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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/347,625	06/01/2021	11021437	24050.0001US	8118

76447 7590 05/12/2021

Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

The Patent Term Adjustment is 120 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

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

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

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

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

Hassan Almoazen, Hassan, TN;
Iono Pharma, LLC, Bartlett, TN;

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

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Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

Courtesy Reminder for
Application Serial No: 16/347,625

Attorney Docket No: 24050.0001US
Customer Number: 76447
Date of Electronic Notification: 04/20/2021

This is a courtesy reminder that new correspondence is available for this application. If you have not done so already, please review the correspondence. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

An email notification regarding the correspondence was sent to the following email address(es) associated with your customer number:
eofficeaction@appcoll.com
sfentress@veritaygroup.com

To view your correspondence online or update your email addresses, please visit us anytime at **https://ppair-my.uspto.gov/pair/PrivatePair.**
If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov or call 1-866-217-9197.

PART B - FEE(S) TRANSMITTAL

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

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

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

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

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

76447 7590 04/20/2021

Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

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

Certificate of Mailing or Transmission

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/347,625	05/06/2019	Hassan Almoazen	24050.0001US	8118

TITLE OF INVENTION: PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	07/20/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
STRONG, TORI	1629	514-653000

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

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

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

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

1 Veritay Group IP PLLC
2 Susan B. Fentress
3

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

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

(A) NAME OF ASSIGNEE: Tono Pharmaceuticals, LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Bartlett, TN

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

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

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

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

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

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

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

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

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

Authorized Signature: Susan B. Fentress Date: May 27, 2021

Typed or printed name: Susan B. Fentress Registration No. 31327

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 003

Electronic Patent Application Fee Transmittal

Application Number:	16347625
Filing Date:	06-May-2019
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	Hassan Almoazen
Filer:	Susan Bennett Fentress
Attorney Docket Number:	24050.0001US

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	600	600

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**600**

Electronic Acknowledgement Receipt

EFS ID:	42563839
Application Number:	16347625
International Application Number:	
Confirmation Number:	8118
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	Hassan Almoazen
Customer Number:	76447
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001US
Receipt Date:	27-APR-2021
Filing Date:	06-MAY-2019
Time Stamp:	12:27:04
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$600
RAM confirmation Number	E20214QC27360284
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	issuefee.pdf	665527 7342a2d172b0af1d8583ce40d0d4660ad970a00d	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30301 293d8acff4ef4e4cc044fa1b7e5e2159977b4bea	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	695828		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

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NOTICE OF ALLOWANCE AND FEE(S) DUE

76447 7590 04/20/2021

Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

EXAMINER
STRONG, TORI

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 04/20/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/347,625	05/06/2019	Hassan Almoazen	24050.0001US	8118

TITLE OF INVENTION: PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	07/20/2021

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

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

HOW TO REPLY TO THIS NOTICE:

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

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

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

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

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

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

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

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 008

PART B - FEE(S) TRANSMITTAL

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

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

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

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

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

76447 7590 04/20/2021

Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

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

Certificate of Mailing or Transmission

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/347,625	05/06/2019	Hassan Almoazen	24050.0001US	8118

TITLE OF INVENTION: PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	07/20/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
STRONG, TORI	1629	514-653000

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

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

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

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

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

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

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

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

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

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

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

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

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

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

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

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 009

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/347,625	05/06/2019	Hassan Almoazen	24050.0001US	8118

76447 7590 04/20/2021

Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

EXAMINER	
STRONG, TORI	

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 04/20/2021

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

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

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

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

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 010

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

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

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

Privacy Act Statement

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

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

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

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005, pdf Page 011

Notice of Allowability	Application No. 16/347,625	Applicant(s) Almoazen, Hassan	
	Examiner TORI STRONG	Art Unit 1629	AIA (FITF) Status Yes

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

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

1. ☑ This communication is responsive to after final filed 23 March 2021.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3. ☑ The allowed claim(s) is/are 1,19-20 and 23-24 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

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

   Certified copies:

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

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

   * Certified copies not received: _____ .

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

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

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

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

Attachment(s)

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

/TORI STRONG/ Examiner, Art Unit 1629	/Kortney L. Klinkel/ Primary Examiner, Art Unit 1699

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Status of Claims

Claims 1, 19, 20, 23 and 24 are pending in the instant application; claims 1 and 19 are amended; claims 3 and 21 are cancelled; claims 23 and 24 are newly presented; claims 1, 19, 20, 23 and 24 are the subject of the Office Action below.

Examination Considerations

Applicant's Amendments filed March 23, 2021 have been received and entered into the present application. Claims 1, 19, 20, 23 and 24 are pending and are herein examined on the merits.

Applicant's Reply, filed March 23, 2021 has been fully considered and found persuasive. Rejections from previous Office Actions are hereby withdrawn.

Claim Rejections - 35 USC § 103 – Withdrawn

Claims 1, 3 and 19-21 rejected under 35 U.S.C. 103 as being unpatentable over Rawas-Qalaji *et al.* (US 2007/0202163 A1; cited in IDS) in view of Bodor (US 4,145,441; cited in IDS) is ***withdrawn***.

Applicant has amended claims and persuasively argued the unexpected result of the claimed epinephrine prodrug genus having a rapid half-life ranging from 1 to 6 minutes. Applicant points out that prior art prodrugs have 30 minute half-life. The instantly claimed genus is thus suitable for sublingual or buccal administration having a much shorter half-life. Subsequent to persuasive arguments the rejection is withdrawn.

Statement of Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

None of the prior art teaches in a single disclosure, nor fairly suggest in any combination, Applicants' claimed product of a compound of the claimed Formula, formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration. Applicants have demonstrated novel compound structures in their disclosure as originally filed. Applicants' disclosure includes embodiments built around the claimed Formula and discloses the species embodiments and their LogP values. Applicants' disclose that epinephrine formulations have disintegrations times ranging from 10 to 30 seconds (see specification, p.14, Table 5) and further disclose exemplified embodiment of epinephrine release from hydrolysis where the half-life is within 4 minutes (see Drawings, Fig.9).

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

Allowable Subject Matter

Claims 1, 19, 20, 23 and 24 are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI STRONG whose telephone number is (571)272-6333. The examiner can normally be reached on Monday - Friday 8:00 am - 5:00 pm (EST).

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

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on (571)272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kortney L. Klinkel/
Primary Examiner, Art Unit 1699

TORI STRONG
Examiner
Art Unit 1629

/TORI STRONG/
Examiner, Art Unit 1629

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/347,625	Almoazen, Hassan
	Examiner	**Art Unit**
	TORI STRONG	1629

CPC						
Symbol					**Type**	**Version**
C07C	/	219	/	30	F	2013-01-01
A61K	/	9	/	006	I	2013-01-01
A61K	/	47	/	02	I	2013-01-01
A61K	/	47	/	10	I	2013-01-01
A61K	/	47	/	12	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01
A61K	/	47	/	46	I	2013-01-01
A61K	/	31	/	137	A	2013-01-01

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

/TORI STRONG/ Examiner, Art Unit 1629	10 April 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	5	
/Kortney L. Klinkel/ Primary Examiner, Art Unit 1699	13 April 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20210408

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/347,625	Almoazen, Hassan
	Examiner	**Art Unit**
	TORI STRONG	1629

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C07C	/	219	/	30
A61K	/	9	/	00
A61K	/	47	/	02
A61K	/	47	/	10
A61K	/	47	/	12
A61K	/	47	/	26
A61K	/	47	/	46
A61K	/	31	/	137

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

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

/TORI STRONG/ Examiner, Art Unit 1629	10 April 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	5	
/Kortney L. Klinkel/ Primary Examiner, Art Unit 1699	13 April 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20210408

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/347,625	Almoazen, Hassan
	Examiner	**Art Unit**
	TORI STRONG	1629

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

CLAIMS

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

/TORI STRONG/ Examiner, Art Unit 1629	10 April 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	5	
/Kortney L. Klinkel/ Primary Examiner, Art Unit 1699	13 April 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/347,625	Almoazen, Hassan
	Examiner	Art Unit
	TORI STRONG	1629

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
(A61K31/137 OR A61K9/006 OR A61P37/08 OR C07C215/00 OR C07C219/30)	02/19/2021	TMS

US Classification - Searched*			
Class	Subclass	Date	Examiner

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

Search Notes		
Search Notes	Date	Examiner
Review of Global Dossier	12/16/2020	TMS
Structure search performed in STNext	12/16/2020	TMS
Background search in Google	12/16/2020	TMS
Inventor search in PE2E	12/16/2020	TMS
Text search performed in EAST	02/19/2021	TMS
Interference search - Utilized Structure Search	02/19/2021	TMS

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
Structure	Search	02/19/2021	TMS

/TORI STRONG/ Examiner, Art Unit 1629	

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 020

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/347,625	Almoazen, Hassan
	Examiner	Art Unit
	TORI STRONG	1629

/TORI STRONG/ Examiner, Art Unit 1629	

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 021

OK TO ENTER: /T.S/

docket no. 24050.0001US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CONFIRMATION NO.:	8188
APPLICATION NO.:	16/347,625
FILED:	05/06/2019
ART UNIT:	1629
TITLE:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

AMENDMENT AFTER FINAL

Dear Sir:

In response to the office action dated 03/03/2021, please amend the above-identified applications as follows:

Amendments to the Specification: none,

Amendments to the Abstract: none.

