent and Trademark Office* is enclosed to cover the filing fee and application size fee (if applicable).

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge the filing fee and application size fee (if applicable) or credit any overpayment to Deposit Account Number: 194293

130.00

TOTAL FEE AMOUNT (\$)

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. 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 10 hours 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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PROVISIONAL APPLICATION FOR PATENT COVER SHEET – Page 2 of 2

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒

No.

☐

Yes, the invention was made by an agency of the U.S. Government. The U.S. Government agency name is: _____

☐

Yes, the invention was made under a contract with an agency of the U.S. Government. The name of the U.S. Government agency and Government contract number are: _____

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.

SIGNATURE /Harold H. FOX REG#41498/ DATE May 5, 2016

TYPED OR PRINTED NAME Harold H. Fox REGISTRATION NO. 41,498
(if appropriate)

TELEPHONE 202-429-3000 DOCKET NUMBER 18460.0014P1

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.

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	18460.0014P1
		Application Number	
Title of Invention	ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS		
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	
	Alexander	M.	Schobel		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Whitehouse Station	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	6 Demott Drive				
Address 2					
City	Whitehouse Station	State/Province	NJ		
Postal Code	08889	Country	US		

Inventor	2				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Stephanie	M.	Varjan		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Oradell	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	151 Prospect Avenue				
Address 2					
City	Oradell	State/Province	NJ		
Postal Code	07649	Country	US		

Inventor	3				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Stephen	P.	Wargacki		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number		18460.0014P1	
		Application Number			
Title of Invention	ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS				
City	Somerset	State/Province	NJ	Country of Residence	US
Mailing Address of Inventor:					
Address 1	199 Pierce Street, Apt. 1227				
Address 2					
City	Somerset	State/Province	NJ		
Postal Code	08873	Country	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	27890		
Email Address	ipdocketing@step toe.com	Add Email	Remove Email
Email Address	hfox@step toe.com	Add Email	Remove Email

Application Information:

Title of the Invention	ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS		
Attorney Docket Number	18460.0014P1	Small Entity Status Claimed	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	12	Suggested Figure for Publication (if any)	

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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0014P1
		Application Number	
Title of Invention	ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS		

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	27890		

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

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).

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0014P1
		Application Number	
Title of Invention	ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS		

			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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	18460.0014P1
	Application Number	
Title of Invention	ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS	

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.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0014P1
		Application Number	
Title of Invention	ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS		

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	MONOSOL RX, LLC	
Mailing Address Information For Applicant:		
Address 1	30 Technology Drive	
Address 2		
City	Warren	State/Province
Country	US	Postal Code
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.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0014P1
		Application Number	
Title of Invention	ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS		

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.			☒
Organization Name	MONOSOL RX, LLC		
Mailing Address Information For Assignee including Non-Applicant Assignee:			
Address 1	30 Technology Drive		
Address 2			
City	Warren	State/Province	NJ
Country ⁱ	US	Postal Code	07059
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:

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Signature	/Harold H. FOX REG#41498/		Date (YYYY-MM-DD)	2016-05-05	
First Name	Harold	Last Name	Fox	Registration Number	41,498
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0014P1
		Application Number	
Title of Invention	ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS		