Amendments to the Claims: begin on page 2 of this paper.

Amendments to the Drawings: None.

Remarks/Arguments: begin on page 4 of this pager.

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 022

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

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/347,625	Filing Date 05/06/2019	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

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

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/DEIDRE C KING-WOODWARD/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/347,625	05/06/2019	Hassan Almoazen	24050.0001US	8118

76447 7590 03/26/2021

Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

EXAMINER	
STRONG, TORI	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
03/26/2021	ELECTRONIC

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

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

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

eofficeaction@appcoll.com
sfentress@veritaygroup.com

Applicant-Initiated Interview Summary	**Application No.** 16/347,625	**Applicant(s)** Almoazen, Hassan		
	Examiner TORI STRONG	**Art Unit** 1629	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
TORI STRONG	Examiner	Telephonic
Susan Fentress	Attorney of Record	
Hassan Almoazen	Inventor	

Date of Interview: 23 March 2021

Issues Discussed:

Proposed Amendment(s)

Applicant proposes amendment including the requirements of being a rapidly dissolving film and the substituents having a half life ranging from 1-6 minutes. Applicant argued that prior art epinephrine prodrug has a half life of 30 minutes. It was suggested that this appears to be an unexpected result. It was suggested to further explain how the claimed substituents have the unexpected result of quicker hydrolysis. It was also indicated that this on its face overcomes the prior art of record, however, that further search and consideration would be required to indicate allowance.

☑ Attachment

/TORI STRONG/ Examiner, Art Unit 1629	/Kortney L. Klinkel/ Primary Examiner, Art Unit 1699

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CONFIRMATION NO.:	8188
APPLICATION NO.:	16/347,625
FILED:	05/06/2019
ART UNIT:	1629
TITLE:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

AMENDMENT AFTER FINAL

Dear Sir:

In response to the office action dated 03/03/2021, please amend the above-identified applications as follows:

Amendments to the Specification: none,

Amendments to the Abstract: none.

Amendments to the Claims: begin on page 2 of this paper.

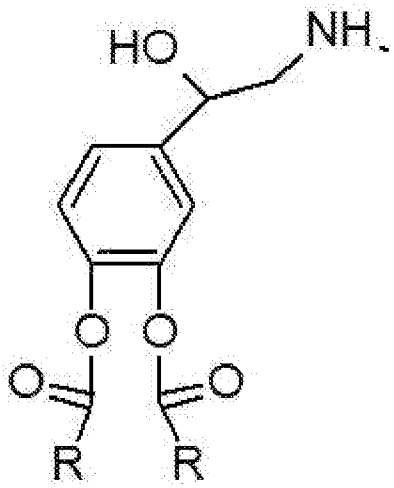
Amendments to the Drawings: None.

Remarks/Arguments: begin on page 4 of this pager.

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 026

AMENDMENTS TO THE CLAIMS

1. (currently amended) A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:

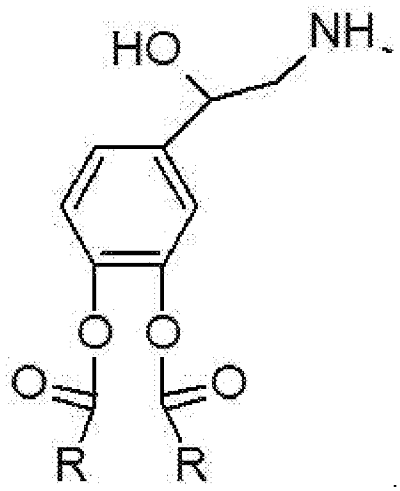


wherein R is selected from the group consisting of: $-CHCH_2$, $-CHCHCH_3$, $-CH_2-CH_2-Cl$, $-CHCH_2I$, $-CH(Cl)CH_2(Cl)$, $-CH(I)CH_2(I)$, $-CH(CH_3)CH_2(CH_3)$, $-CH_2C(CH_3)_3$, $-CH_2CH_2CH_3$, $-CH_2Cl$, $-CH_2I$, $-CH_2F$, H, Cl, I, F, $-CH(CH_3)CH(CH_3)_2$, $-CH(Cl)CH(Cl)_2$, $-CH(I)CH(I)_2$, $-CH(F)CH(F)_2$, $-CH_2CHCH_2$, $-C(Cl)_2CH(Cl)_2$, $-C(I)_2CH(I)_2$, $-C(Cl)_3$, $C(I)_3$, $-CH_2COCH_3$, $-CH_2COCl$, $-CH_2CO(I)$, $-CH_2OCH_3$, $-CH(I)(CH_3)$, $-C(Cl)_2(CH_3)$, $-CH_2CH(CH3)_2$, $-CH_2CH(Cl)_2$, $-CH_2CH(I)_2$, $-CH_2C(Cl)_3$, $-CH_2C(I)_3$, $-CH(Cl)_2$, $-CH(I)_2$, $-C(CH3)_2CH(CH3)_2$, $-NH-C(CH_3)_3$, $-NH-CH(CH_3)_2$, $-NH-CH_2CH_3$, $-NH-CH_3$, $-SCH_3$, $-SCH_2CH_3$, $-SCH(CH3)_2$, $-SC(CH_3)_3$, $-CH_2C_6H_5$ and $-C_6H_5$ or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0 and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

2.-18 (cancelled)

19. (currently amended) A compound of a Formula:

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 027



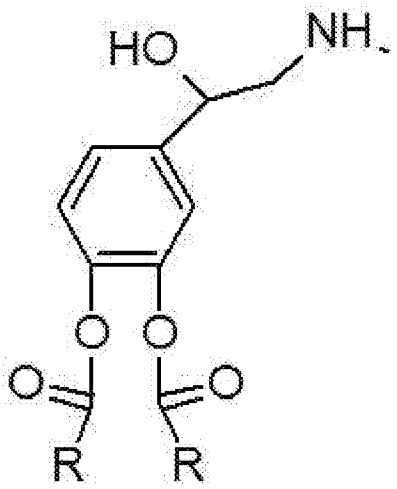
wherein R is selected from the group consisting of: CH_3, CH_2CH_3, and $CH(CH_3)_2$ wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

20. (previously presented) The compound of claim 19, wherein the compound is selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate**;** 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

21-22. (cancelled).

23. (new) A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 028



wherein R is comprised of $-C(Cl)_2CH_3$.

24. (new) The composition of claim 23 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 029

Remarks:

This application is a § 371 National Stage Application of PCT/US17/60761 application filed 11-09-2017 wherein claims 1, 3-14,16,18-22 were found in the International Preliminary Report on Patentability as amended by article 34) to be novel, non-obvious and have technical merit.

Support for the amended claims is found at:

"A pro-drug is a derivative of epinephrine selected for fast permeability through sub-lingual and buccal membranes (*i.e.,* a compound that dissolves in the oral cavity) and fast hydrolysis (half-life $t_{1/2}$ range from 1-6 minutes) by plasma enzymes to form epinephrine when delivered." Para 00023

The pending claims stand rejected as being obvious to one skilled in the art. Applicant respectfully disagrees and asserts that claims pending are nonobvious over Rawas-Qalaji read in view of Bodor.

Anwar A. Hussain and James E. Truelove were granted patents related to the synthesis of novel esters of [(methylamino)methyl] benzyl alcohol which is epinephrine. The purpose of the Hussain's *et. al.* invention was to develop a prodrug of epinephrine HCl with superior lipid solubility to enhance penetration through the cornea of the eye to treat glaucoma. Hussain *et. al.* synthesized four different prodrugs for this purpose. These four molecules were tested in human, rabbit and horse plasmas and found that 3, 4 –dipivalyl-α-[(methylamino) methyl] benzyl alcohol hydrochloride shows the best penetration profile into the eye. Hussain's et. al. didn't evaluate the log P of these molecules nor did they evaluate the sublingual or buccal permeability or absorption. Their main focus was to develop a prodrug specifically for the eye. Dipivalyl-α-[(methylamino)] benzyl alcohol hydrochloride was further developed into a drug delivery system for glaucoma (Dipivefrin or Propine).

Hussain and Truelove selected the dipivalyl prodrug for further development because of several physicochemical and biological qualities. The first quality was estimating the delay before onset of seizure for this prodrug was about 8-10 minutes,

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 030

the second quality was the rate of hydrolysis expressed as $t_{1/2}$ in human plasma was about 1,800 seconds and the third quality was the $t_{1/2}$ hydrolysis and oxidation *in vitro* was 700 and 300 days respectively. In a separate publication (Journal of Pharmaceutical Sciences, Vol. 65, No. 10, October 1976, p: 1510-1512), Hussain *et. al.* shared the graphs for the *in vitro* hydrolysis of this particular prodrug using rabbit eye homogenate and compared the hydrolysis among three different plasmas (human, rabbit, rabbit) and eye homogenate.

In 1977 Bodor filed a patent application that issued into US patent no 4,145,441 disclosed the use of sympathomimetic amine derivatives to treat hemorrhoids (rat model). The drug was applied topically to reduce rat ear swelling.

It should be noted that the generic formula disclosed by Bodor covering pages 2-3 of the patent covers thousands of compounds. When a claimed compound is not specifically named in a reference, but instead it is necessary to select portions of teachings within the reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated.

In *In re Petering*, the prior art disclosed a generic chemical formula "wherein X, Y, Z, P, and R'- represent either hydrogen or alkyl radicals, R a side chain containing an OH group." The court held that this formula, without more, could not anticipate a claim to 7-methyl-9-[d, l'-ribityl]-isoalloxazine because the generic formula encompassed a vast number and perhaps even an infinite number of compounds. However, the reference also disclosed preferred substituents for X, Y, Z, P, R, and R' as follows: where X, P, and R' are hydrogen, where Y and Z may be hydrogen or methyl, and where R is one of eight specific isoalloxazines. The court determined that this more limited generic class consisted of about 20 compounds. The limited number of compounds covered by the preferred formula in combination with the fact that the number of substituents was low at each site, the ring positions were limited, and there was a large unchanging structural nucleus, resulted in a finding that the reference sufficiently described "each of the various permutations here involved as fully as if he had drawn each structural formula or had written each name." The claimed compound

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was 1 of these 20 compounds. Therefore, the reference "described" the claimed compound and the reference anticipated the claims. In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962).

However, this is not the situation here: It is noted that compound no 7: 3-(trimethylaceloxy) alpha-[(methyl amino) methyl]-benzyl alcohol **is similar** to the elected species: CCl_2CH_3. Bodor does not disclose or suggest a trichloro derivative and it is not obvious to one skilled in the art to change trimethyl to trichloro since chlorine is electron withdrawing and methyl is electron donating group. This different compound will have different log P and different hydrolysis half-life in human plasma. Therefore, the specific species set out in the claims are not anticipated nor obvious in view of Bodor.

The claims have been amended to add the limitation of hydrolysis rate. This further differentiates the Bodor's patent, compound 7 because Hussain showed hydrolysis data for the trimethyl derivative of 30 minutes. This rate of hydrolysis is too long to treat anaphylaxis and as such Bodor teaches away from the presently claimed subject matter.

As we indicated, the main objective of Hussain and Trulove's research was developing a prodrug that shows a good penetrating ability into the cornea as contrary to Epinephrine which is not lipid soluble and will not penetrate biological membranes. At the same time, Hussain-Trulove wanted a prodrug design that hydrolyze in plasma at 30 minutes or more. Opposite to Hussain and Trulove idea, and in order to treat anaphylaxis, we need to develop a prodrug that is capable of penetrating biological membranes such as sublingual tissues, but also hydrolyzes quickly. As the trimethyl derivate showed a hydrolysis rate of 30 minutes with electron donating group, we anticipate with the use of electron withdrawing group such chorine the hydrolysis half-life will decrease, and the lipophilicity will increase which will allow the prodrug to penetrate the biological membrane quickly. This critical aspect of the inventive subject matter was missing in the Rawas-Qalaji teaching. Rawas-Qalaji never referred to Log P nor did they mention anything about the ability of epinephrine to penetrate biological membranes. What is striking about the rabbit data of Rawas-Qalaji is that they needed 40mg of epinephrine in a sublingual tablet to mimic the area under the curve of 0.3mg of Epinephrine IM injection. It is difficult for someone skilled in the art to look at this data

and predict success at human clinical level. It is also impossible for anyone skilled in the art to look at Bodor's molecules and pick compound 7 as a choice for sublingual delivery to treat anaphylaxis without any published data on its ability to penetrate biological membranes or its hydrolysis half-life in human plasma.

Specifically, the independent pending claims 1 and 19 are nonobvious over the cited references at least because:

(1) The cited references fail to disclose each and every recited claim element:

None of the cited references disclose the claimed prodrugs. Bodor doesn't disclose or suggest trichloro which is not obvious to one skilled in the art to change trimethyl to trichloro since chlorine is electron withdrawing and methyl is electron donating group. This different compound will have different log P and different hydrolysis half-life. It is noted that the generic formula disclosed by Bodor covers the elected species; Bodor does list tri fluoro derivatives, but the fluorine group is attached to a phenyl ring as part of the side R substituent

(2) One of skill would not have been motivated to modify the disclosure in Rawas-Qalaji read in view of Bodor in order to arrive at the instantly claimed prodrugs.

It is beyond the knowledge of someone skillful in the art to combine the teachings of Rawas-Qalaji with Bodor to obtain the claimed invention. There is no scientific rationale to use Bodor's compounds for anaphylaxis as he teaches for the treatment of hemorrhoids (topical rectal application) and he doesn't show how long it takes for each prodrug to be effective. On the other hand, Rawas-Qalaji teaches treating anaphylaxis by sublingual or buccal absorption of epinephrine. Bodor doesn't teach that any compounds included in structures I, II and III are effective for treating anaphylaxis. To the contrary, Bodor teaches that his compounds are active locally in the rectal area. Usually, Hemorrhoids are treated locally and not by oral or sublingual route (this is a medical fact). It is novel for someone to propose that Bodor's compounds can be used

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to treat anaphylaxis and it is beyond the knowledge of someone skillful in the art. In the present invention, epinephrine prodrugs are expected to get absorbed by sublingual tissues then cleaved in plasma in order to release epinephrine.

(3) Neither the Office Action nor the cited references themselves provide a reasonable expectation of success; and

Rawas-Qalaji discloses a fast-disintegrating epinephrine tablet for buccal or sublingual administration. It should be noted that this patent application was published in 2007. Yet at present, epinephrine is delivered by an injection. Rawas-Qalaji did not provide an enabling solution to this technical problem because animal data does not guarantee success in human studies as the permeability barriers in humans are more challenging. A review article in 2007. "Update on Epinephrine for the Treatment of Anaphylaxis" in Current Opinion in Pediatrics 19:94-98, at page 96 states that "alternative delivery systems are especially desirable for treatment of anaphylaxis.: The author then cites to the rabbit model data by Rawas-Qalaji. However, to date, no pharmaceutical industry has marketed a sublingual tablet of epinephrine simply because of the limited absorption behavior of epinephrine observed in many of Rawas-Qalaji's published animal studies. To solve this technical problem, a suitable pro-drug needed to be identified.

Dependent claims:

The dependent claims are not obvious as they include all of the limitations present in the independent claims which are not obvious to one skilled in the art for the aforementioned reasons. However, applicant would like to address the subject matter set out in claims 3 and 21 "The compound of claim 1 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film."

One skilled in the art would understand that the term wafer is not a film. A wafer is a solid matrix that is surgically inserted into biological systems for long term or sustained drug release. A fast-dissolving film is a thin and flexible polymerized matrix that dissolves very quickly and releases the drug instantaneously. **Rawas-Qalaji**

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teaches about a wafer as an alternative approach to make sublingual tablets. "Other known methods for manufacturing buccal or sublingual ODTS include lyophilization (e.g., Lyoc (Farmalyoc, now Cephalon, Franzer, PA) and QuickSolv (Janssen Pharmaceutica, Beerse, Belgium). Lyoc is a porous, Solid **wafer** manufactured by lyophilizing an oil-in-water emulsion placed directly in a blister and subsequently sealed. The **wafer** can accommodate high drug dosing and disintegrates rapidly but has poor mechanical strength (see EP 0159237).QuickSolv tablets are made with a similar technology that creates a porous solid matrix by freezing an aqueous dispersion or Solution of the matrix formulation." Consequently Rawas-Qalaji doesn't teach a wafer is a film as taught in the specification.