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Figure 1

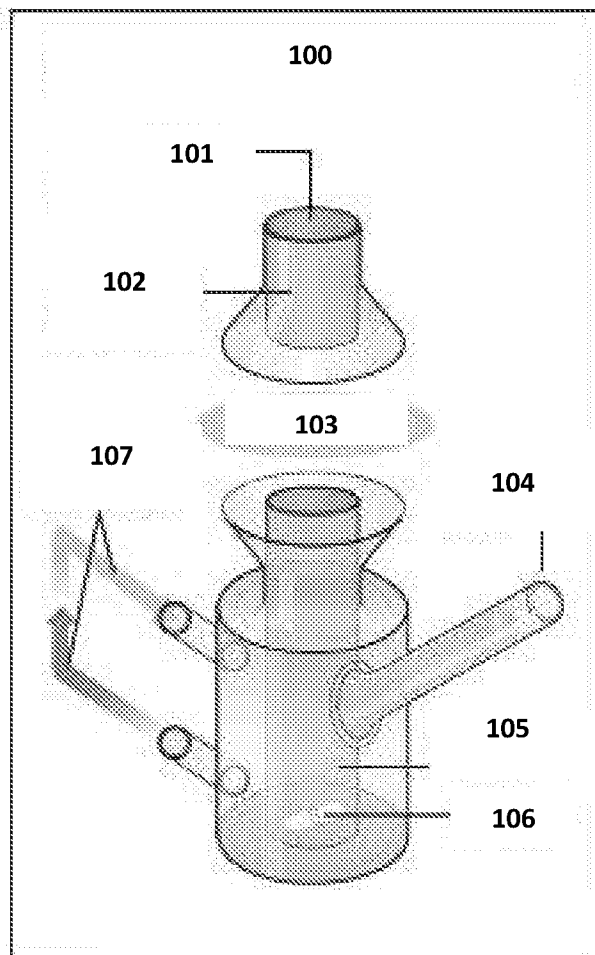


Figure 2a

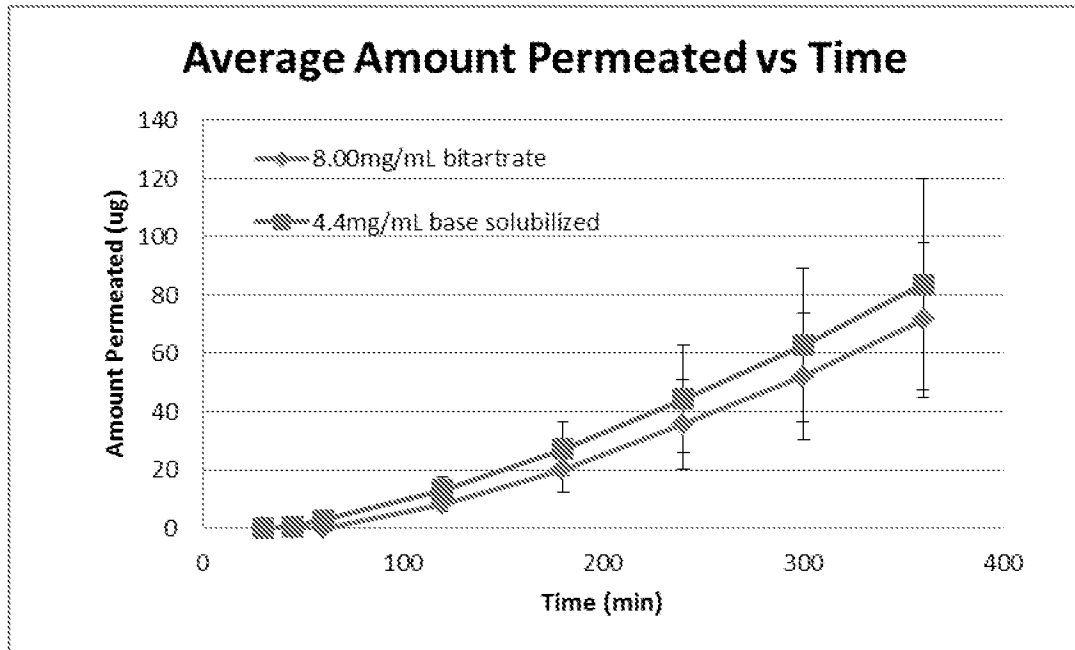


Figure 2b

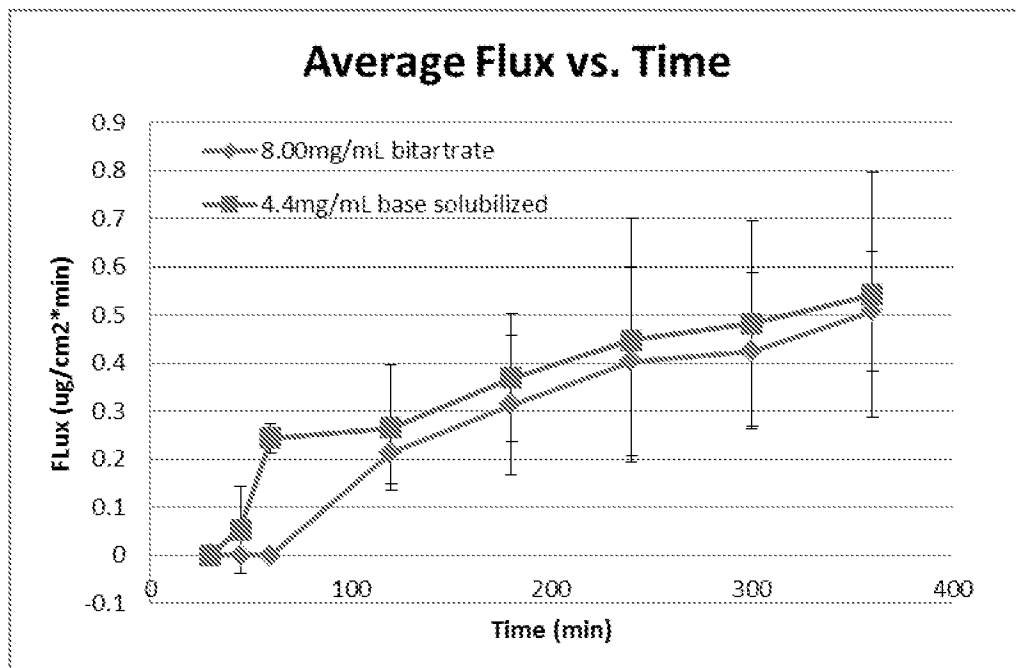


Figure 3

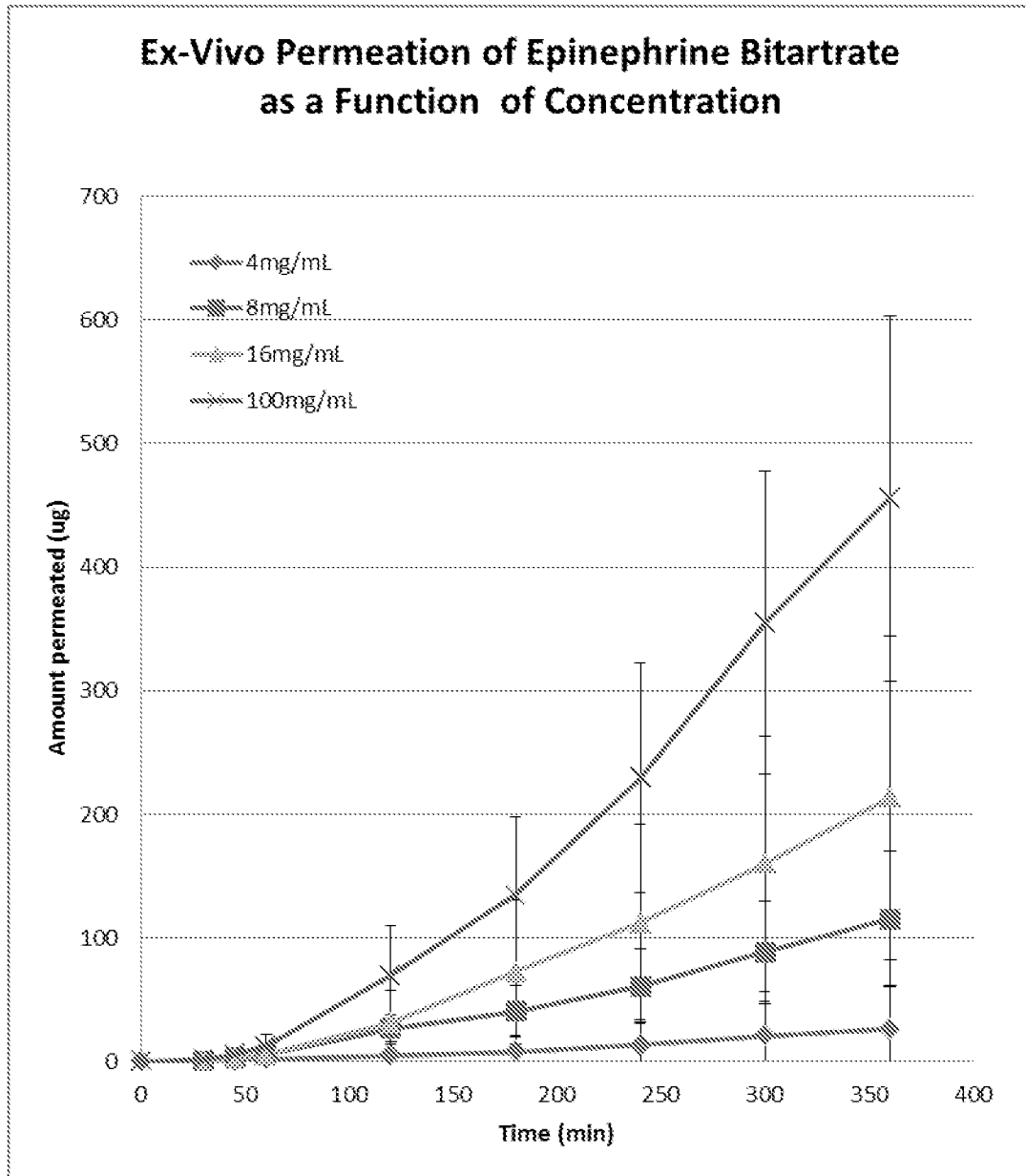


Figure 4

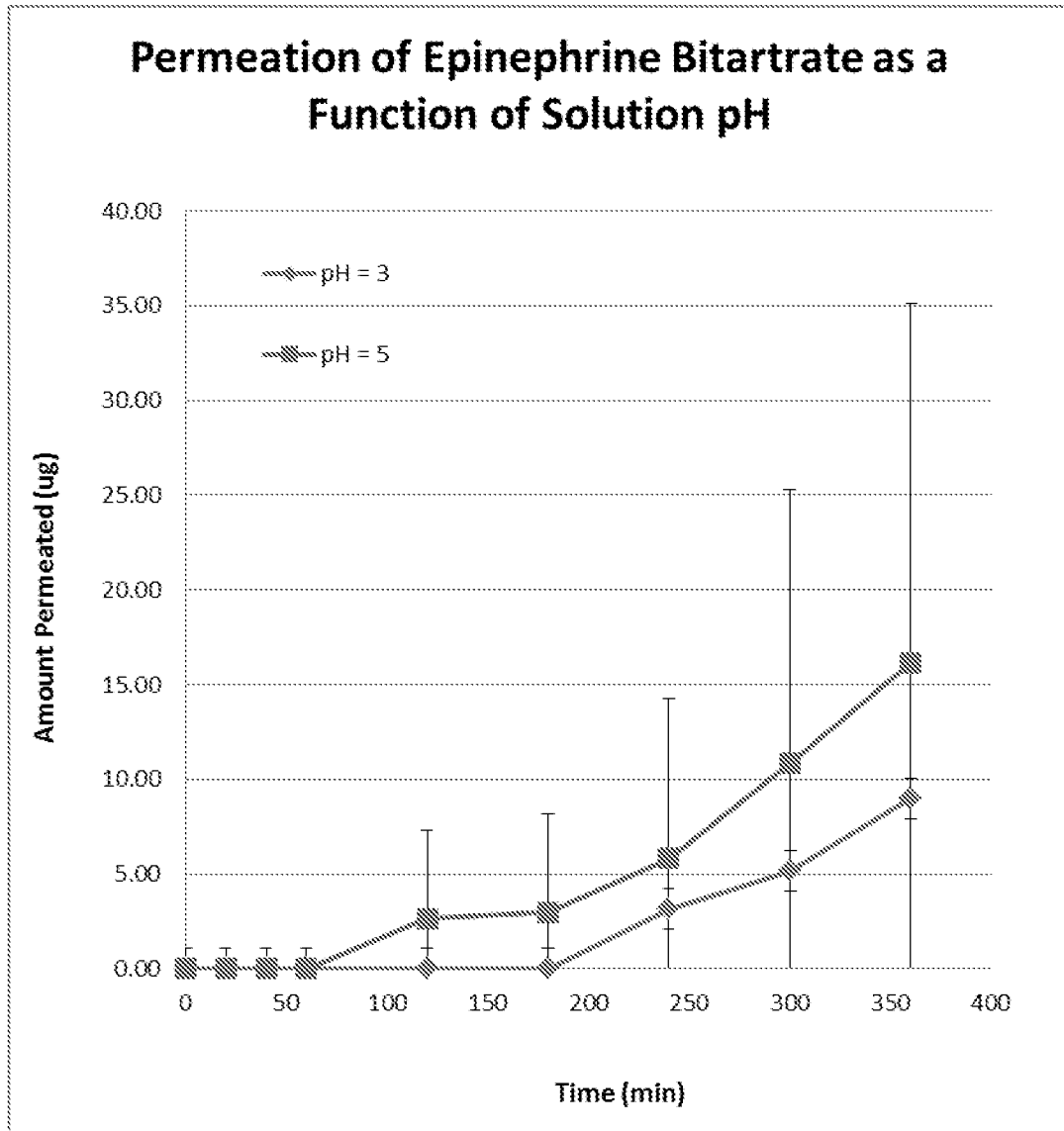


Figure 5

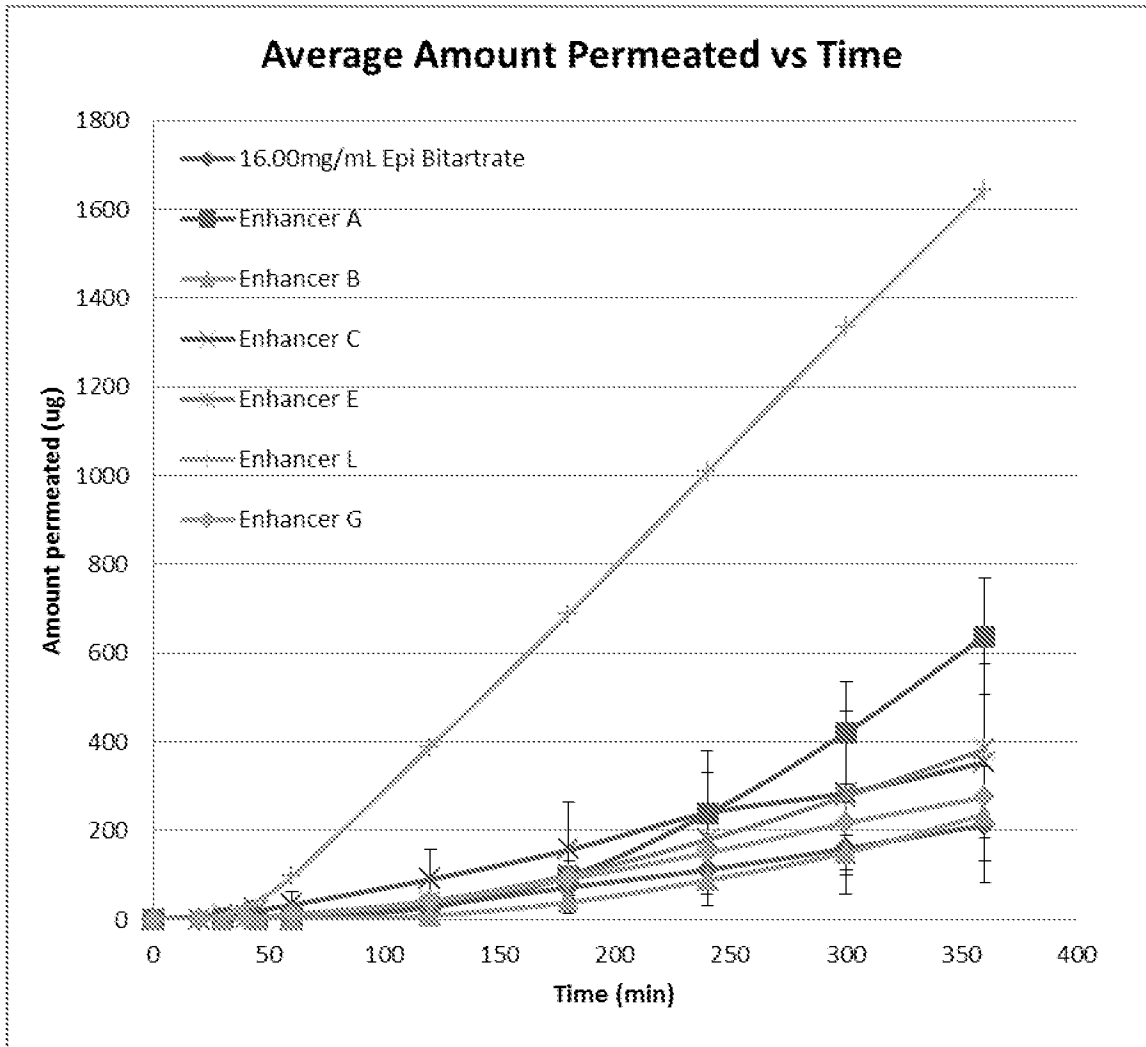


Figure 6a

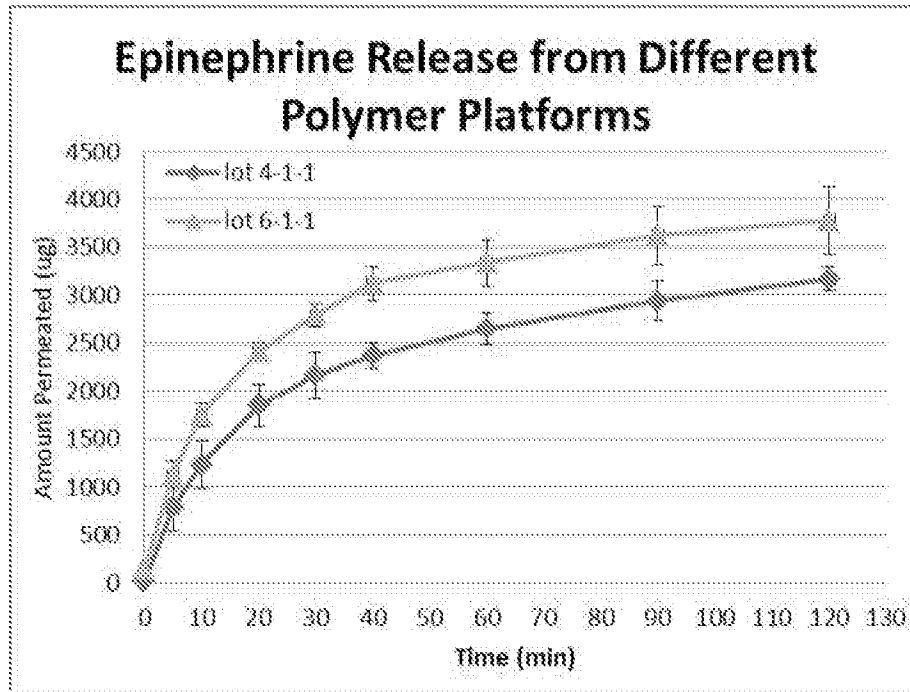


Figure 6b

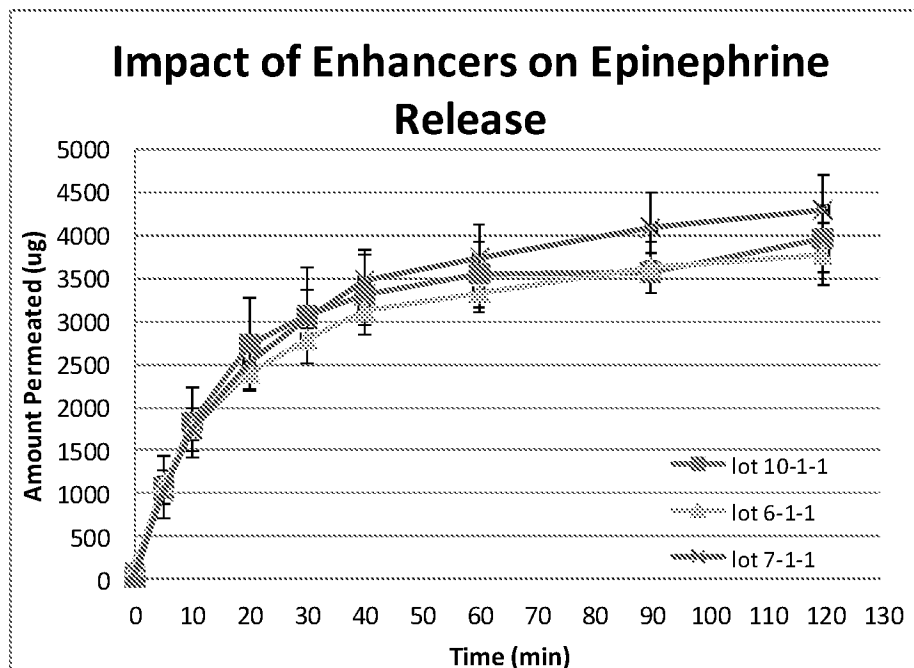


Figure 7

Epinephrine Plasma Concentration vs Time Profiles Following an Intravenous or Intramuscular Epinephrine Administration to Male Miniature Swine

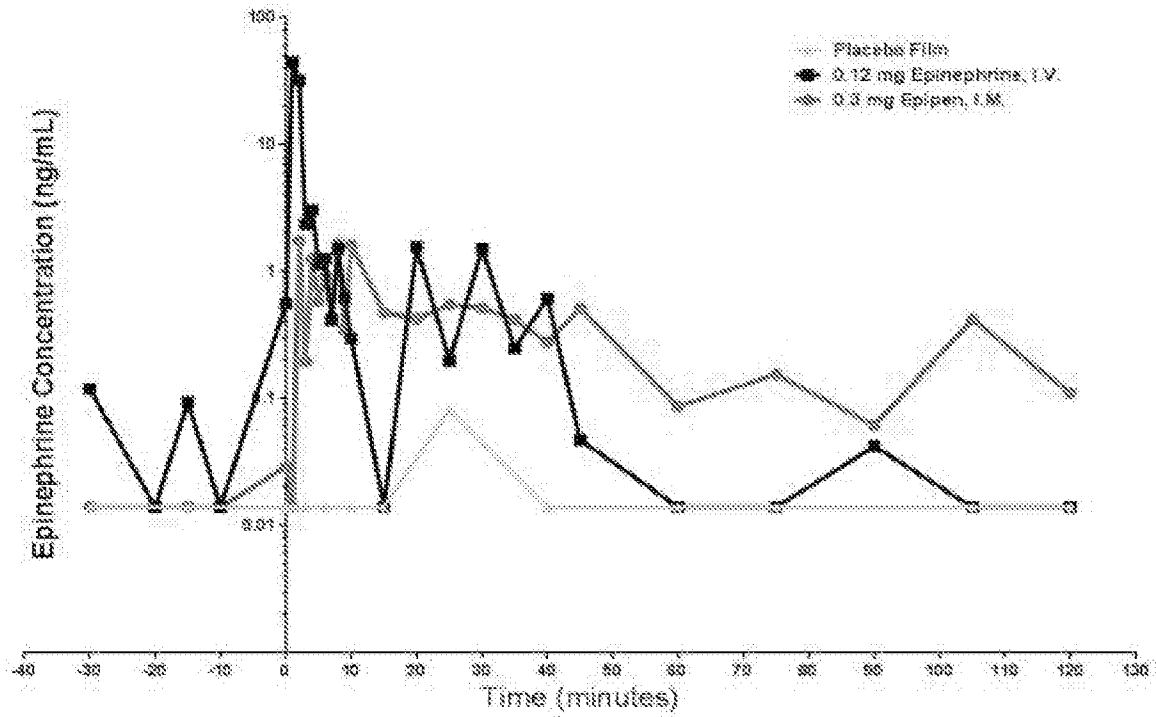


Figure 8

Epinephrine Plasma Concentration vs Time Profiles Following a Sublingual or Intramuscular Epinephrine Administration to Male Miniature Swine