Conclusion:

Rawlas-Qalaji discloses epinephrine sublingual or buccal formulations. However, to date, no pharmaceutical industry was able to develop and secure FDA approval to market a sublingual tablet of epinephrine. The reason for this is because of the limited absorption behavior of epinephrine observed in many of Rawas-Qalaji's published animal studies. Rawlas-Qalaji taken in context teaches away from the claimed subject matter. Bodor does not disclose any of the claimed compositions in the specific compounds he listed. He teaches away from the discovery as the desirable hydrolysis rate for the Bodor compounds is not disclosed or unknown.

Applicant respectfully submits that the pending claims are in condition for allowance based on the patent prosecution highway request filed herewith. The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. 60-1480.

Respectfully submitted,

/Susan B Fentress/

Susan B. Fentress, Agent of Record
Reg. No. 31327
20 S Dudley, No 803
Memphis, Tennessee 38103

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Telephone No. (901) 525-1455

Dated: March 18, 2021.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/347,625	05/06/2019	Hassan Almoazen	24050.0001US

CONFIRMATION NO. 8118

POA ACCEPTANCE LETTER

76447
Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

OC000000124297882

Date Mailed: 03/24/2021

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/21/2021.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/yteferra/

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

PTO/SB/434 (05-13)

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

Practitioner Docket No.:	Application No.:	Filing Date:
24050.0001US	16/347,625	2019-05-07
First Named Inventor:	**Title:**	
Dr. Hassan Almoazen	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE	

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

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).
2. The above-identified application contains an outstanding final rejection.
3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.
4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.
5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.
6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).
7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]
8. By filing this certification and request, applicant acknowledges the following:
    - Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
    - The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
        - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
        - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
            - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
            - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

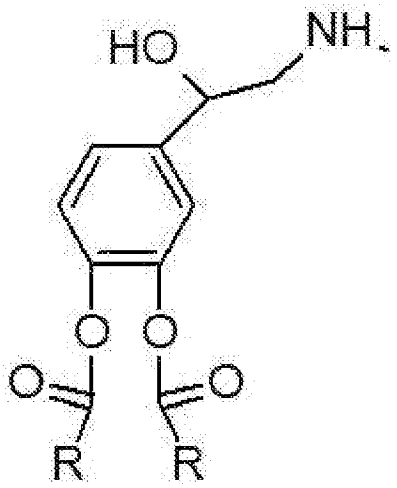
Signature	Date
/susan fentress/	2021-03-23
Name (Print/Typed)	**Practitioner Registration No.**
susan fentress	31327

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

☐ * Total of _____ forms are submitted.

AMENDMENTS TO THE CLAIMS

1. (currently amended) A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:

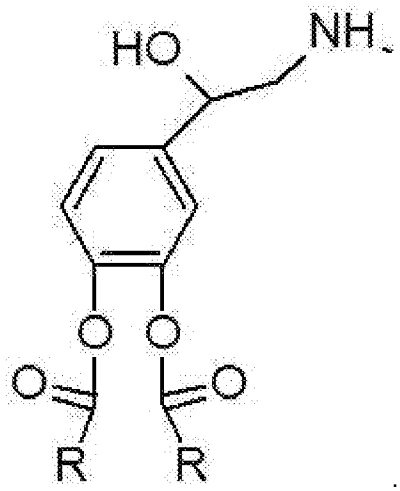


wherein R is selected from the group consisting of: $-CHCH_2$, $-CHCHCH_3$, $-CH_2-CH_2-Cl$, $-CHCH_2I$, $-CH(Cl)CH_2$ (Cl), $-CH(I)CH_2(I)$, $-CH(CH_3)CH_2(CH_3)$, $-CH_2C(CH_3)_3$, $-CH_2CH_2CH_3$, $-CH_2Cl$, $-CH_2I$, $-CH_2F$, H, Cl, I, F, $-CH(CH_3)CH(CH_3)_2$, $-CH(Cl)CH(Cl)_2$, $-CH(I)CH(I)_2$, $-CH(F)CH(F)_2$, $-CH_2CHCH_2$, $-C(Cl)_2CH(Cl)_2$, $-C(I)_2CH(I)_2$, $-C(Cl)_3$, $C(I)_3$, $-CH_2COCH_3$, $-CH_2COCl$, $-CH_2CO(I)$, $-CH_2OCH_3$, $-CH(I)(CH_3)$, $-C(Cl)_2(CH_3)$, $-CH_2CH(CH3)_2$, $-CH_2CH(Cl)_2$, $-CH_2CH(I)_2$, $-CH_2C(Cl)_3$, $-CH_2C(I)_3$, $-CH(Cl)_2$, $-CH(I)_2$, $-C(CH3)_2CH(CH3)_2$, $-NH-C(CH_3)_3$, $-NH-CH(CH_3)_2$, $-NH-CH_2CH_3$, $-NH-CH_3$, $-SCH_3$, $-SCH_2CH_3$, $-SCH(CH3)_2$, $-SC(CH_3)_3$, $-CH_2C_6H_5$ and $-C_6H_5$ or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0 and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

2.-18 (cancelled)

19. (currently amended) A compound of a Formula:

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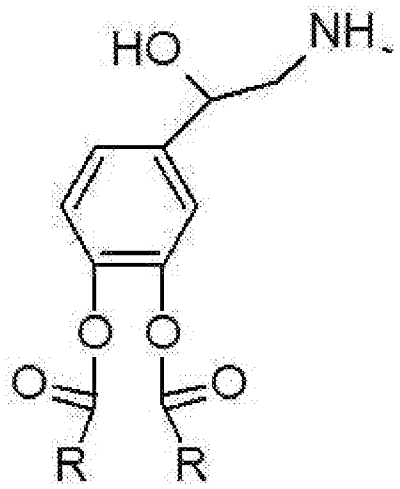
wherein R is selected from the group consisting of: CH_3, CH_2CH_3, and $CH(CH_3)_2$ wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

20. (previously presented) The compound of claim 19, wherein the compound is selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

21-22. (cancelled).

23. (new) A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:

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wherein R is comprised of $-C(Cl)_2CH_3$.

24. (new) The composition of claim 23 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

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Electronic Acknowledgement Receipt

EFS ID:	42259410
Application Number:	16347625
International Application Number:	
Confirmation Number:	8118
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	Hassan Almoazen
Customer Number:	76447
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001US
Receipt Date:	23-MAR-2021
Filing Date:	06-MAY-2019
Time Stamp:	16:02:47
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	After Final Consideration Program Request	afreview.pdf	832873 0563ee6970a607e9387987d961a34fdbf7d67bca	no	1

Warnings:

Information:					
2	Claims	afclaims.pdf	193891 61f44bdc1d5524d37494fbd6d94310fc96631613	no	3
Warnings:					
Information:					
3	Applicant Arguments/Remarks Made in an Amendment	amendmentafterfinal.pdf	1205923 b7cc56d89c6dbbbfefb8effeb65e413e8ca883b9	no	8
Warnings:					
Information:					
			Total Files Size (in bytes):	2232687	

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CONFIRMATION NO.:	8188
APPLICATION NO.:	16/347,625
FILED:	05/06/2019
ART UNIT:	1629
TITLE:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

AMENDMENT AFTER FINAL

Dear Sir:

In response to the office action dated 03/03/2021, please amend the above-identified applications as follows:

Amendments to the Specification: none,

Amendments to the Abstract: none.

Amendments to the Claims: begin on page 2 of this paper.

Amendments to the Drawings: None.

Remarks/Arguments: begin on page 4 of this pager.

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Remarks:

This application is a § 371 National Stage Application of PCT/US17/60761 application filed 11-09-2017 wherein claims 1, 3-14,16,18-22 were found in the International Preliminary Report on Patentability as amended by article 34) to be novel, non-obvious and have technical merit.

Support for the amended claims is found at:

"A pro-drug is a derivative of epinephrine selected for fast permeability through sub-lingual and buccal membranes (*i.e.,* a compound that dissolves in the oral cavity) and fast hydrolysis (half-life $t_{1/2}$ range from 1-6 minutes) by plasma enzymes to form epinephrine when delivered." Para 00023

The pending claims stand rejected as being obvious to one skilled in the art. Applicant respectfully disagrees and asserts that claims pending are nonobvious over Rawas-Qalaji read in view of Bodor.

Anwar A. Hussain and James E. Truelove were granted patents related to the synthesis of novel esters of [(methylamino)methyl] benzyl alcohol which is epinephrine. The purpose of the Hussain's *et. al.* invention was to develop a prodrug of epinephrine HCl with superior lipid solubility to enhance penetration through the cornea of the eye to treat glaucoma. Hussain *et. al.* synthesized four different prodrugs for this purpose. These four molecules were tested in human, rabbit and horse plasmas and found that 3, 4 –dipivalyl-α-[(methylamino) methyl] benzyl alcohol hydrochloride shows the best penetration profile into the eye. Hussain's et. al. didn't evaluate the log P of these molecules nor did they evaluate the sublingual or buccal permeability or absorption. Their main focus was to develop a prodrug specifically for the eye. Dipivalyl-α-[(methylamino)] benzyl alcohol hydrochloride was further developed into a drug delivery system for glaucoma (Dipivefrin or Propine).

Hussain and Truelove selected the dipivalyl prodrug for further development because of several physicochemical and biological qualities. The first quality was estimating the delay before onset of seizure for this prodrug was about 8-10 minutes,

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the second quality was the rate of hydrolysis expressed as $t_{1/2}$ in human plasma was about 1,800 seconds and the third quality was the $t_{1/2}$ hydrolysis and oxidation *in vitro* was 700 and 300 days respectively. In a separate publication (Journal of Pharmaceutical Sciences, Vol. 65, No. 10, October 1976, p: 1510-1512), Hussain *et. al.* shared the graphs for the *in vitro* hydrolysis of this particular prodrug using rabbit eye homogenate and compared the hydrolysis among three different plasmas (human, rabbit, rabbit) and eye homogenate.

In 1977 Bodor filed a patent application that issued into US patent no 4,145,441 disclosed the use of sympathomimetic amine derivatives to treat hemorrhoids (rat model). The drug was applied topically to reduce rat ear swelling.

It should be noted that the generic formula disclosed by Bodor covering pages 2-3 of the patent covers thousands of compounds. When a claimed compound is not specifically named in a reference, but instead it is necessary to select portions of teachings within the reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated.

In *In re Petering*, the prior art disclosed a generic chemical formula "wherein X, Y, Z, P, and R'- represent either hydrogen or alkyl radicals, R a side chain containing an OH group." The court held that this formula, without more, could not anticipate a claim to 7-methyl-9-[d, l'-ribityl]-isoalloxazine because the generic formula encompassed a vast number and perhaps even an infinite number of compounds. However, the reference also disclosed preferred substituents for X, Y, Z, P, R, and R' as follows: where X, P, and R' are hydrogen, where Y and Z may be hydrogen or methyl, and where R is one of eight specific isoalloxazines. The court determined that this more limited generic class consisted of about 20 compounds. The limited number of compounds covered by the preferred formula in combination with the fact that the number of substituents was low at each site, the ring positions were limited, and there was a large unchanging structural nucleus, resulted in a finding that the reference sufficiently described "each of the various permutations here involved as fully as if he had drawn each structural formula or had written each name." The claimed compound

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was 1 of these 20 compounds. Therefore, the reference "described" the claimed compound and the reference anticipated the claims. In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962).

However, this is not the situation here: It is noted that compound no 7: 3-(trimethylaceloxy) alpha-[(methyl amino) methyl]-benzyl alcohol **is similar** to the elected species: CCl_2CH_3. Bodor does not disclose or suggest a trichloro derivative and it is not obvious to one skilled in the art to change trimethyl to trichloro since chlorine is electron withdrawing and methyl is electron donating group. This different compound will have different log P and different hydrolysis half-life in human plasma. Therefore, the specific species set out in the claims are not anticipated nor obvious in view of Bodor.

The claims have been amended to add the limitation of hydrolysis rate. This further differentiates the Bodor's patent, compound 7 because Hussain showed hydrolysis data for the trimethyl derivative of 30 minutes. This rate of hydrolysis is too long to treat anaphylaxis and as such Bodor teaches away from the presently claimed subject matter.

What we learned from Hussain-Truelove patent is that higher carbon chain leads to higher hydrolysis half-life in plasma. The trimethyl alkyl derivative (compound 7) in Bodor's patent is similar in structure to Hussain's trimethyl alkyl (Dipivifrin) which has 1800 seconds (30 minutes) half-life in plasma. For a successful epinephrine prodrug to be used for anaphylaxis, the half-life should be 1-6 minutes. It is surprising that substitution of methyl with chloro would lower the half-life since chloro is also hydrophobic. Furthermore, and to our knowledge no prodrug had similar structure or similar chloro substitution making the discovery of these compounds more novel and unexpected.

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As we indicated, the main objective of Hussain and Trulove's research was developing a prodrug that shows a good penetrating ability into the cornea as contrary to Epinephrine which is not lipid soluble and will not penetrate biological membranes. At the same time, Hussain-Trulove wanted a prodrug design that hydrolyze in plasma at 30 minutes or more. Opposite to Hussain and Trulove idea, and in order to treat anaphylaxis, we need to develop a prodrug that is capable of penetrating biological membranes such as sublingual tissues, but also hydrolyzes quickly. As the trimethyl derivate showed a hydrolysis rate of 30 minutes with electron donating group, we anticipate with the use of electron withdrawing group such chorine the hydrolysis half-life will decrease, and the lipophilicity will increase which will allow the prodrug to penetrate the biological membrane quickly. This critical aspect of the inventive subject matter was missing in the Rawas-Qalaji teaching. Rawas-Qalaji never referred to Log P nor did they mention anything about the ability of epinephrine to penetrate biological membranes. What is striking about the rabbit data of Rawas-Qalaji is that they needed 40mg of epinephrine in a sublingual tablet to mimic the area under the curve of 0.3mg of Epinephrine IM injection. It is difficult for someone skilled in the art to look at this data and predict success at human clinical level. It is also impossible for anyone skilled in the art to look at Bodor's molecules and pick compound 7 as a choice for sublingual delivery to treat anaphylaxis without any published data on its ability to penetrate biological membranes or its hydrolysis half-life in human plasma.

Specifically, the independent pending claims 1 and 19 are nonobvious over the cited references at least because:

(1) The cited references fail to disclose each and every recited claim element:

None of the cited references disclose the claimed prodrugs. Bodor doesn't disclose or suggest trichloro which is not obvious to one skilled in the art to change trimethyl to trichloro since chlorine is electron withdrawing and methyl is electron donating group. This different compound will have different log P and different hydrolysis half-life. It is noted that the generic formula disclosed by Bodor covers the

elected species; Bodor does list tri fluoro derivatives, but the fluorine group is attached to a phenyl ring as part of the side R substituent

(2) One of skill would not have been motivated to modify the disclosure in Rawas-Qalaji read in view of Bodor in order to arrive at the instantly claimed prodrugs.

It is beyond the knowledge of someone skillful in the art to combine the teachings of Rawas-Qalaji with Bodor to obtain the claimed invention. There is no scientific rationale to use Bodor's compounds for anaphylaxis as he teaches for the treatment of hemorrhoids (topical rectal application) and he doesn't show how long it takes for each prodrug to be effective. On the other hand, Rawas-Qalaji teaches treating anaphylaxis by sublingual or buccal absorption of epinephrine. Bodor doesn't teach that any compounds included in structures I, II and III are effective for treating anaphylaxis. To the contrary, Bodor teaches that his compounds are active locally in the rectal area. Usually, Hemorrhoids are treated locally and not by oral or sublingual route (this is a medical fact). It is novel for someone to propose that Bodor's compounds can be used to treat anaphylaxis and it is beyond the knowledge of someone skillful in the art. In the present invention, epinephrine prodrugs are expected to get absorbed by sublingual tissues then cleaved in plasma in order to release epinephrine.