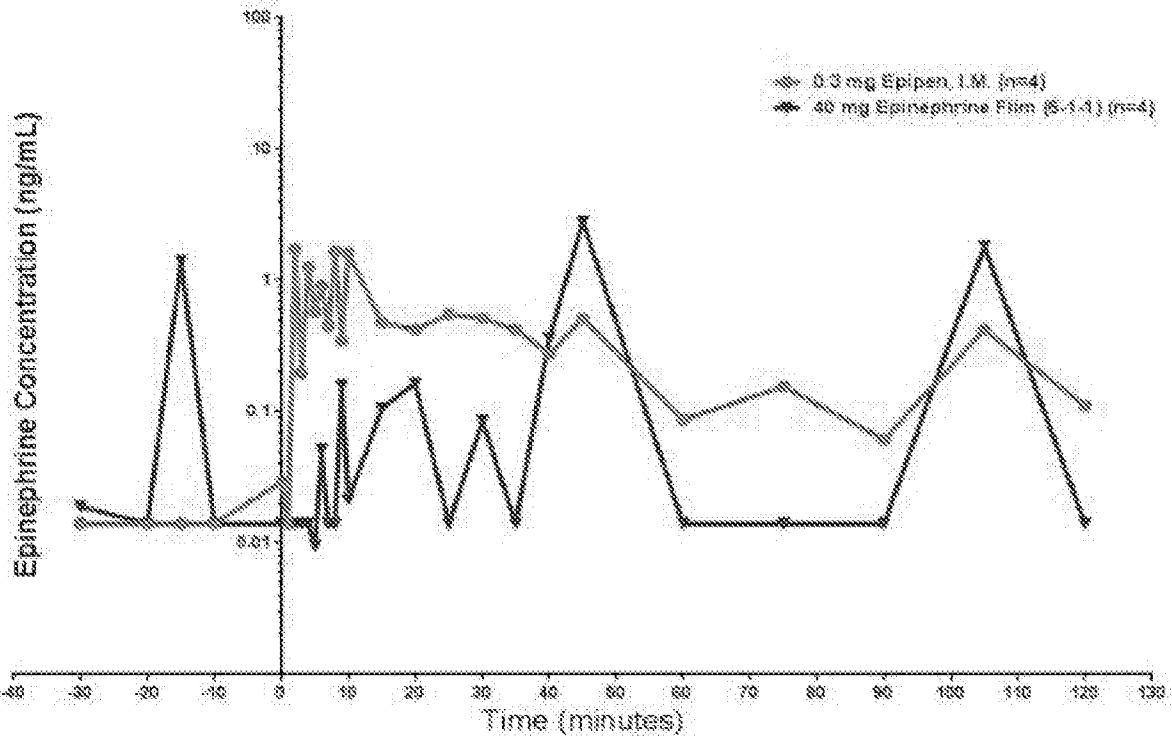


Figure 9

Epinephrine Plasma Concentration vs Time Profiles Following a Sublingual or Intramuscular Epinephrine Administration to Male Miniature Swine

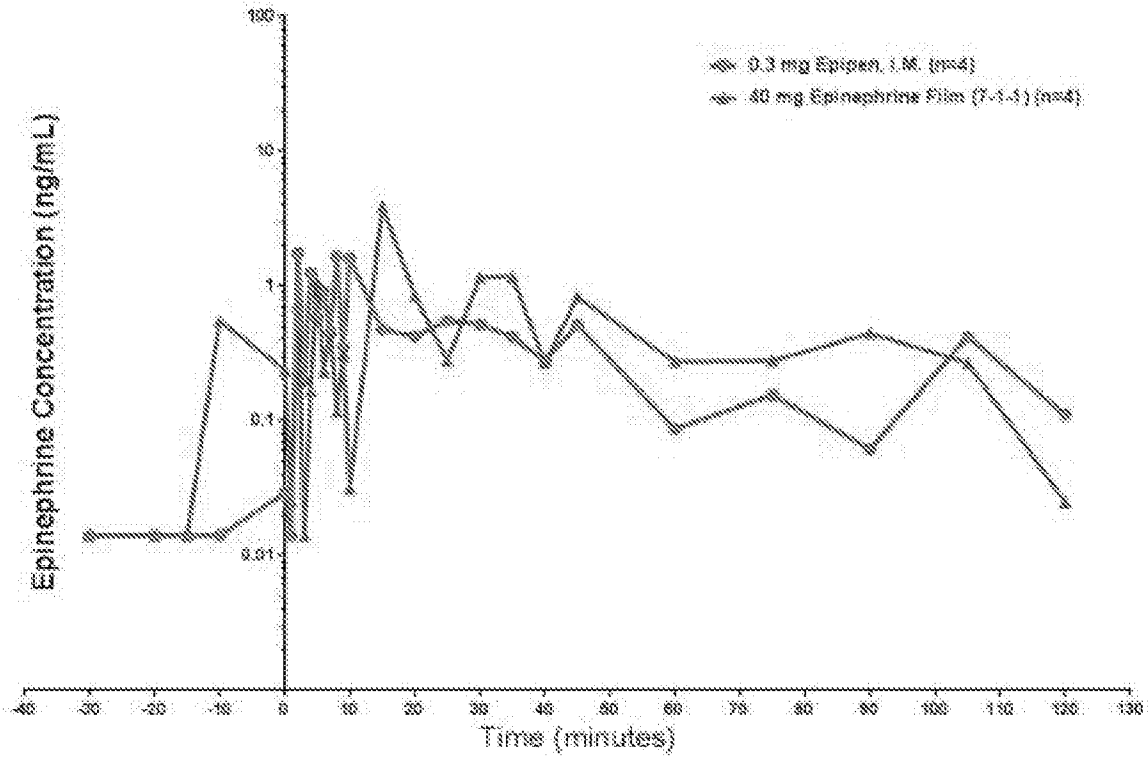


Figure 10

Epinephrine Plasma Concentration vs Time Profiles Following Sublingual or Intramuscular Epinephrine Administration to Male Miniature Swine

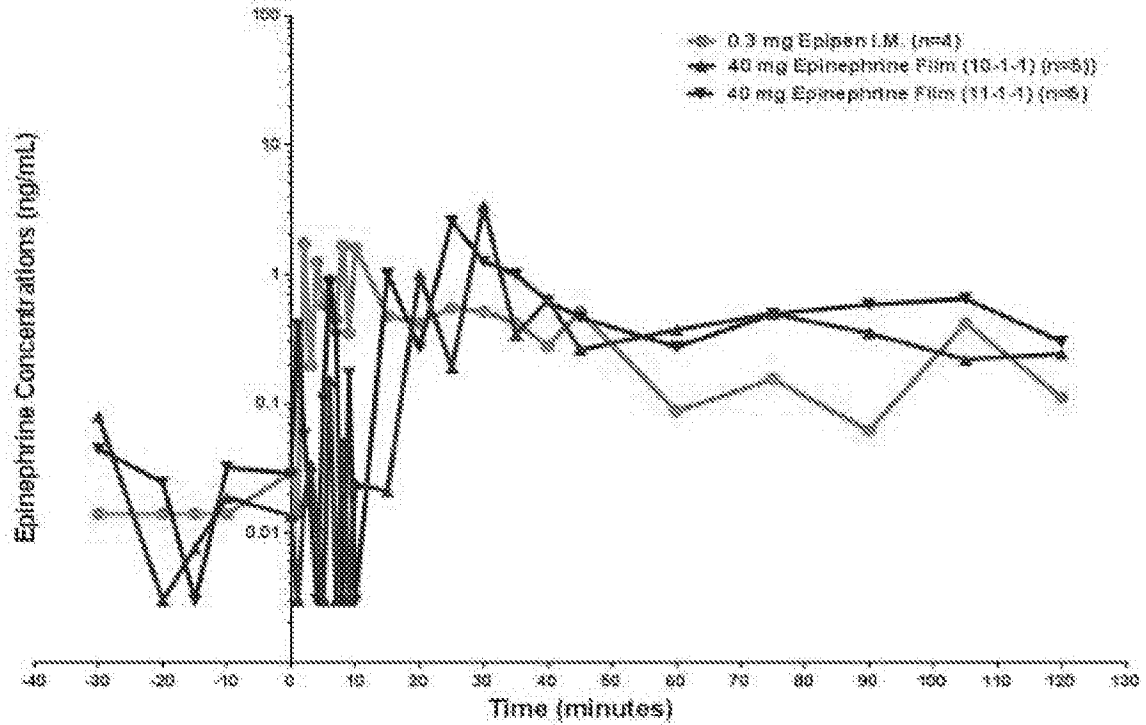


Figure 11

Epinephrine Plasma Concentration vs Time Profiles Following Sublingual or Intramuscular Epinephrine Administration to Male Miniature Swine

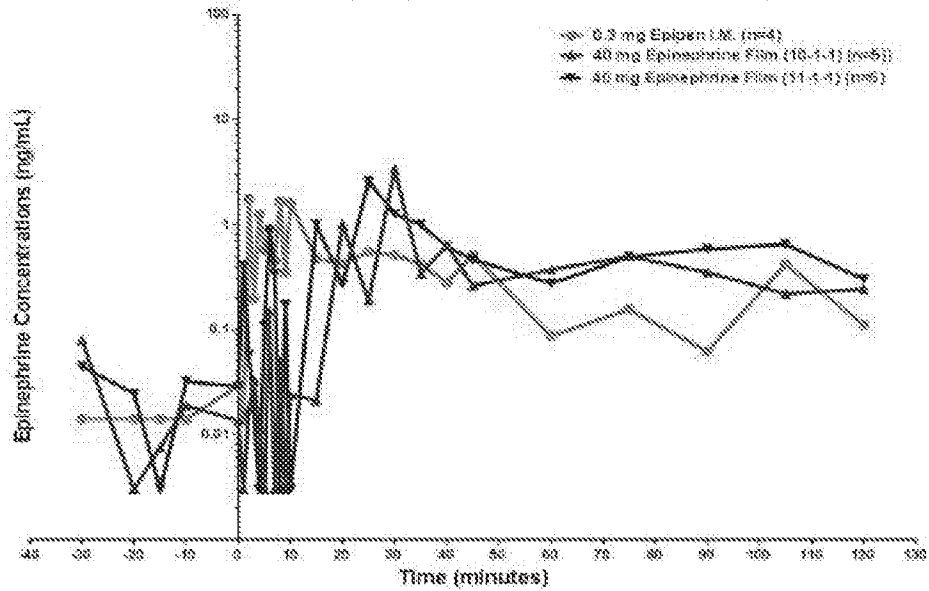


Figure 12

Epinephrine Plasma Concentration vs Time Profiles Following Sublingual or Intramuscular Epinephrine Administration to Male Miniature Swine

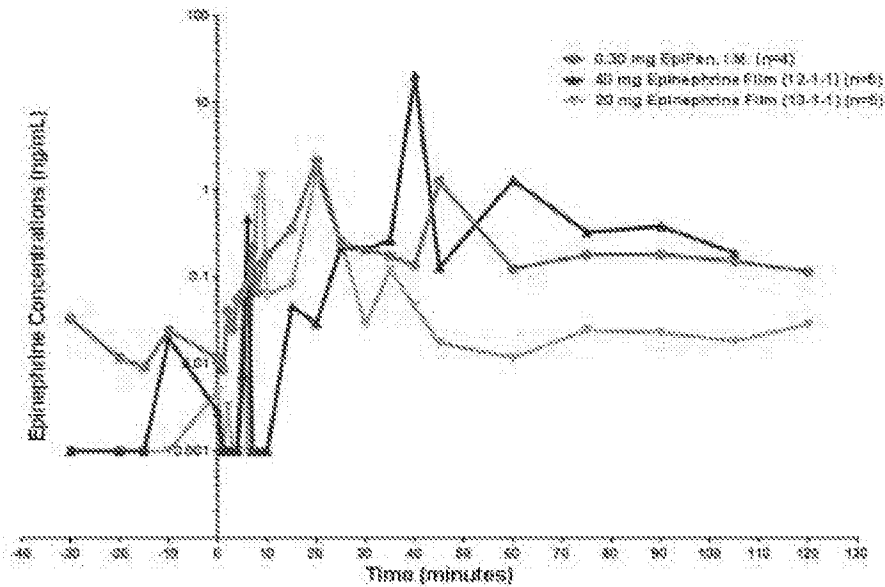


Figure 13

Epinephrine Plasma Concentration vs Time Profiles Following Sublingual or Intramuscular Epinephrine Administration to Male Miniature Swine