(3) Neither the Office Action nor the cited references themselves provide a reasonable expectation of success; and

Rawas-Qalaji discloses a fast-disintegrating epinephrine tablet for buccal or sublingual administration. It should be noted that this patent application was published in 2007. Yet at present, epinephrine is delivered by an injection. Rawas-Qalaji did not provide an enabling solution to this technical problem because animal data does not guarantee success in human studies as the permeability barriers in humans are more challenging. A review article in 2007. "Update on Epinephrine for the Treatment of Anaphylaxis" in Current Opinion in Pediatrics 19:94-98, at page 96 states that "alternative delivery systems are especially desirable for treatment of anaphylaxis.: The author then cites to

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 049

the rabbit model data by Rawas-Qalaji. However, to date, no pharmaceutical industry has marketed a sublingual tablet of epinephrine simply because of the limited absorption behavior of epinephrine observed in many of Rawas-Qalaji's published animal studies. To solve this technical problem, a suitable pro-drug needed to be identified.

Dependent claims:

The dependent claims are not obvious as they include all of the limitations present in the independent claims which are not obvious to one skilled in the art for the aforementioned reasons. However, applicant would like to address the subject matter set out in claims 3 and 21 "The compound of claim 1 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film."

One skilled in the art would understand that the term wafer is not a film. A wafer is a solid matrix that is surgically inserted into biological systems for long term or sustained drug release. A fast-dissolving film is a thin and flexible polymerized matrix that dissolves very quickly and releases the drug instantaneously. **Rawas-Qalaji** teaches about a wafer as an alternative approach to make sublingual tablets. "Other known methods for manufacturing buccal or sublingual ODTS include lyophilization (e.g., Lyoc (Farmalyoc, now Cephalon, Franzer, PA) and QuickSolv (Janssen Pharmaceutica, Beerse, Belgium). Lyoc is a porous, Solid **wafer** manufactured by lyophilizing an oil-in-water emulsion placed directly in a blister and subsequently sealed. The **wafer** can accommodate high drug dosing and disintegrates rapidly but has poor mechanical strength (see EP 0159237).QuickSolv tablets are made with a similar technology that creates a porous solid matrix by freezing an aqueous dispersion or Solution of the matrix formulation." Consequently Rawas-Qalaji doesn't teach a wafer is a film as taught in the specification.

Conclusion:

Rawlas-Qalaji discloses epinephrine sublingual or buccal formulations. However, to date, no pharmaceutical industry was able to develop and secure FDA approval to market a sublingual tablet of epinephrine. The reason for this is because of the limited absorption behavior of epinephrine observed in many of Rawas-Qalaji's published

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 050

animal studies. Rawlas-Qalaji taken in context teaches away from the claimed subject matter. Bodor does not disclose any of the claimed compositions in the specific compounds he listed. He teaches away from the discovery as the desirable hydrolysis rate for the Bodor compounds is not disclosed or unknown.

Applicant respectfully submits that the pending claims are in condition for allowance based on the patent prosecution highway request filed herewith. The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. 60-1480.

Respectfully submitted,

/Susan B Fentress/

Susan B. Fentress, Agent of Record
Reg. No. 31327
20 S Dudley, No 803
Memphis, Tennessee 38103
Telephone No. (901) 525-1455
Dated: March 23, 2021.

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 051

Electronic Acknowledgement Receipt

EFS ID:	42236524
Application Number:	16347625
International Application Number:	
Confirmation Number:	8118
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	Hassan Almoazen
Customer Number:	76447
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001US
Receipt Date:	21-MAR-2021
Filing Date:	06-MAY-2019
Time Stamp:	10:56:34
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	poasigned.pdf	181779 0fc7442d5dc13438e83b314905b4b23ab54cebc5	no	2

Warnings:

Information:	
Total Files Size (in bytes):	181779

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/96 (11-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: IONO PHARMA, LLC

Application No./Patent No.: 16347625 Filed/Issue Date: 05/06/2019

Titled: PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEF

IONO PHARMA, LLC, a CORPORATION

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☐ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above, by virtue of either:

A. ■ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 049098, Frame 0992, or a copy* is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel_____, Frame_____, or a copy* is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel_____, Frame_____, or a copy* is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel_____, Frame_____, or a copy* is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ *As required by 37 CFR 3.73(b)(1)(i), if a copy/copies is/are attached, the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Hassan ALMOAZEN — Signature

3-19-2021 — Date

Hassan ALMOAZEN — Printed or Typed Name

_____ — Title or Registration Number

This collection of information is required by 37 CFR 3.73(b). 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 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

PTO/AIA/80 (07-17)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

[X] Practitioners associated with Customer Number: 76447

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

[X] The address associated with Customer Number: 76447

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Iono Pharma, LLC. 3133 Hill Lake Drive Bartlett, Tennessee 38135

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature Hassan ALMOAZEN	Date 2021-03-19
Name Hassan ALMOAZEN for Iono Pharma, LLC	Telephone 901-448-2239
Title Founder and CEO	

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 18 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

Doc Code: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorized/Internet Communications Authorization Withdrawn

PTO/SB/439 (11-15)

AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS		
	Application No.	16/347,625
	Filing Date	2019-05-07
	First Named Inventor	Dr. Hassan Almoazen
	Art Unit	1629
	Examiner Name	Tori Strong
	Practitioner Docket No.	24050.0001US

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

I. To authorize permission for Internet Communications.

☑ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

II. To withdraw authorization for Internet Communications.

☐ The authorization given on _____, to the USPTO to communicate with the undersigned and any practitioner in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via Internet communications such as video conferencing, instant messaging, or electronic mail is hereby withdrawn. I understand that the withdrawal is effective when approved rather than when received.

I am the

☐ applicant.

☐ attorney or agent of record. Registration number _____.

☑ attorney or agent acting under 37 CFR 1.34. Registration number 31327.

/susan fentress/ — Signature

March 18, 2021 — Date

susan fentress — Typed or printed name

901 371 6664 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Juristic entities must be represented by a patent practitioner (see 37 CFR 1.31, which is applicable to any paper filed on or after September 16, 2012, that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

Electronic Acknowledgement Receipt

EFS ID:	42224709
Application Number:	16347625
International Application Number:	
Confirmation Number:	8118
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	Hassan Almoazen
Customer Number:	76447
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001US
Receipt Date:	19-MAR-2021
Filing Date:	06-MAY-2019
Time Stamp:	09:37:18
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Internet Communications Authorized	internetauthorizationupdated.pdf	399037 b5a3ae83ae52c809945e2dea7fb898d7e04758cf	no	1

Warnings:

Information:	
Total Files Size (in bytes):	399037

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/347,625	05/06/2019	Hassan Almoazen	24050.0001US	8118

76447 7590 03/03/2021

Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

EXAMINER	
STRONG, TORI	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
03/03/2021	ELECTRONIC

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

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

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

eofficeaction@appcoll.com
sfentress@veritaygroup.com

Office Action Summary	Application No. 16/347,625	Applicant(s) Almoazen, Hassan	
	Examiner TORI STRONG	Art Unit 1629	AIA (FITF) Status Yes

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

Period for Reply

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

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

Status

1)☑ Responsive to communication(s) filed on 22 January 2021.

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

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

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

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

Disposition of Claims*

5) ☑ Claim(s) 1,3 and 19-21 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,3 and 19-21 is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Status of Claims

Claims 1, 3 and 19-21 are pending in the instant application and are the subject of the Office Action below.

Examination Considerations

Applicant's Arguments, filed January 22, 2021 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Applicant's Affidavit, filed January 22, 2021 has been entered and considered.

Claim Objections - Withdrawn

Claim 18 objected to because of the informalities is ***withdrawn***.

The appropriate correction has been made removing recitation of the cancelled claim.

Claim Rejections - 35 USC § 103 – Maintained

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

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

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3 and 19-21 rejected under 35 U.S.C. 103 as being unpatentable over Rawas-Qalaji *et al.* (US 2007/0202163 A1; cited in IDS) in view of Bodor (US 4,145,441; cited in IDS) is ***maintained***.

Response to Applicant's Arguments:

Applicant traverses rejection and alleges the claims are nonobvious over the cited art of record. Applicant argues that the references fail to disclose each and every recited claim element, arguing that Rawas-Qalaji teaches a fast-disintegrating epinephrine tablet, but the pharmaceutical industry has not marketed it because of

erratic absorption behavior or epinephrine. Applicant further argues that Bodor discloses sympathomimetic amines for hemorrhoidal activity and does not teach an epinephrine compound claimed, teaching -$C(CH_3)_3$ as a side chain where the claimed R group is –$CH_2C(CH_3)_3$ and thus would not have the inherent functional features. Applicant alleges that one would have been motivated to modify the primary reference in view of Bodor to arrive at the instantly claimed invention; arguing that Rawas-Qalaji teaches compounds for anaphylaxis by sublingual route and that Bodor teaches local rectal treatment of hemorrhoids. Applicant thus concludes there is no reasonable expectation of success based on the cited references. Applicant further allege that there is a long felt medical need that the instant claims have met. Applicant argues, and submits a declaration, by way of affidavit filed 01/22/2021, prompt injection of epinephrine is the recommended first-aid treatment of anaphylaxis and that at present sublingual or buccal administration of epinephrine is not available to treat patients.

Applicant's argument is found unpersuasive due to not providing objective evidence of establishing a long-felt need. Applicant has alleged that even though Rawas-Qalaji teaches a fast-disintegrating tablet, that the industry has not marketed a sublingual or buccal tablet. However, Applicant has not presented objective evidence that this a need that has been persistent and recognized by those of ordinary skill in the art (see *In re Gershon*). Applicant asserting that a tablet is not marketed, or that Rawas-Qalaji demonstrated erratic absorption behavior, is not in itself evidence that one of ordinary skill is aware of there being a persistent problem and that there is evidence of prior unsuccessful attempts to resolve the persistent problem. Furthermore, Applicant has not established that Rawas-Qalaji did not solve the alleged problem, or that no one

has not solved the problem. Despite there being absorption issues and not yet marketed, does not mean that Rawas-Qalaji does not provide an enabling solution to the problem. Rawas-Qalaji's teaching may not be an optimum solution, however, there is explicit teaching of providing a sublingual or buccal formulation of epinephrine. Likewise, long-felt need is analyzed as of the date the problem is identified and articulated, and there is evidence of efforts to solve that problem (see MPEP 716.04, II). Applicant has not provided the evidence of such analysis.

Furthermore, while Bodor does teach catecholamine having anti-hemorrhoidal activity, Bodor teaches generating stable prodrugs of those catecholamines. It is noted that Bodor teaches a species that has only one substitution with -C(CH3)3 as a side chain for referenced compound 7, however, Bodor teaches compounds of formula (I) where R1 and R2 are acyl that is alkanoyl having 1-22 carbon atoms. This teaching overlaps the claimed R being $-CH_2CH_2CH_3$, amongst others. Therefore Bodor teaches a species that can be readily envisaged that overlaps with claimed species. Those overlapping species would inherently have the claimed function, unless evidence to the contrary. Applicant provides no evidence of unexpected results where the prior establishes that epinephrine can be formulated for sublingual or buccal administration as well as a prodrug formulated as claimed.

Applicant's arguments are found unpersuasive and the instant claims remain prima facie obvious over the art of record.

Reiterated Rejection:

Applicant's invention, according to **claim 1**, is directed to a compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of the depicted Formula wherein R is the elected $-C(Cl)_2CH_3$ in the alternative or $-CH_2C(CH_3)_3$ in the alternative; wherein said compound has a Log P value in the range of about 0.5 to 6.0.

It is noted by Applicant's own admission the claimed invention is directed to delivery of an epinephrine, or prodrug formulation of epinephrine, for rapid delivery through sublingual or buccal administration (see specification, p.1, [0001]). The claimed formula is a prodrug construct of epinephrine. Furthermore, the claimed limitation of Log P value is deemed inherent to the claimed structures, unless evidence to the contrary.

Rawas-Qalaji teaches formulations for fast-disintegrating epinephrine tablets which can be prepared for buccal or sublingual administration (abs). Rawas-Qalaji teaches the formulation to provide epinephrine plasma concentrations similar to those achieved by traditional injectable forms (p.3, [0025]). Rawas-Qalaji teaches as a preferred embodiment the use of epinephrine bitartrate or HCl salt, however, Rawas-Qalaji further teaches that any suitable form of epinephrine can be used for the disclosed buccal or sublingual formulation. Rawas-Qalaji does not explicitly teach the claimed species of epinephrine.

Bodor teaches prodrug epinephrine compounds, where Bodor teaches the compounds are stable and cleavable to the parent epinephrine compound (col.1, l.40-42). Bodor teaches compounds of Formula I, where R can be methyl and R_1 and R_2 can be an acyl member which is alkanoyl (col.1-2, bridging para). Bodor explicitly teaches compound (7) 3-(trimethylaceloxy)-α-[(methylamino)methyl]benzyl alcohol (col.5, l.18)

which corresponds to the claimed R being $-CH_2C(CH_3)_3$. Bodor establishes the claimed species as a known epinephrine compound.

One of ordinary skill in the art would arrive at the instant claims having a reasonable expectation of success based on the combine teaching because Rawas-Qalaji establishes the use of sublingual and buccal formulations of epinephrine compounds generally where Bodor teaches epinephrine prodrugs and particularly a claimed species of epinephrine prodrug. A skilled artisan would glean from Rawas-Qalaji formulating sublingual or buccal epinephrine where it is further taught that any form of epinephrine can be used within the formulation, where Bodor establishes a known form of epinephrine. As mentioned above, the resultant function having a Log P value in the claimed range is inherent to the structure of the compounds, unless evidence to the contrary. Therefore it was *prima facie* obvious to arrive at the instant claim based on the combined teaching of Rawas-Qalaji and Bodor.

Applicant's invention, according to **claim 3**, limits claim 1 and requires being formulated in a unit dosage form as a rapidly dissolving film.

It is noted that Applicant describes film as that active ingredient incorporated into a sheet, dried and then cut into individual doses (specification, p.3, [0005]).

Rawas-Qalaji teaches formulation in other matrix forms, such as a wafer-like formulation that is quick dissolving (p.6, [0068]) thus Rawas-Qalaji teaches that formulations can be a film that is rapidly dissolving; where a wafer is being broadly and reasonably considered a type of film. Thus the limitation is met and the instant claim remains *prima facie* obvious over the combined art.

Applicant's invention, according to **claims 19-21**, is directed to a compound of the claimed Formula wherein R is $CH(CH_3)_2$ in the alternative formulated for sublingual or buccal administration, where claim 20 requires the species in the alternative and claim 21 requires being formulated in a unit dosage form as a rapidly dissolving film.

As mentioned above Rawas-Qalaji teaches epinephrine sublingual or buccal formulations, where Bodor teaches prodrug species of epinephrine. The claimed species and the taught species by Bodor differ in methyl substitutions on the R group. The courts precedence deems that interchange of alkyl and hydrogen are obvious variants in and of itself (*Ex parte Bluestone*) and not a patentable modification absent unexpected result (*In re Wood*), particularly where the compounds will have the same properties as the prior art compounds (*In re Dillion*). The claimed modification is provided to generate another prodrug form of epinephrine, thus having the same properties of the embodiment taught by Bodor. Furthermore, Rawas-Qalaji teaches a rapidly dissolving film for sublingual and buccal administration. Therefore the instant claims remain *prima facie* obvious over the combined art of Rawas-Qalaji and Bodor.

Conclusion

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

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI STRONG whose telephone number is (571)272-6333. The examiner can normally be reached on Monday - Friday 8:00 am - 5:00 pm (EST).

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

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on (571)272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Kortney L. Klinkel/
Primary Examiner, Art Unit 1699

TORI STRONG
Examiner
Art Unit 1629

/TORI STRONG/
Examiner, Art Unit 1629

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/347,625	Almoazen, Hassan
	Examiner	Art Unit
	TORI STRONG	1629

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
(A61K31/137 OR A61K9/006 OR A61P37/08 OR C07C215/00 OR C07C219/30)	02/19/2021	TMS

US Classification - Searched*			
Class	Subclass	Date	Examiner

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

Search Notes		
Search Notes	Date	Examiner
Review of Global Dossier	12/16/2020	TMS
Structure search performed in STNext	12/16/2020	TMS
Background search in Google	12/16/2020	TMS
Inventor search in PE2E	12/16/2020	TMS
Text search performed in EAST	02/19/2021	TMS
Interference search - Utilized Structure Search	02/19/2021	TMS

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
Structure	Search	02/19/2021	TMS

/TORI STRONG/ Examiner, Art Unit 1629	

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/347,625	Almoazen, Hassan
	Examiner	Art Unit
	TORI STRONG	1629

/TORI STRONG/ Examiner, Art Unit 1629	

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2	"16347625"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2021/02/19 15:27
L2	3	"62109943".FMID.	US-PGPUB; USPAT; FPRS; JPO	OR	OFF	2021/02/19 15:27
L3	250,104	((A61K31/137 OR A61K9/006 OR A61P37/08 OR C07C215/00 OR C07C219/30).CPC.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2021/02/19 15:31
L4	1,737	L3 and epinephrine and (sublingual or buccal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2021/02/19 15:31
L5	5	L3 and (epinephrine near prodrug) and (sublingual or buccal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2021/02/19 15:32