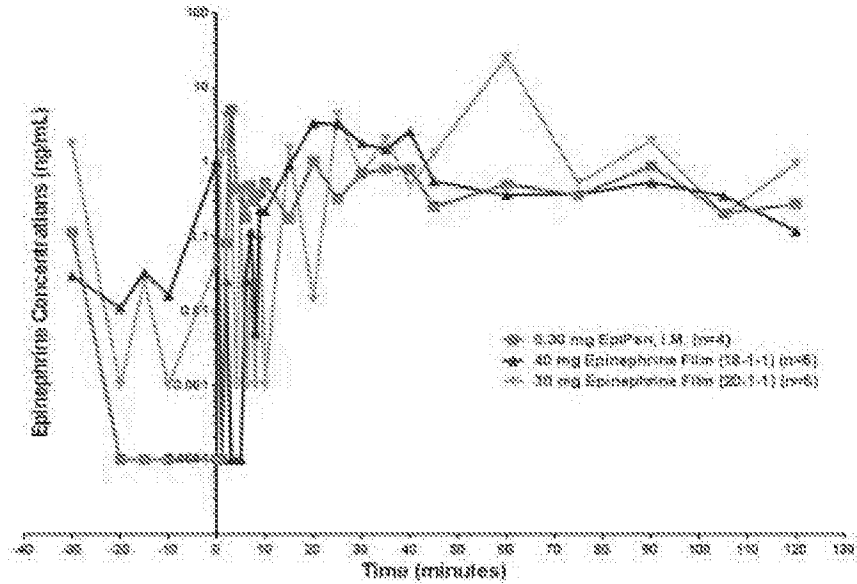
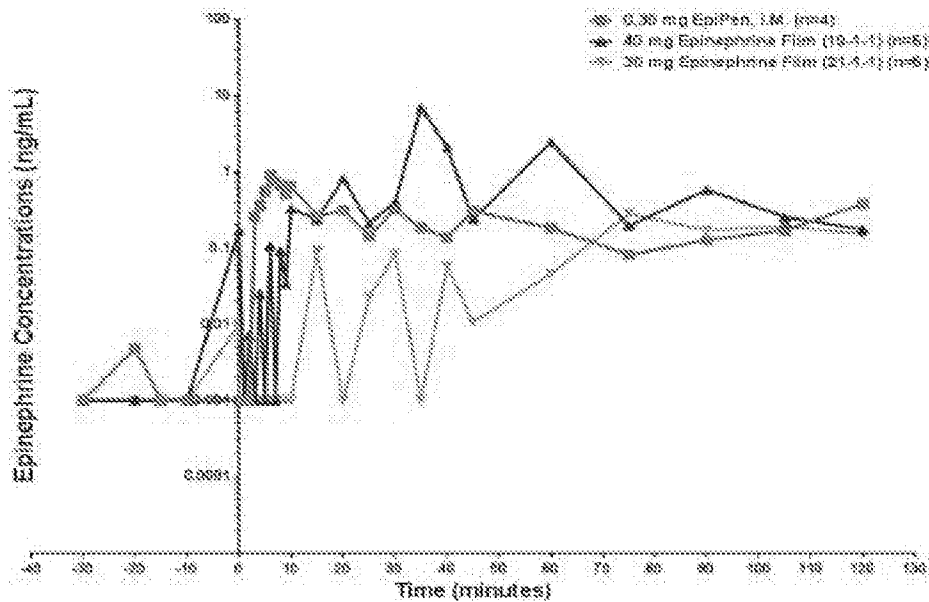


Figure 14

Epinephrine Plasma Concentration vs Time Profiles Following Sublingual or Intramuscular Epinephrine Administration to Male Miniature Swine



ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS

TECHNICAL FIELD

This invention relates to pharmaceutical compositions.

BACKGROUND

Active ingredients, such as drugs or pharmaceuticals, are delivered to patients in deliberate fashion. Delivery of drugs or pharmaceuticals using film transdermally or transmucosally can require that the drug or pharmaceutical permeate or otherwise cross a biological membrane in an effective and efficient manner.

SUMMARY

In general a pharmaceutical composition can include a polymeric matrix, epinephrine in the polymeric matrix, and a permeation enhancer including a phytoextract.

The composition can be a film further comprising a polymeric matrix, the pharmaceutically active component being dispersed in the polymeric matrix.

In certain embodiments, the phytoextract includes a phenylpropanoid.

In other embodiments, the phenylpropanoid is eugenol.

In other embodiments, the phenylpropanoid is eugenol acetate. In certain embodiments, the phenylpropanoid is a cinnamic acid. In other embodiments, the phenylpropanoid is a cinnamic acid ester. In other embodiments, phenylpropanoid is a cinnamic aldehyde.

In other embodiments, the phenylpropanoid is a hydrocinnamic acid. In certain embodiments, the phenylpropanoid is chavicol. In other embodiments, the phenylpropanoid is safrole.

In certain embodiments, the phytoextract is an essential oil extract of a clove plant. In other examples, the phytoextract is an essential oil extract of a leaf of a clove plant.

The phytoextract is an essential oil extract of a flower bud of a clove plant. In other embodiments, the phytoextract is an essential oil extract of a stem of a clove plant.

In certain embodiments, the phytoextract is synthetic. In certain embodiments, the phytoextract includes 60-95% eugenol. In certain embodiments, the phytoextract includes 80-95% eugenol.

In certain embodiments, the polymer matrix includes a water soluble polymer.

In certain embodiments, the polymer matrix includes a polyethylene oxide.

In certain embodiments, the polymer matrix includes a cellulosic polymer is selected from the group of: hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, and carboxymethyl cellulose.

In certain embodiments, the polymeric matrix comprises hydroxypropyl methylcellulose.

In certain embodiments, the polymeric matrix comprises polyethylene oxide and hydroxypropyl methylcellulose.

In certain embodiments, the polymeric matrix comprises at least one polymer selected from the group of: pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, ethylene oxide-propylene oxide co-polymers, collagen, albumin, poly-amino acids, polyphosphazenes, polysaccharides, chitin, chitosan, and derivatives thereof.

In certain embodiments, the pharmaceutical composition further includes a stabilizer.

In general a method of making a pharmaceutical composition includes mixing a permeation enhancer including a phytoextract with a pharmaceutically active component.

BRIEF DESCRIPTION OF THE FIGURES

Referring to **Figure 1**, a Franz diffusion cell 100 includes a donor compound 101, a donor chamber 102, a membrane 103, sampling port 104, receptor chamber 105, stir bar 106, and a heater/circulator 107.

Referring to **Figures 2a** and **2b**, the graphs show the permeation of Epinephrine Base – solubilized in-situ vs. the inherently soluble Epinephrine Bitartrate. No meaningful differences were observed. Epinephrine Bitartrate was selected for further development based on ease of processing. Flux is derived as slope of the amount permeated as a function of time. Steady state flux is taken from plateau of flux vs time curve time the volume of receiver media.

Referring to **Figure 2a**, this graph shows average amount permeated vs. time, with 8.00 mg/mL bitartrate and 4.4 mg/mL based solubilized.

Referring to **Figure 2b**, this graph shows average flux vs. time, with 8.00 mg/mL bitartrate and 4.4 mg/mL based solubilized.

Referring to **Figure 3**, this graph shows ex-vivo permeation of epinephrine bitartrate as a function of concentration. The study compared concentrations of 4 mg/mL, 8 mg/mL, 16 mg/mL and 100 mg/mL. Results showed that increasing concentration resulted in increased permeation, and level of enhancement reduces at higher loading. The study compared concentrations of 4 mg/mL, 8 mg/mL, 16 mg/mL and 100 mg/mL.

Referring to **Figure 4**, this graph shows permeation of epinephrine bitartrate as a function of solution pH. Acidic conditions explored to promote stability. The results compared Epinephrine Bitartrate pH 3 buffer and Epinephrine Bitartrate pH 5 buffer, and found that the Epinephrine Bitartrate pH 5 buffer was slightly favorable.

Referring to **Figure 5**, this graph shows the influence of enhancers on permeation of epinephrine, indicated as amount permeated as a function of time. Multiple enhancers were screened, including Labrasol, capryol 90, Plurol Oleique, Labrafil, TDM, SGDC, Gelucire 44/14 and clove oil. Significant impact on time to onset and steady state flux was achieved, and surprisingly enhanced permeation was achieved for clove oil and labrasol.

Referring to **Figure 6a and 6b**, these graphs show the release of epinephrine on polymer platforms and the effect of enhancers on its release, indicated as amount permeated (in μg) vs. time. Figure 6a shows the epinephrine release from different polymer platforms. Figure 6b shows the impact of enhancers on epinephrine release.

Referring to **Figure 7**, this graph shows a pharmacokinetic model in the male yucatan, miniature swine. The study compares a 0.3 mg Epipen, a 0.12 mg Epinephrine IV and a placebo.

Referring to **Figure 8**, this graphs shows the impact of no enhancer on the concentration profiles of a 0.3 mg Epipen and a 40 mg Epinephrine film.

Referring to **Figure 9**, this graph shows the impact of Enhancer A (labrasol) on the concentration profiles of a 0.3 mg Epipen and a 40 mg Epinephrine film.

Referring to **Figure 10**, this graph shows the impact of Enhancer L (clove oil) on the concentration profiles of a 0.3 mg Epipen and a 40 mg Epinephrine film (10-1-1) and (11-1-1).

Referring to **Figure 11**, this graph shows the epinephrine plasma concentration vs. time profile and influence of film dimensions and impact of Enhancer L (clove oil).

Referring to **Figure 12**, this graph shows this graph shows the varying ratio of epinephrine plasma concentration vs. time profile with Enhancer L (clove oil).

Referring to **Figure 13**, the graph shows the varying dose in a constant matrix for Enhancer L (clove oil).

Referring to **Figure 14**, the graph shows the varying dose in a constant matrix for Enhancer A (labrasol).

DETAILED DESCRIPTION

Mucosal surfaces, such as the oral mucosa, are a convenient route for delivering drugs to the body due to the fact that they are highly vascularized and permeable, providing increased bioavailability and rapid onset of action because it does not pass through the digestive system and thereby avoids first pass metabolism. In particular, the buccal and sublingual tissues offer advantageous sites for drug delivery because they are highly permeable regions of the oral mucosa, allowing drugs diffusing from the oral mucosa to have direct access to systemic circulation. This also offers increased convenience and therefore increased compliance in patients. For certain drugs, or pharmaceutically active components, a permeation enhancer can help to overcome the mucosal barrier and improve permeability. Permeation enhancers reversibly modulate the permeability of the barrier layer in favor of drug absorption. Permeation enhancers facilitate transport of molecules through the epithelium. Absorption profiles can be controlled and tuned by a variety of parameters, such as but not limited to film size, drug loading, enhancer type/loading, and polymer matrix release rate.

A pharmaceutical composition can be designed to deliver a pharmaceutically active component in a deliberate and tailored way. However, solubility and permeability of the pharmaceutically active component in vivo, in particular, in the mouth of a subject, can vary tremendously. A particular class of permeation enhancer can improve the uptake and bioavailability of the pharmaceutically active component in vivo. In particular, when delivered to the mouth via a film, the permeation enhancer can improve the permeability of the

pharmaceutically active component through the mucosa and into the blood stream of the subject. The permeation enhancer can improve absorption rate and amount of the pharmaceutically active component by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200% or more depending on the other components in the composition.

Penetration enhancers have been described in J. Nicolazzo, et al., *J. of Controlled Disease*, 105 (2005) 1-15, which is incorporated by reference in its entirety.

There are many reasons why the buccal mucosa might be an attractive site for the delivery of therapeutic agents into the systemic circulation. Due to the direct drainage of blood from the buccal epithelium into the internal jugular vein first-pass metabolism in the liver and intestine may be avoided. This first-pass effect can be a major reason for the poor bioavailability of some compounds when administered orally. Additionally, the mucosa lining the oral cavity is easily accessible, which ensures that a dosage form can be applied to the required site and can be removed easily in the case of an emergency. However, like the skin, the buccal mucosa acts as a barrier to the absorption of xenobiotics, which can hinder the permeation of compounds across this tissue. Consequently, the identification of safe and effective penetration enhancers has become a major goal in the quest to improve oral mucosal drug delivery.

Chemical penetration enhancers are substances that increase the permeation rate of a coadministered drug through a biological membrane. While extensive research has focused on obtaining an improved understanding of how penetration enhancers might alter intestinal and transdermal permeability, far less is known about the mechanisms involved in buccal penetration enhancement.

The buccal mucosa delineates the inside lining of the cheek as well as the area between the gums and upper and lower lips and it has an average surface area of 100 cm². The surface of the buccal mucosa consists of a stratified squamous epithelium which is separated from the underlying connective tissue (lamina propria and submucosa) by an undulating basement membrane (a continuous layer of extracellular material approximately 1–2 Am in thickness). This stratified squamous epithelium consists of differentiating layers of cells (keratinocytes) which change in size, shape, and content as they travel from the basal region to the superficial region, where the cells are shed. There are approximately 40–50 cell layers, resulting in a buccal mucosa which is 500–600 Am thick.

The permeability of the buccal mucosa is greater than that of the skin, but less than that of the intestine. This does not only result from the greater surface area provided by the small intestine, but also from the structural differences between each of the tissues. The absence of organized lipid lamellae in the intercellular spaces of the buccal mucosa results in a greater permeability to exogenous compounds, compared to keratinized epithelia.

The barrier properties of the buccal mucosa have been attributed to the upper one-third to one-quarter of the buccal epithelium. Researchers have learned that the permeability barrier of nonkeratinized oral mucosa could be attributed to contents extruded from the membrane-coating granules into the epithelial intercellular spaces.

The intercellular lipids of the nonkeratinized regions of the oral cavity are of a more polar nature than the lipids of the epidermis, palate, and gingiva, and this difference in the chemical nature of the lipids may contribute to the differences in permeability observed between these tissues. Consequently, it appears that it is not only the greater degree of intercellular lipid packing in the stratum corneum of keratinized epithelia that creates a more effective barrier, but also the chemical nature of the lipids present within that barrier.

The existence of hydrophilic and lipophilic regions in the oral mucosa has lead the majority of researchers to postulate the existence of two routes of drug transport through the buccal mucosa—paracellular (between the cells) and transcellular (across the cells).

Since drug delivery through the buccal mucosa is limited by the barrier nature of the epithelium and the area available for absorption, various enhancement strategies are required in order to deliver therapeutically relevant amounts of drug to the systemic circulation. Various methods, including the use of chemical penetration enhancers, prodrugs, and physical methods may be employed to overcome the barrier properties of the buccal mucosa.

A chemical penetration enhancer, or absorption promoter, is a substance added to a pharmaceutical formulation in order to increase the membrane permeation or absorption rate of a coadministered drug, without damaging the membrane and causing toxicity. There have been many studies investigating the effect of chemical penetration enhancers on the delivery of compounds across the skin, nasal mucosa, and intestine, and in recent years, more attention has been given to the effect of these agents on the permeability of the buccal mucosa. Since permeability across the buccal mucosa is considered to be a passive diffusion process the steady

state flux (J_{ss}) should increase with increasing donor chamber concentration (CD) according to Fick's first law of diffusion.

Surfactants and bile salts have been shown to enhance the permeability of various compounds across the buccal mucosa, both in vitro and in vivo, and data obtained from these studies strongly suggest that the enhancement in permeability is due to an effect of the surfactants on the mucosal intercellular lipids.

Fatty acids have also been shown to enhance the permeation of a number of drugs through the skin, and this has been shown by DSC and FTIR to be related to an increase in the fluidity of intercellular lipids.

Additionally, pretreatment with ethanol has been shown to enhance the permeability of tritiated water and albumin across ventral tongue mucosa, and to enhance caffeine permeability across porcine buccal mucosa. There are also several reports of the enhancing effect of Azone® on the permeability of compounds through oral mucosa. Further, chitosan, a biocompatible and biodegradable polymer, has been shown to enhance drug delivery through various tissues, including the intestine and nasal mucosa.

Oral transmucosal drug delivery (OTDD) is the administration of pharmaceutically active agents through the oral mucosa to achieve systemic effects. Permeation pathways and predictive models for OTDD are described, e.g. in M. Sattar, Oral transmucosal drug delivery – Current status and future prospects, *Int'l. Journal of Pharmaceutics*, 47(2014) 498-506, which is incorporated by reference herein. OTDD continues to attract the attention of academic and industrial scientists. Despite limited characterization of the permeation pathways in the oral cavity compared with skin and nasal routes of delivery, recent advances in our understanding of the extent to which ionized molecules permeate through buccal epithelium are encouraging as well as the emergence of new analytical techniques to study the oral cavity, and the progressing development of in silico models predictive of buccal and sublingual permeation.

In order to deliver broader classes of drugs across the buccal mucosa, reversible methods of reducing the barrier potential of this tissue must be employed. This requisite has fostered the study of penetration enhancers that will safely alter the permeability restrictions of the buccal mucosa. It has been shown that buccal penetration can be improved by using various classes of transmucosal and transdermal penetration enhancers such as bile salts, surfactants, fatty acids

and derivatives, chelators, cyclodextrins and chitosan. Among these chemicals used for the drug permeation enhancement, bile salts are most common.

In vitro studies on enhancing effect of bile salts on the buccal permeation of compounds is discussed in Sevda Senel, Drug permeation enhancement via buccal route: possibilities and limitations, *Journal of Controlled Release* 72 (2001) 133–144, which is incorporated by reference herein. That article also discusses recent studies on the effects of buccal epithelial permeability of dihydroxy bile salts, sodium glycodeoxycholate (GDC) and sodium taurodeoxycholate (TDC) and tri-hydroxy bile salts, sodium glycocholate(GC) and sodium taurocholate (TC) at 100 mM concentration including permeability changes correlated with the histological effects. Fluorescein isothiocyanate (FITC), morphine sulfate were each used as the model compound.

Chitosan has also been shown to promote absorption of small polar molecules and peptide / protein drugs through nasal mucosa in animal models and human volunteers. Other studies have shown an enhancing effect on penetration of compounds across the intestinal mucosa and cultured Caco-2 cells.

The permeation enhancer can be a phytoextract. A phytoextract can be an essential oil or composition including essential oils extracted by distillation of the plant material. In certain circumstances, the phytoextract can include a synthetic analogues of the compounds extracted from the plant material (i.e., compounds made by organic synthesis). The phytoextract can include a phenylpropanoid, for example, phenyl alanine, eugenol, eugenol acetate, a cinnamic acid, a cinnamic acid ester, a cinnamic aldehyde, a hydrocinnamic acid, chavicol, or safrole, or a combination thereof. The phytoextract can be an essential oil extract of a clove plant, for example, from the leaf, stem or flower bud of a clove plant. The clove plant can be *Syzygium aromaticum*. The phytoextract can include 60-95% eugenol, for example, 80-95% eugenol. The extract can include caryophyllene. Other permeation enhancers may be added to the device to improve absorption of the drug. Suitable permeation enhancers include natural or synthetic bile salts such as sodium fusidate; glycocholate or deoxycholate; fatty acids and derivatives such as sodium laurate, oleic acid, oleyl alcohol, monoolein, and palmitoylcarnitine; chelators such as disodium EDTA, sodium citrate and sodium laurylsulfate, azone, sodium cholate, sodium 5-

methoxysalicylate, sorbitan laurate, glyceryl monolaurate, octoxynonyl-9, laureth-9, polysorbates, sterols, or glycerides, such as caprylocaproyl polyoxylglycerides, e.g., Labrasol.

The pharmaceutical composition can be a gel, cream, tablet, liquid or film. The composition can include textures, for example, at the surface, such as microneedles or micro-protrusions.

The term “film” can include films and sheets, in any shape, including rectangular, square, or other desired shape. A film can be any desired thickness and size. In preferred embodiments, a film can have a thickness and size such that it can be administered to a user, for example, placed into the oral cavity of the user. A film can have a relatively thin thickness of from about 0.1 to about 10 mils, or a film can have a somewhat thicker thickness of from about 10 to about 40 mils. For some films, the thickness may be even larger, i.e., greater than about 40 mils. A film can be a single layer or a film can be multi-layered, including laminated or multiple cast films.

Oral dissolving films can fall into three main classes: fast dissolving, moderate dissolving and slow dissolving. Fast dissolving films can dissolve in about 1 second to about 30 seconds in the mouth. Moderate dissolving films can dissolve in about 1 to about 30 minutes in the mouth, and slow dissolving films can dissolve in more than 30 minutes in the mouth. As a general trend, fast dissolving films can include (or consist of) low molecular weight hydrophilic polymers (e.g., polymers having a molecular weight between about 1,000 to 9,000, or polymers having a molecular weight up to 200,000). In contrast, slow dissolving films generally include high molecular weight polymers (e.g., having a molecular weight in millions). Moderate dissolving films can tend to fall in between the fast and slow dissolving films.

It can be preferable to use films that are moderate dissolving films. Moderate dissolving films can dissolve rather quickly, but also have a good level of mucoadhesion. Moderate dissolving films can also be flexible, quickly wettable, and are typically non-irritating to the user. Such moderate dissolving films can provide a quick enough dissolution rate, most desirably between about 1 minute and about 20 minutes, while providing an acceptable mucoadhesion level such that the film is not easily removable once it is placed in the oral cavity of the user. This can ensure delivery of a pharmaceutically active component to a user.

For example, a composition including epinephrine can have a biodelivery profile similar to that of epinephrine administered by injection, for example, using an EpiPen. Epinephrine can

be present in an amount of from about .01 mg to about 100 mg per dosage, for example, at a 0.1mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg or 100 mg dosage.

A film and/or its components can be water-soluble or water-insoluble. The term “water-soluble” can refer to substances that are at least partially dissolvable in an aqueous solvent, including but not limited to water. The term “water-soluble” may not necessarily mean that the substance is 100% dissolvable in the aqueous solvent. The term “water-insoluble” refers to substances that are not dissolvable in an aqueous solvent, including but not limited to water. A solvent can include water, or alternatively can include other solvents (preferably, polar solvents) by themselves or in combination with water.

The composition can include a polymeric matrix. Any desired polymeric matrix may be used, provided that it is orally dissolvable or erodible. Desirably, the dosage should have enough bioadhesion to not be easily removed and it should form a gel like structure when administered. They can be moderate-dissolving in the oral cavity and particularly suitable for delivery of pharmaceutically active components, although both fast release, delayed release, controlled release and sustained release compositions are also among the various embodiments contemplated.

A film can be produced by a combination of at least one polymer and a solvent, optionally including other components. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, or any combination thereof. In some embodiments, the solvent may be a non-polar organic solvent, such as methylene chloride. The film may be prepared by utilizing a selected casting or deposition method and a controlled drying process. For example, the film may be prepared through controlled drying processes, which include application of heat and/or radiation energy to the wet film matrix to form a visco-elastic structure, thereby controlling the uniformity of content of the film. Such processes are described in more detail in U.S. Patent No. 8,765,167 and U.S. Patent No. 8,652,378, the contents of which is incorporated herein by reference in its entirety. Alternatively, the films may be extruded as described in U.S. Patent Publication No. 2005/0037055 A1, the contents of which is incorporated herein by reference in their entirety.

A polymer included in the films may be water-soluble, water-swellaable, water-insoluble, or a combination of one or more either water-soluble, water-swellaable or water-insoluble

polymers. The polymer may include cellulose, cellulose derivatives or gums. Specific examples of useful water-soluble polymers include, but are not limited to, polyethylene oxide, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water-insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof. For higher dosages, it may be desirable to incorporate a polymer that provides a high level of viscosity as compared to lower dosages.

As used herein the phrase "water-soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water-swellaable polymers. The materials useful with the present invention may be water-soluble or water-swellaable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water-soluble or water-swellaable at pressures less than atmospheric pressure. In some embodiments, films formed from such water-soluble polymers may be sufficiently water-soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films include biodegradable polymers, copolymers, block polymers and combinations thereof. It is understood that the term "biodegradable" is intended to include materials that chemically degrade, as opposed to materials that physically break apart (i.e., bioerodable materials). Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanes, polyoxalates, poly(alpha-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy)propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid)), copolymers of polyurethane and poly(lactic acid), copolymers of .alpha.-amino acids, copolymers of .alpha.-amino acids and caproic acid,

copolymers of .alpha.-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof. The polymer matrix can include one, two, three, four or more components.

Although a variety of different polymers may be used, it is desired to select polymers that provide mucoadhesive properties to the film, as well as a desired dissolution and/or disintegration rate. In particular, the time period for which it is desired to maintain the film in contact with the mucosal tissue depends on the type of pharmaceutically active component contained in the composition. Some pharmaceutically active components may only require a few minutes for delivery through the mucosal tissue, whereas other pharmaceutically active components may require up to several hours or even longer. Accordingly, in some embodiments, one or more water-soluble polymers, as described above, may be used to form the film. In other embodiments, however, it may be desirable to use combinations of water-soluble polymers and polymers that are water-swellaable, water-insoluble and/or biodegradable, as provided above. The inclusion of one or more polymers that are water-swellaable, water-insoluble and/or biodegradable may provide films with slower dissolution or disintegration rates than films formed from water-soluble polymers alone. As such, the film may adhere to the mucosal tissue for longer periods or time, such as up to several hours, which may be desirable for delivery of certain pharmaceutically active components.

Desirably, an individual film dosage of the pharmaceutical film can have a small size, which is between about 0.25-2 inch by about 0.25-2 inch. The film dosage should have good adhesion when placed in the buccal cavity or in the sublingual region of the user. Further, the film dosage should disperse and dissolve at a moderate rate, most desirably dispersing within about 1 minute and dissolving within about 3 minutes. In some embodiments, the film dosage may be capable of dispersing and dissolving at a rate of between about 1 to about 15 minutes, for example, about 1 to about 10 minutes. Sublingual rates can be shorter than buccal rates.

For instance, in some embodiments, the films may include polyethylene oxide alone or in combination with a second polymer component. The second polymer may be another water-soluble polymer, a water-swellaable polymer, a water-insoluble polymer, a biodegradable polymer or any combination thereof. Suitable water-soluble polymers include, without limitation, any of those provided above. In some embodiments, the water-soluble polymer may include hydrophilic cellulosic polymers, such as hydroxypropyl cellulose and/or

hydroxypropylmethyl cellulose. In some embodiments, one or more water-swellaable, water-insoluble and/or biodegradable polymers also may be included in the polyethylene oxide-based film. Any of the water-swellaable, water-insoluble or biodegradable polymers provided above may be employed. The second polymer component may be employed in amounts of about 0% to about 80% by weight in the polymer component, more specifically about 30% to about 70% by weight, and even more specifically about 40% to about 60% by weight.

Additives may be included in the films. Examples of classes of additives include preservatives, antimicrobials, excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers, anti-tacking agents, anti-static agents and mixtures thereof. These additives may be added with the pharmaceutically active component(s). The stabilizer can be a radical scavenger, an antioxidant, a buffering agent, an antimicrobial or an antifungal, for example, sodium metabisulfite.

Useful additives can include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragacanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVY/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate,

crosslinked gelatin, shellac, water-soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers.

The additional components can range up to about 80%, desirably about 3% to 50% and more desirably within the range of 3% to 20% based on the weight of all composition components. Other additives can include anti-tacking, flow agents and opacifiers, such as the oxides of magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.01% to about 5% by weight and desirably about 0.02% to about 1% based on the weight of all film components.

In certain embodiments, the composition can include plasticizers, which can include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, phytoextracts, fatty acid esters, fatty acids, oils and the like, added in concentrations ranging from about 0.1% to about 40%, and desirably ranging from about 0.5% to about 20% based on the weight of the composition. There may further be added compounds to improve the texture properties of the starch material such as animal or vegetable fats, desirably in their hydrogenated form. The composition can also include compounds to improve the textural properties of the product. Other ingredients can include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, natural gums, pregelatinized starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, and polyvinylalcohols.

Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or unstable pharmaceutically active components may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly, the formation of the inclusion complex permits very insoluble and/or unstable pharmaceutically active components to

be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered well within the scope of the present invention.

Suitable coloring agents include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide. Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides of iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, based on the weight of all the components.

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors. Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., aliphatic citral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), and 2-dodecenal (citrus, mandarin), combinations thereof and the like.

The sweeteners may be chosen from the following non-limiting list: glucose (corn syrup), dextrose, invert sugar, fructose, and combinations thereof, saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof, and natural intensive sweeteners, such as Lo Han Kuo. Other sweeteners may also be used.

Anti-foaming and/or de-foaming components may also be used with the films. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. Such entrapped air may lead to non-uniform films. Dimethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention, however, is not so limited and other anti-foam and/or de-foaming agents may suitably be used. Dimethicone and related agents may be employed for densification purposes. More specifically, such agents may facilitate the removal of voids, air, moisture, and similar undesired components, thereby providing denser and thus more uniform films. Agents or components which perform this function can be referred to as densification or densifying agents. As described above, entrapped air or undesired components may lead to non-uniform films.

Any other optional components described in commonly assigned U.S. Patent No. 7,425,292 and U.S. Patent No. 8,765,167, referred to above, also may be included in the films described herein.

The film compositions further desirably contain a buffer so as to control the pH of the film composition. Any desired level of buffer may be incorporated into the film composition so as to provide the desired pH level encountered as the pharmaceutically active component is released from the composition. The buffer is preferably provided in an amount sufficient to control the release from the film and/or the absorption into the body of the pharmaceutically active component. In some embodiments, the buffer may include sodium citrate, citric acid, bitartrate and combinations thereof.

The pharmaceutical films described herein may be formed via any desired process. Suitable processes are set forth in U.S. Patent Nos. 8,652,378, 7,425,292 and 7,357,891, the entire contents of which are incorporated by reference herein. In one embodiment, the film dosage composition is formed by first preparing a wet composition, the wet composition including a polymeric carrier matrix and a therapeutically effective amount of a pharmaceutically active component. The wet composition is cast into a film and then sufficiently dried to form a self-supporting film composition. The wet composition may be cast into individual dosages, or it may be cast into a sheet, where the sheet is then cut into individual dosages.

The pharmaceutical composition can adhere to a mucosal surface. The present invention finds particular use in the localized treatment of body tissues, diseases, or wounds which may have moist surfaces and which are susceptible to bodily fluids, such as the mouth, the vagina,

organs, or other types of mucosal surfaces. The device carries a pharmaceutical, and upon application and adherence to the mucosal surface, offers a layer of protection and delivers the pharmaceutical to the treatment site, the surrounding tissues, and other bodily fluids. The device provides an appropriate residence time for effective drug delivery at the treatment site, given the control of erosion in aqueous solution or bodily fluids such as saliva, and the slow, natural erosion of the film concomitant or subsequent to the delivery.

The residence time of the device of the composition depends on the erosion rate of the water erodable polymers used in the formulation and their respective concentrations. The erosion rate may be adjusted, for example, by mixing together components with different solubility characteristics or chemically different polymers, such as hydroxyethyl cellulose and hydroxypropyl cellulose; by using different molecular weight grades of the same polymer, such as mixing low and medium molecular weight hydroxyethyl cellulose; by using excipients or plasticizers of various lipophilic values or water solubility characteristics (including essentially insoluble components); by using water soluble organic and inorganic salts; by using crosslinking agents such as glyoxal with polymers such as hydroxyethyl cellulose for partial crosslinking; or by post-treatment irradiation or curing, which may alter the physical state of the film, including its crystallinity or phase transition, once obtained. These strategies might be employed alone or in combination in order to modify the erosion kinetics of the device. Upon application, the pharmaceutical delivery device adheres to the mucosal surface and is held in place. Water absorption softens the device, thereby diminishing the foreign body sensation. As the device rests on the mucosal surface, delivery of the drug occurs. Residence times may be adjusted over a wide range depending upon the desired timing of the delivery of the chosen pharmaceutical and the desired lifespan of the carrier. Generally, however, the residence time is modulated between about a few seconds to about a few days. Preferably, the residence time for most pharmaceuticals is adjusted from about 1 minute to about 24 hours. More preferably, the residence time is adjusted from about 1 minute to about 30 minutes. In addition to providing drug delivery, once the device adheres to the mucosal surface, it also provides protection to the treatment site, acting as an erodable bandage. Slow down lipophilic agents designed to slow down erodability to decrease disintegration and dissolution.

It is also possible to adjust the kinetics of erodability of the devices by adding excipients which are sensitive to enzymes such as amylase, very soluble in water such as water soluble

organic and inorganic salts. Suitable such excipients may include the sodium and potassium salts of chloride, carbonate, bicarbonate, citrate, trifluoroacetate, benzoate, phosphate, fluoride, sulfate, or tartrate. The amount added can vary depending upon how much the erosion kinetics is to be altered as well as the amount and nature of the other components in the device.

Emulsifiers typically used in the water-based emulsions described above are, preferably, either obtained in situ if selected from the linoleic, palmitic, myristoleic, lauric, stearic, cetoleic or oleic acids and sodium or potassium hydroxide, or selected from the laurate, palmitate, stearate, or oleate esters of sorbitol and sorbitol anhydrides, polyoxyethylene derivatives including monooleate, monostearate, monopalmitate, monolaurate, fatty alcohols, alkyl phenols, allyl ethers, alkyl aryl ethers, sorbitan monostearate, sorbitan monooleate and sorbitan monopalmitate.

The amount of pharmaceutically active component to be used depends on the desired treatment strength and the composition of the layers, although preferably, the pharmaceutical component comprises from about 0.001 to about 99, more preferably from about 0.003 to about 75%, and most preferably from about 0.005 to about 50% by weight of the composition. The amounts of other components may vary depending on the drug or other components but typically these components comprise no more than 50%, preferably no more than 30%, most preferably no more than 15% by total weight of the device.

The thickness of the film may vary, depending on the thickness of each of the layers and the number of layers. As stated above, both the thickness and amount of layers may be adjusted in order to vary the erosion kinetics. Preferably, if the device has only two layers, the thickness ranges from 0.05 mm to 3 mm, preferably from 0.1 to 1 mm, and more preferably from 0.1 to 0.5 mm. The thickness of each layer may vary from 10 to 90% of the overall thickness of the layered device, and preferably varies from 30 to 60%. Thus, the preferred thickness of each layer may vary from 0.01 mm to 0.9 mm, and more preferably from 0.03 to 0.6 mm.

As one skilled in the art will appreciate, when systemic delivery, e.g., transmucosal or transdermal delivery is desired, the treatment site may include any area in which the film is capable of delivery and/or maintaining a desired level of pharmaceutical in the blood, lymph, or other bodily fluid. Typically, such treatment sites include the oral, aural, ocular, anal, nasal, and vaginal mucosal tissue, as well as, the skin. If the skin is to be employed as the treatment site,

then usually larger areas of the skin wherein movement will not disrupt the adhesion of the device, such as the upper arm or thigh, are preferred.

The pharmaceutical composition can also be used as a wound dressing. By offering a physical, compatible, oxygen and moisture permeable, flexible barrier which can be washed away, the film can not only protect a wound but also deliver a pharmaceutical in order to promote healing, asepsy, scarification, to ease the pain or to improve globally the condition of the sufferer. Some of the examples given below are well suited for an application to the skin or a wound. As one skilled in the art will appreciate, the formulation might require incorporating a specific hydrophilic/hygroscopic excipient which would help in maintaining good adhesion on dry skin over an extended period of time. Another advantage of the present invention when utilized in this manner is that if one does not wish that the film be noticeable on the skin, then no dyes or colored substances need be used. If, on the other hand, one desires that the film be noticeable, a dye or colored substance may be employed.

While the pharmaceutical composition can adhere to mucosal tissues, which are wet tissues by nature, it can also be used on other surfaces such as skin or wounds. The pharmaceutical film can adhere to the skin if prior to application the skin is wet with an aqueous-based fluid such as water, saliva, wound drainage or perspiration. The film can adhere to the skin until it erodes due to contact with water by, for example, rinsing, showering, bathing or washing. The film may also be readily removed by peeling without significant damage to tissue.

The following examples are provided to illustrate pharmaceutical compositions, as well as, methods of making and using, pharmaceutical composition devices of the present invention.

Example 1

Permeation Enhancers - Epinephrine

Permeation enhancement was studied using the following permeation enhancers with Epinephrine Bitartrate 16.00 mg/mL concentration. The results show significant flux enhancement represented in the data below. For 100% Eugenol and 100% Clove Oil, the results showed steady state flux reached at a significant earlier time point along with an unexpectedly heightened % flux enhancement.

Donor Solution	Average Steady State Flux (ug/cm²*min)	% Flux enhancement	Permeability
			Coefficient (cm/s)

Epinephrine Bitartrate (conc 16.00mg/mL) ¹	1.3173	N/A	1.37E-06
3% Clove Oil	8.2704	527.84	8.61E-06
3% Clove Oil Repeat	5.3776	308.24	5.60E-06
3% Eugenol	7.1311	441.35	7.43E-06
3% Eugenyl Acetate	1.8945	43.82	1.97E-06
3% B-Caryophyllene	3.5200	167.22	3.67E-06
0.3% Eugenol*	3.9735	201.65	4.14E-06
100% Eugenol ¹	36.8432	2696.92	3.84E-05
0.3% Clove Oil*	3.6806	179.41	3.83E-06
100% Clove Oil ¹	52.5304	3887.81	5.47E-05
3% Cinnamaldehyde	60.1628	4467.22	6.27E-05
3% Phenol	4.5790	247.61	4.77E-06
3% Phenol Repeat	4.1753	216.97	4.35E-06
3% Linoleic Acid	2.1788	65.40	2.27E-06
50% Clove Oil	2.5673	94.89	2.67E-06
0.3% Labrasol	3.5221	167.38	3.67E-06
3% Vanillyl Alcohol+ 6% Ethanol	1.10243	-16.31	1.15E-06
3% Safrole	2.60634	97.86	2.71E-06
3% Oleic Acid	2.06597	56.84	2.15E-06
3% Oleic Acid + 1% PEG200	2.73655	107.74	2.85E-06

For these examples, clove oil was obtained from clove leaf. Similar results may be obtained from clove oil from clove bud and clove stem. Based on this data, similar permeability enhancement results can be expected from pharmaceutical compounds structurally similar to epinephrine.

Example 2

General Permeation Procedure – Ex vivo Permeation Study Protocol

In one example, a permeation procedure is conducted as follows. A temperature bath is set to 37 degrees C, and receiver media is placed in a water bath to adjust the temperature and begin degassing. A franz diffusion cell is obtained and prepared. The franz diffusion cell includes a donor compound, a donor chamber, a membrane, sampling pot, receptor chamber, stir bar, and a heater/circulator. An insert bar is stirred into a franz diffusion cell. Tissue is placed over the franz diffusion cell, and it is ensured that the tissue covers the entire area with an overlap onto a glass joint. The top of a diffusion cell is placed over a tissue, and the top of the cell is clamped to the bottom. About 5 mL of receptor media is loaded into a receiver area to

ensure that no air bubbles are trapped in a received portion of the cell. This ensures that all 5mL can fit into the receiver area. Stirring is begun, and temperature is allowed to equilibrate for about 20 minutes. Meanwhile, High Performance Liquid Chromatography (HPLC) vials are labelled by cell number and time point. One must then check again for air bubbles as the solution will degas during heating.

If testing films, one can perform the following next steps: (1) weigh films, punch to match diffusion area (or smaller), reweigh, record pre- and post-punching weight; (2) wet a donor area with approximately 100 μ L of phosphate buffer; (3) place film on a donor surface, top with 400 μ L of phosphate buffer, and start timers.

For solution studies, one can perform the following steps: (1) using a micropipette, dispense 500 μ L of the solution into each donor cell, start the timers; (2) sample 200 μ L at the following time points (time = 0 min, 20 min, 40 min, 60 min, 120 min, 180 min, 240 min, 300min, 360min), and place in labelled HPLC vials, ensure no air is trapped in the bottom of the vial by tapping the closed vials; (3) replace each sample time with 200 μ L of receptor media (to maintain 5mL); (4) When all time points completed, disassemble the cells and dispose of all materials properly.

Example 3

Ex vivo Permeation Evaluation

An exemplary ex vivo permeation evaluation is as follows.

1. Tissue is freshly excised and shipped (e.g. overnight) at 4 degrees C.
2. The tissue is processed and frozen at -20 degrees C for up to three weeks prior to use.
3. The tissue is dermatomed to precise thickness.
4. The tissue is placed in a franz diffusion cell, which includes a donor compound, a donor chamber, a membrane, sampling pot, receptor chamber, stir bar, and a heater/circulator.
5. Approximately 0.5 mL of donor solution is applied or 8 mm circular film and wetted with 500 μ L PBS buffer.
6. Approximately 5 mL of receiving media is added to the receiving compartment. The media is selected to ensure sink conditions.

7. A membrane (400 μm) is applied for porcine mucosa.

Example 4

Transbuccal delivery of doxepin

The following is an exemplary permeation study on the transbuccal delivery of doxepin. The studies were conducted under a protocol approved by the Animal Experimentation Ethics Committee of the University of Barcelona (Spain) and the Committee of Animal Experimentation of the regional autonomous government of Catalonia (Spain). 3–4-month-old female pigs were used. The porcine buccal mucosa from the cheek region was obtained immediately after the pigs had been sacrificed in the animal facility at Bellvitge Campus (University of Barcelona, Spain) using an overdose of sodium thiopental anesthesia. The fresh buccal tissues were transferred from the hospital to the laboratory in containers filled with Hank's liquid. The remaining specimens were stored at -80 degrees C in containers with a PBS mixture containing 4% albumin and 10% DMSO as cryoprotective agents.

For the permeation studies, the porcine buccal mucosa was cut to 500 to 50 mm thick sheets, which contributes to the diffusional barrier (Sudhakar et al., 2006), using an electric dermatome (GA 630, Aesculap, Tuttlingen, Germany) and trimmed with surgical scissors in adequate pieces. The majority of the underlying connective tissue was removed with a scalpel.

Membranes were then mounted in specially designed membrane holders with a permeation orifice diameter of 9 mm (diffusion area 0.636 cm^2). Using the membrane holder, each porcine buccal membrane was mounted between the donor (1.5 mL) and the receptor (6 mL) compartments with the epithelium side facing the donor chamber and the connective tissue region facing the receiver of static Franz-type diffusion cells (Vidra Foc Barcelona, Spain) avoiding bubbles formation.

Infinite dose conditions were ensured by applying 100 mL as donor solution of a saturated doxepin solution into the receptor chamber and sealed by Parafilm1 immediately to prevent water evaporation. Prior to conducting the experiments, the diffusion cells were incubated for 1 h in a water bath to equalize the temperature in all cells (37 $\pm$ degrees C). Each cell contained a small Teflon1 coated magnetic stir bar which was used to ensure that the fluid in the receptor compartment remained homogenous during the experiments.

Sink conditions were ensured in all experiments by initial testing of doxepin saturation concentration in the receptor medium. Samples (300 mL) were drawn via syringe from the center of the receptor compartment at pre-selected time intervals (0.1, 0.2, 0.3, 0.7, 1, 2, 3, 4, 5 and 6 h) for 6 h. The removed sample volume was immediately replaced with the same volume of fresh receptor medium (PBS; pH 7.4) with great care to avoid trapping air beneath the membrane. Additional details can be found at A. Gimemo, et al. Transbuccal delivery of doxepin: Studies on permeation and histological evaluation, *International Journal of Pharmaceutics* 477 (2014), 650-654.

Example 5

Oral transmucosal delivery

Porcine oral mucosal tissue has similar histological characteristics to human oral mucosal tissue (Heaney and Jones, 1978; Collins et al., 1981). Lesch et al. (1989) reported that the water permeability of porcine buccal mucosa was not significantly different from human buccal mucosa but the floor of the mouth was more permeable in human tissue than in pig tissue. Comparisons between fresh porcine tissue specimens and those stored at -80 degrees C also revealed no significant effect on permeability as a result of freezing. Porcine buccal mucosal absorption has been studied for a wide range of drug molecules both in vitro and in vivo (see, e.g., Table 1 of M. Sattar, Oral transmucosal drug delivery – current status and future prospects, *International Journal of Pharmaceutics* 471 (2014) 498-506). Typically, in vitro studies involve mounting excised porcine buccal tissue in Ussing chambers, Franz cells or similar diffusion apparatus. The in vivo studies described in the literature involve the application of the drug as a solution, gel or device to the buccal mucosa of pigs followed by plasma sampling.

Nicolazzo et al. (2003) investigated the effects of various in vitro conditions on the permeability of porcine buccal tissue using caffeine and oestradiol as model hydrophilic and lipophilic marker molecules. Drug permeation in the buccal mucosa was studied using modified Ussing chambers. Comparative permeation studies were performed through full thickness and epithelial tissues, fresh and frozen tissues. Tissue integrity was monitored by the absorption of the fluorescein isothiocyanate (FITC)-labeled dextran 20 kDa (FD20) and tissue viability was assessed using an MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide)

biochemical assay and histological evaluation. Permeability through the buccal epithelium was 1.8-fold greater for caffeine and 16.7-fold greater for oestradiol compared with full thickness buccal tissue. Flux values for both compounds were comparable for fresh and frozen buccal epithelium although histological evaluation demonstrated signs of cellular death in frozen tissue. The tissue appeared to remain viable for up to 12 h postmortem using the MTT viability assay which was also confirmed by histological evaluation.

Kulkarni et al. (2009) investigated the relative contributions of the epithelium and connective tissue to the barrier properties of porcine buccal tissue. In vitro permeation studies were conducted with antipyrine, buspirone, bupivacaine and caffeine as model permeants. The permeability of the model diffusants across buccal mucosa with thickness of 250, 400, 500, 600, and 700 mm was determined. A bilayer membrane model was developed to delineate the relative contribution to the barrier function of the epithelium and the connective tissue. The relative contribution of the connective tissue region as a permeability barrier significantly increased with increasing mucosal tissue thickness. A mucosal tissue thickness of approximately 500 mm was recommended by the authors for in vitro transbuccal permeation studies as the epithelium represented the major permeability barrier for all diffusants at this thickness. The authors also investigated the effects of a number of biological and experimental variables on the permeability of the same group of model permeants in porcine buccal mucosa (Kulkarni et al., 2010). Significantly, higher permeability of the permeants was observed for the thinner region behind the lip (170–220 mm) compared with the thicker cheek (250–280 mm) region. Porcine buccal mucosa retained its integrity in Kreb's bicarbonate ringer solution at 4 °C for 24 h. Heat treatment to separate the epithelium from underlying connective tissue did not adversely affect its permeability and integrity characteristics compared with surgical separation.

Additional details can be found at M. Sattar, Oral transmucosal drug delivery – current status and future prospects, *International Journal of Pharmaceutics* 471 (2014) 498-506.

Example 6

Cryopreservation of buccal mucosa

Different areas of porcine buccal mucosa have different pattern of permeability, there is significantly higher permeability in the region behind the lips in comparison to cheek region, because in porcine buccal mucosa, the epithelium acts as a permeability barrier, and the

thickness of the cheek epithelium is greater than that of the region behind the lips (Harris and Robinson, 1992). In exemplary permeation studies, the fresh or frozen porcine buccal mucosa from the same area was cut to 500 ± 50 μm thick sheets, which contributes to the diffusional barrier (Sudhakar et al., 2006), were obtained using an electric dermatome (model GA 630, Aesculap, Tuttlingen, Germany) and trimmed with surgical scissors in adequate pieces. All devices utilized were previously sterilized. The majority of the underlying connective tissue was removed with a scalpel. The tissue handling was done by following basic safety standards for protection against possible exposure to pathogens.

Then membranes were then mounted in specially designed membrane holders with a permeation orifice diameter of 9 mm (diffusion area 0.63 cm^2). Using the membrane holder, each porcine buccal membrane was mounted between the donor (1.5 mL) and the receptor (6 mL) compartments with the epithelium faced the donor chamber and the connective tissue region facing the receiver of static Franz-type diffusion cells (Vidra Foc, Barcelona, Spain) avoiding bubbles formation. Experiments were performed using PP, which has lipophilic characteristics ($\log P = 1.16$; n-octanol/PBS, pH 7.4), ionisable ($\text{pK}_a = 9.50$) and a MW= 259.3 g/mol, as a model drug (Modamio et al., 2000).

Infinite dose conditions were ensured by applying 300 μL as a donor solution of a saturated solution of PP ($C_0 = 588005 \pm 5852$ $\mu\text{g/mL}$ at 37 ± 1 $^\circ\text{C}$, $n = 6$), in PBS (pH 7.4) into the receptor chamber and sealed by Parafilm immediately to prevent water evaporation.

Prior to conducting the experiments, the diffusion cells were incubated for 1 h in a water bath to equalize the temperature in all cells (37 ± 1 $^\circ\text{C}$). Each cell contained a small Teflon coated magnetic stir bar which was used to ensure that the fluid in the receptor compartment remained homogenous during the experiments. Sink conditions were ensured in all experiments after initial testing of PP saturation concentration in the receptor medium.

Samples (300 μL) were drawn via syringe from the center of the receptor compartment at the following time intervals: 0.25, 0.5, 1, 2, 3, 4, 5 and 6 h. The removed sample volume was immediately replaced with the same volume of fresh receptor medium (PBS; pH 7.4) with great care to avoid trapping air beneath the dermis. Cumulative amounts of the drug (μg) penetrating the unit surface area of the mucosa membrane (cm^2) were corrected for sample removal and plotted versus time (h). The diffusion experiments were carried out 27 times for the fresh and 22 times for the frozen buccal mucosa.

Additional details can be found at S. Amores, An improved cryopreservation method for porcine buccal mucosa in ex vivo drug permeation studies using Franz diffusion cells, *European Journal of Pharmaceutical Sciences* 60 (2014) 49–54.

Example 7

Permeation of quinine across sublingual mucosa sections

Since porcine and human oral membranes are similar in composition, structure and permeability measurements, porcine oral mucosa is a suitable model for human oral mucosa. Permeability across the porcine oral mucosa is not metabolically linked therefore it is not important for the tissue to be viable.

To prepare the porcine membranes, porcine floor of mouth and ventral (underside) tongue mucosa membranes were excised by blunt dissection using a scalpel. The excised mucosa were cut into approximately 1 cm squares and frozen on aluminium foil at -20°C until used (<2 weeks). For non-frozen ventral surface of porcine tongue, the mucosa was used in the permeation studies within 3 h of excision.

The permeability of the membranes to quinine was determined using all-glass Franz diffusion cells with a nominal receptor volume of 3.6mL and diffusional area of 0.2 cm^2 . The cell flanges were greased with high performance vacuum grease and the membranes mounted between the receptor and donor compartments, with the mucosal surface uppermost. Clamps were used to hold the membranes into position before the receptor compartments were filled with degassed phosphate buffered saline (PBS), pH 7.4. Micromagnetic stirrer bars were added to the receptor compartments and the complete cells were placed in a water bath at 37°C . The membranes were equilibrated with PBS applied to the donor compartments for 20 min before being aspirated with a pipette. Aliquots of $5\mu\text{L}$ of the quinine solution or $100\mu\text{L}$ of the saturated solutions of Q/2-HP- β -CD complex in different vehicles were applied to each of the donor compartments. In the study to determine the effect of saliva on the permeation of quinine across the ventral surface of the tongue, $100\mu\text{L}$ of sterile saliva was added to the donor compartments before adding $5\mu\text{L}$ of the quinine solution.

At 2, 4, 6, 8, 10 and 12 h, the receptor phases were withdrawn from the sampling ports and aliquots of 1mL samples were transferred to HPLC autosampler vials, before being replaced

with fresh PBS stored at 37 °C. Apart from the studies involving Q/2-HP- β -CD saturated solutions (where an infinite dose was applied at the start of the experiments), 5¹ L of the respective quinine solution was reapplied to the donor phase up to 10 h. The purpose of this was to represent a hypothetical in-use finite dosing regimen based upon an interval of 2 h between doses. At least 3 replicates were carried out for each study.

Additional details can be found at C. Ong, Permeation of quinine across sublingual mucosa, in vitro, *International Journal of Pharmaceutics* 366 (2009) 58–64.

Example 8

Ex-Vivo Initial Study – Form of the API

In this example, the permeation of Epinephrine Base was tested – solubilized in situ vs. the inherently soluble Epinephrine Bitartrate and no differences were found. Epinephrine Bitartrate was selected for further development based on ease of processing. Flux was derived as slope of the amount permeated as a function of time. Steady state flux taken from plateau of flux vs time curve time the volume of receiver media. The graph in **Figure 2a** shows average amount permeated vs. time, with 8.00 mg/mL bitartrate and 4.4 mg/mL based solubilized. The graph in **Figure 2b** shows average flux vs. time, with 8.00 mg/mL bitartrate and 4.4 mg/mL based solubilized.

Donor Solution	Average Steady State Flux (ug/cm2*min)
Epinephrine Base (conc 4.4mg/mL)	0.512
Epinephrine Bitartrate (conc 8.00mg/mL)	0.466

Example 9

Concentration dependence on permeation/flux

In this study, ex-vivo permeation of Epinephrine Bitartrate as a function of concentration was studied. **Figure 3** shows ex-vivo permeation of epinephrine bitartrate as a function of concentration. The study compared concentrations of 4 mg/mL, 8 mg/mL, 16 mg/mL and 100 mg/mL. Results showed that increasing concentration resulted in increased permeation, and level of enhancement reduces at higher loading. The study compared concentrations of 4 mg/mL, 8 mg/mL, 16 mg/mL and 100 mg/mL.

Donor Solution	Average Steady State Flux ($\mu\text{g}/\text{cm}^2\cdot\text{min}$)
Epinephrine Bitartrate (conc 4mg/mL)	0.167
Epinephrine Bitartrate (conc 8mg/mL)	0.456
Epinephrine Bitartrate (conc 16mg/mL)*	1.317
Epinephrine Bitartrate (conc 100mg/mL)	2.942

Donor Solution	Ratio of enhancement	Theoretical enhancement
Epinephrine Bitartrate (4.00mg/mL)	N/A	N/A
Epinephrine Bitartrate (8.00mg/mL)	2.8	2
Epinephrine Bitartrate (16.00mg/mL)	7.9	4
Epinephrine Bitartrate (100.00mg/mL)	17.6	25

Example 10

Influence of pH

In this example, the permeation of Epinephrine Bitartrate as a function of solution pH was studied. In this example, acidic conditions were explored for the ability to promote stability. The results showed that pH 5 was slightly favorable to pH 3. The inherent pH of epinephrine bitartrate in solution is 4.5-5. No pH adjustment with buffers was required.

Figure 4 shows permeation of epinephrine bitartrate as a function of solution pH. Acidic conditions explored to promote stability. The results compared Epinephrine Bitartrate pH 3 buffer and Epinephrine Bitartrate pH 5 buffer, and found that the Epinephrine Bitartrate pH 5 buffer was slightly favorable.

Example 11

Influence of enhancers on permeation of epinephrine

In this example, the permeation of epinephrine to test for sublingual delivery was studied as the amount permeated (μg) vs. time (in minutes). The following enhancers were screened for concentration effects in a solution containing 16.00 mg/mL Epinephrine. The graph on **Figure 5** demonstrates the results of these enhancers as a function of time.

Legend	Enhancer	Average Steady State Flux (ug/cm²*min)	Percent Enhancement
No Enhancer	None	1.317	N/A
Enhancer A	3% Labrasol	5.208	395
Enhancer B	3% capryol 90	2.385	181
Enhancer C	3% Plurol Oleique	1.482	112
Enhancer D	3% Labrafil	0.281	21
Enhancer E	3% TDM	2.642	201
Enhancer F	3% SGDC	0.342	26
Enhancer G	3% Gelucire 44/14	1.641	125
Enhancer H	3% Ethanol	0.163	12
Enhancer I	6% Ethanol	0.254	19
Enhancer J	6% Labrasol	4.444	337
Enhancer K	6% Plurol Oleique	0.306	23
Enhancer L	3% clove oil	8.216	624

Enhancers were selected and designed with functionality influencing different barriers in the mucosa. While all tested enhancers did improve the amount permeated over time, clove oil and Labrasol, in particular has shown significantly and unexpectedly high enhancement of permeation.

8.00mg/0.500mL
40mg/ strip
no enhancer

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (ug/cm²*min)	std dev set 2	steady state flux average
30	0	0	0	0	
45	2.5	4.33012702	0.260416667	0.4510549	1.317274
60	5.5	7.08872344	0.3125	0.3125	
120	31.33333333	26.1549868	0.672743056	0.5050226	
180	72.66666667	58.215834	1.076388889	0.8496863	
240	112.1666667	80.1878004	1.028645833	0.5733604	

300	160.1666667	103.254943	1.25	0.6036108	
360	213.3333333	131.305306	1.384548611	0.7308311	

8.00mg/0.500mL
40mg/ strip
 labrasol

Time (min)	set 1 (A,B,C) average amount permeated (ug)	std dev set 1 amount perm	set 1 (A, B,C) average flux (ug/cm2*min)	std dev set 1	
0	0	0	0	0	
30	0.5	0.8660254	0.026041667	0.0451055	5.208333
45	2.666666667	0.28867513	0.225694444	0.0601407	
60	4	1.80277564	0.138888889	0.1674245	
120	28	16.3935963	0.625	0.3836177	
180	98	53.3291665	1.822916667	0.9701176	
240	238.1666667	93.0017921	3.650173611	1.136722	
300	421.1666667	115.153521	4.765625	0.6675003	
360	638.1666667	130.709921	5.651041667	0.4732495	

8.00mg/0.500mL
40mg/strip
 capryol 90

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (ug/mL*min)	std dev set 2	
0	0	0	0	0	
30	0.00	0	0	0	
45	0.00	0	0	0	1.931424
60	0.00	0	0	0	
120	9.17	5.79511288	0.238715278	0.1509144	
180	38.67	16.7655401	0.768229167	0.2864583	
240	88.50	30.2654919	1.297743056	0.4018216	
300	150.67	39.6936183	1.618923611	0.3269068	
360	236.83	51.9358579	2.243923611	0.4999616	

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (ug/mL*min)	std dev set 2	
0	0.8	1.78885438	0	0	

8.00mg/0.500mL
40mg/strip
 plurol oleique

30	10.80	13.325727	0.520833333	0.7186273	
45	20.90	22.1624683	1.052083333	0.9356173	1.481771
60	33.00	30.8058436	1.260416667	0.9319861	
120	90.70	68.1951245	1.502604167	1.005753	
180	157.00	107.373763	1.7265625	1.0427891	
240	239.80	140.586539	2.15625	1.2085059	
300	285.60	184.236397	1.192708333	1.484335	
360	353.60	221.81676	1.770833333	0.993644	

8.00mg/0.500mL
40mg/strip
 TDM

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (ug/mL*min)	std dev set 2	
0	0.00	0.00	0.00	0.00	
20	0.00	0.00	0.00	0.00	
40	3.00	2.43	0.23	0.32	2.642144
60	8.83	4.86	0.46	0.35	
120	41.33	15.08	0.85	0.49	
180	99.75	30.17	1.52	0.79	
240	179.92	48.30	2.09	0.98	
300	276.92	72.35	2.53	1.19	
360	382.83	102.02	2.76	1.38	

8.00mg/0.500mL
40mg/strip
 SGDC

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (ug/mL*min)	std dev set 2	
0	0	0	0	0	
30	0.00	0	0	0	
45	0.67	1.30384048	0.069444444	0.1261521	0.341797
60	1.58	1.94935887	0.095486111	0.1063147	
120	7.00	9.44325156	0.141059028	0.1910856	
180	16.17	22.0323626	0.238715278	0.316132	
240	28.58	37.6191441	0.323350694	0.3977149	
300	43.00	54.3927844	0.375434028	0.4112124	
360	54.83	65.7976063	0.308159722	0.3008536	

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (ug/mL*min)	std dev set 2	
0	0.8	1.15108644	0	0	

8.00mg/0.500mL
40mg/strip
 Labrafil

30	1.10	1.51657509	0.015625	0.0232924	
45	1.10	1.51657509	0	0	0.28125
60	1.10	1.51657509	0	0	
120	4.00	4.89897949	0.075520833	0.0984775	
180	9.10	10.9167303	0.1328125	0.1671035	
240	15.20	18.7169709	0.158854167	0.2034753	
300	25.70	29.8487856	0.2734375	0.2910091	
360	36.80	43.3093523	0.2890625	0.3532943	

8.00mg/0.500mL
40mg/strip
 Gelucire 44/14

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (ug/mL*min)	std dev set 2	
0	0	0	0	0	
20	0.33	0.89442719	0.026041667	0.0637888	
40	3.83	5.94138031	0.2734375	0.378725	1.629774
60	11.50	17.1850225	0.598958333	0.8405853	
120	41.58	48.5059275	0.783420139	0.8042794	
180	91.92	82.5124233	1.310763889	0.9525224	
240	150.17	118.949569	1.516927083	0.9914576	
300	217.50	158.792947	1.753472222	1.0756081	
360	275.33	189.967563	1.506076389	0.9083155	

8.00mg/0.500mL
40mg/strip
 clove oil

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (ug/cm2*min)	std dev set 2	
0	0	0	0	0	
20	0	0	0	0	
40	28.66666667	27.360251	2.239583333	2.1375196	8.270399
60	96.5	79.5424415	5.299479167	4.0954816	
120	389.6666667	278.072533	7.634548611	5.2070528	
180	688.6666667	451.678628	7.786458333	4.5210426	
240	1009.166667	603.252089	8.346354167	3.9590828	
300	1333.5	759.653046	8.446180556	4.1168559	
360	1644.333333	878.2762	8.094618056	3.2301203	

8.00mg/0.500mL

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (ug/mL*min)	std dev set 2	
0	0	0	0	0	

40mg/strip
3% labrasol
+1%TDM

20	0	0	0	0	3.161892
40	1.666666667	2.88675135	0.130208333	0.2255274	
60	6.833333333	11.8356805	0.403645833	0.6991351	
120	68.83333333	92.6907942	1.614583333	2.1084505	
180	103.6666667	101.539812	0.907118056	0.3351021	
240	180	130.184484	1.987847222	0.7476876	
300	291.5	149.81572	2.903645833	0.5193664	
360	422.8333333	164.032263	3.420138889	0.5530917	

Example 12

Impact of enhancers on epinephrine release

Release profiles of epinephrine were studied to determine the impact of enhancers (Labrasol and clove oil) on epinephrine release. **Figure 6a** shows the epinephrine release from different polymer platforms. **Figure 6b** shows the impact of enhancers on epinephrine release. The results showed that the amount permeated leveled off after about 40 minutes to be between approximately 3250 and 4250 μg . The tested enhancers were shown not to restrict the release of epinephrine from the matrix.

Example 13

Accelerated stability

The stabilizer (Sodium Metabisulfite) loading variants were tested. Enhancer loading was deemed to impact chemical stability.

	Formulation 10	Formulation 10 with 0.25% Stabilizer	Formulation 10 with 1% Stabilizer
Time (weeks) @ 40°C/75% R.H.	EPI mg/film	EPI mg/film	EPI mg/film
0	39.3	37.9	38.3
2	35.2	36.8	34.7
4	37.7	36.8	36.2
6	35.2		
8	38.2		

Example 14

Impact of Enhancer

A pharmacokinetic model in the male yucatan, miniature swine was studied. The graph on **Figure 7** shows the results of a pharmacokinetic model in the male yucatan, miniature swine. The study compares a 0.3 mg Epipen, a 0.12 mg Epinephrine IV and a placebo.

The impact of no enhancer is shown in **Figure 8** on the concentration profiles of a 0.3 mg Epipen and a 40 mg Epinephrine film.

The impact of enhancer 3% labrasol is shown in **Figure 9**, which shows the impact of Enhancer A (labrasol) on the concentration profiles of a 0.3 mg Epipen and a 40 mg Epinephrine film.

Figure 10 shows the impact of Enhancer L (clove oil) on the concentration profiles of a 0.3 mg Epipen and a 40 mg Epinephrine film (10-1-1) and (11-1-1)

In addition, the influence of film dimensions and impact of clove oil (3%) is also shown in **Figure 11**. This study was carried out comparing 0.30 mg EpiPen (n=4), a 40 mg Epinephrine Film (10-1-1) (n=5) and a 40 mg Epinephrine Film (21-1-1) (n=5). The concentration vs. time profiles followed sublingual or intramuscular epinephrine administration to male miniature swine.

Studies were performed to vary the ratio of epinephrine to an enhancer. These studies were also concentration vs. time profiles following sublingual or intramuscular epinephrine administration to male miniature swine. Varying the ratio of Epinephrine to clove oil (Enhancer L) produced the results shown in **Figure 12**. This study was carried out comparing 0.30 mg EpiPen (n=4), a 40 mg Epinephrine Film (12-1-1) (n=5) and a 20 mg Epinephrine Film (13-1-1) (n=5).

Example 15

A varying dose study was carried out in constant matrix with enhancer labrasol (3%) and clove oil (3%) as shown in **Figures 13** and **14** respectively. The study in **Figure 13** was carried out comparing 0.30 mg EpiPen (n=4), a 40 mg Epinephrine Film (18-1-1) (n=5) and a 30 mg Epinephrine Film (20-1-1) (n=5). The study in **Figure 14** was carried out comparing 0.30 mg EpiPen (n=4), a 40 mg Epinephrine Film (19-1-1) (n=5) and a 30 mg Epinephrine Film (21-1-1)

(n=5). These studies were also concentration vs. time profiles following sublingual or intramuscular epinephrine administration to male miniature swine.

All references cited herein are hereby incorporated by reference in their entirety.

Other embodiments are within the scope of the following claims.

CLAIMS:

1. A pharmaceutical composition, comprising:
 - a polymeric matrix;
 - epinephrine in the polymeric matrix; and
 - a permeation enhancer including a phytoextract.
2. The pharmaceutical composition according to claim 1, wherein the composition is a film further comprising a polymeric matrix, the pharmaceutically active component being dispersed in the polymeric matrix.
3. The pharmaceutical composition according to claim 1 or claim 2, wherein the phytoextract includes a phenylpropanoid.
4. The pharmaceutical composition according to claim 3, wherein the phenylpropanoid is eugenol.
5. The pharmaceutical composition according to claim 3, wherein the phenylpropanoid is eugenol acetate.
6. The pharmaceutical composition according to claim 3, wherein the phenylpropanoid is a cinnamic acid.
7. The pharmaceutical composition according to claim 3, wherein the phenylpropanoid is a cinnamic acid ester.
8. The pharmaceutical composition according to claim 3, wherein the phenylpropanoid is a cinnamic aldehyde.
9. The pharmaceutical composition according to claim 3, wherein the phenylpropanoid is a hydrocinnamic acid.
10. The pharmaceutical composition according to claim 3, wherein the phenylpropanoid is chavicol.
11. The pharmaceutical composition according to claim 3, wherein the phenylpropanoid is safrole.
12. The pharmaceutical composition according to claim 1 or claim 2, wherein the phytoextract is an essential oil extract of a clove plant.

13. The pharmaceutical composition according to claim 1 or claim 2, wherein the phytoextract is an essential oil extract of a leaf of a clove plant.
14. The pharmaceutical composition according to claim 1 or claim 2, wherein the phytoextract is an essential oil extract of a flower bud of a clove plant.
15. The pharmaceutical composition according to claim 1 or claim 2, wherein the phytoextract is an essential oil extract of a stem of a clove plant.
16. The pharmaceutical composition according to claim 1 or claim 2, wherein the phytoextract is synthetic.
17. The pharmaceutical composition according to claim 1 or claim 2, wherein the phytoextract includes 60-95% eugenol.
18. The pharmaceutical composition according to claim 1 or claim 2, wherein the phytoextract includes 80-95% eugenol.
19. The pharmaceutical composition according to any one of the claims 3 - 18, wherein the polymer matrix includes a water soluble polymer.
20. The pharmaceutical composition according to any one of the claims 3 - 18, wherein the polymer matrix includes a polyethylene oxide.
21. The pharmaceutical composition according to any one of the claims 3 - 18, wherein the polymer matrix includes a cellulosic polymer is selected from the group of: hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, and carboxymethyl cellulose.
22. The pharmaceutical composition according to any one of the claims 3 - 18, wherein the polymeric matrix comprises hydroxypropyl methylcellulose.
23. The pharmaceutical composition according any one of the claims 3 - 18, wherein the polymeric matrix comprises polyethylene oxide and hydroxypropyl methylcellulose.
24. The pharmaceutical composition according to any one of the claims 3 - 18, wherein the polymeric matrix comprises at least one polymer selected from the group of: pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, ethylene oxide-propylene oxide co-polymers, collagen, albumin, poly-amino acids, polyphosphazenes, polysaccharides, chitin, chitosan, and derivatives thereof.

25. The pharmaceutical composition according to any one of the claims 3 - 18, further comprising a stabilizer.
26. A method of making a pharmaceutical composition of any one of claims 1-25, comprising:
mixing a permeation enhancer including a phytoextract with epinephrine.

ABSTRACT

Pharmaceutical compositions having enhanced active component permeation properties are described.

Electronic Patent Application Fee Transmittal

Application Number:				
Filing Date:				
Title of Invention:	ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS			
First Named Inventor/Applicant Name:	Alexander M. Schobel			
Filer:	Harold H. Fox			
Attorney Docket Number:	18460.0014P1			
Filed as Small Entity				
Filing Fees for Provisional				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Provisional Application Filing Fee	2005	1	130	130
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				130

Electronic Acknowledgement Receipt

EFS ID:	25690062
Application Number:	62331996
International Application Number:	
Confirmation Number:	3115
Title of Invention:	ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS
First Named Inventor/Applicant Name:	Alexander M. Schobel
Customer Number:	27890
Filer:	Harold H. Fox
Filer Authorized By:	
Attorney Docket Number:	18460.0014P1
Receipt Date:	05-MAY-2016
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Application Type:	Provisional

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Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 130
RAM confirmation Number	8620
Deposit Account	194293
Authorized User	FOX, HAROLD H.

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	0014P1ProvTransmit.pdf	1538816	no	3
			dd6825de4d727f001fdcd0b0c6e4f491f2582981		
Warnings:					
Information:					
2	Application Data Sheet	0014P1ADS.pdf	1823232	no	9
			b9fa9001da16ab2608fda775b494ce2b23764709		
Warnings:					
Information:					
3	Drawings-other than black and white line drawings	14figures.pdf	999083	no	12
			1d4f6ff5bcb11d5cb3a4ddbfeebe115cd2a6fb84		
Warnings:					
Information:					
4		14specification.pdf	1514946	yes	39
			c030e315e0994605bebaac9244a638c3c87e8b3b		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	35	
	Claims		36	38	
	Abstract		39	39	
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	29929	no	2
			85834b461a1659d588e6607774c1c3a54e06dd9a		
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