EAST Search History (Interference)

<This search history is empty>

2/19/2021 3:34:44 PM
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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/347,625	Filing Date 05/06/2019	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	01/22/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 5	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

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

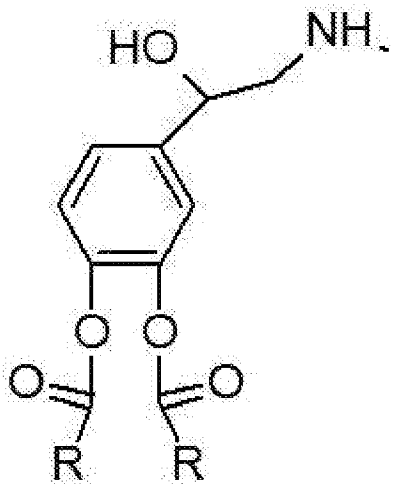
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/TERRY BRYANT/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number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

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

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

AMENDMENTS TO THE CLAIMS

1. (previously presented) A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:



wherein R is selected from the group consisting of: $-CHCH_2$, $-CHCHCH_3$, $-CH_2-CH_2-Cl$, $-CHCH_2I$, $-CH(Cl)CH_2(Cl)$, $-CH(I)CH_2(I)$, $-CH(CH_3)CH_2(CH_3)$, $-CH_2C(CH_3)_3$, $-CH_2CH_2CH_3$, $-CH_2Cl$, $-CH_2I$, $-CH_2F$, H, Cl, I, F, $-CH(CH_3)CH(CH_3)_2$, $-CH(Cl)CH(Cl)_2$, $-CH(I)CH(I)_2$, $-CH(F)CH(F)_2$, $-CH_2CHCH_2$, $-C(Cl)_2CH(Cl)_2$, $-C(I)_2CH(I)_2$, $-C(Cl)_3$, $C(I)_3$, $-CH_2COCH_3$, $-CH_2COCl$, $-CH_2CO(I)$, $-CH_2OCH_3$, $-CH(I)(CH_3)$, $-C(Cl)_2(CH_3)$, $-CH_2CH(CH3)_2$, $-CH_2CH(Cl)_2$, $-CH_2CH(I)_2$, $-CH_2C(Cl)_3$, $-CH_2C(I)_3$, $-CH(Cl)_2$, $-CH(I)_2$, $-C(CH3)_2CH(CH3)_2$, $-NH-C(CH_3)_3$, $-NH-CH(CH_3)_2$, $-NH-CH_2CH_3$, $-NH-CH_3$, $-SCH_3$, $-SCH_2CH_3$, $-SCH(CH3)_2$, $-SC(CH_3)_3$, $-CH_2C_6H_5$ and $-C_6H_5$ or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0.

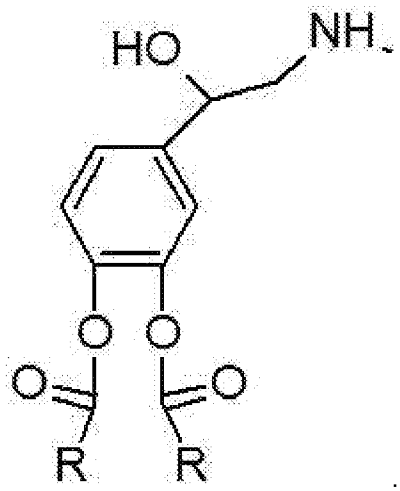
2. (cancelled)

3. (previously presented) The compound of claim 1 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

4.-18 (cancelled)

19. (previously presented) A compound of a Formula:

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wherein R is selected from the group consisting of: CH_3, CH_2CH_3, and $CH(CH_3)_2$ wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration.

20. (previously presented) The compound of claim 19, wherein the compound is selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

21 (original) The compound of claim 19, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

22. (cancelled).

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CONFIRMATION NO.:	8188
APPLICATION NO.:	16/347,625
FILED:	05/06/2019
ART UNIT:	1629
TITLE:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

DECLARATION UNDER 37 CFR 1.132

1. I, Kafait U. Malik am a professor at the University of Tennessee Health Science Center in Memphis, Tennessee
2. In the field of pharmacology, I have studied:
3. Prompt injection of epinephrine in the mid-outer thigh (vastus lateralis muscle) using an auto-injector is the recommended first-aid treatment of anaphylaxis in community settings. At present, sublingual or buccal administration of epinephrine is not available to treat patients.
4. To date, no pharmaceutical industry was able to develop and market a sublingual tablet of epinephrine simply because of the erratic absorption behavior of epinephrine observed in many of Rawas-Qalaji's published animal studies.
5. However, effective sublingual or buccal administration of a pharmaceutical composition to treat anaphylaxis would meet a long felt need in the medical field.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, Section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application of any patent issued thereon.



Kafait U. Malik, D.Sc., Ph.D., FAHA
Professor of Pharmacology and Medicine

DATE: 01/19/2021

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 076

Electronic Acknowledgement Receipt

EFS ID:	41725100
Application Number:	16347625
International Application Number:	
Confirmation Number:	8118
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	Hassan Almoazen
Customer Number:	76447
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001US
Receipt Date:	22-JAN-2021
Filing Date:	06-MAY-2019
Time Stamp:	20:37:11
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	amendmenttoaupdated.pdf	939897 460373bd890ed359ca214a76e6f58e3997d65953	no	8

Warnings:

Information:					
2	Claims	amendedclaimsupdated.pdf	165885 6d0c0d0e99f1bb1e8b18ee48f05d0b7a260f112c	no	2
Warnings:					
Information:					
3	Affidavit-traversing rejectns or objectns rule 132	132updated.pdf	131131 49b42f266a9bb6b8b88a3c386766b17a5d95d1ca	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1236913	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CONFIRMATION NO.:	8188
APPLICATION NO.:	16/347,625
FILED:	05/06/2019
ART UNIT:	1629
TITLE:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

AMENDMENT

Dear Sir:

Un response to the office action dated 12/24/2020, please amend the above-identified applications as follows:

Amendments to the Specification: none,

Amendments to the Abstract: none.

Amendments to the Claims: begin on page 2 of this paper.

Amendments to the Drawings: None.

Remarks/Arguments: begin on page 4 of this pager.

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Remarks:

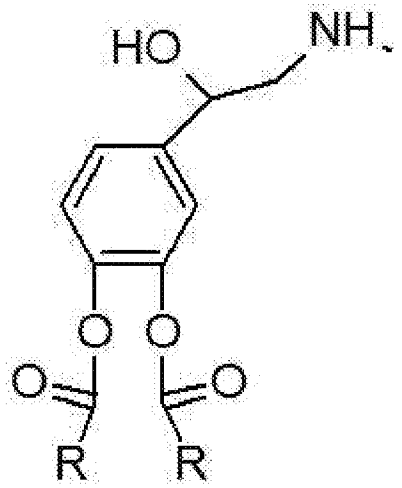
This application is a § 371 National Stage Application of PCT/US17/60761 application filed 11-09-2017 wherein claims 1, 3-14,16,18-22 were found in the International Preliminary Report on Patentability as amended by article 34) to be novel, non-obvious and have technical merit.

The pending claims stand rejected as being obvious to one skilled in the art. Applicant respectfully disagrees and asserts that claims pending are nonobvious over Rawas-Qalaji read in view of Bodor.

Specifically, the independent pending claims 1 and 19 are nonobvious over the cited references at least because:

(1) The cited references fail to disclose each and every recited claim element;

(2) One of skill would not have been motivated to modify the disclosure in Rawas-Qalaji read in view of Bodor in order to arrive at the instantly claimed compounds formulated as: Claim 1: A pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:



wherein R is selected from the group consisting of: $-CHCH_2$, $-CHCHCH_3$, $-CH_2-CH_2-Cl$, $-CHCH_2I$, $-CH(Cl)CH_2$ (Cl), $-CH(I)CH_2(I)$, $-CH(CH_3)CH_2(CH_3)$, $-CH_2C(CH_3)_3$, $-CH_2CH_2CH_3$, $-CH_2Cl$, $-CH_2I$, $-CH_2F$, H, Cl, I, F, $-CH(CH_3)CH(CH_3)_2$, $-CH(Cl)CH(Cl)_2$, -

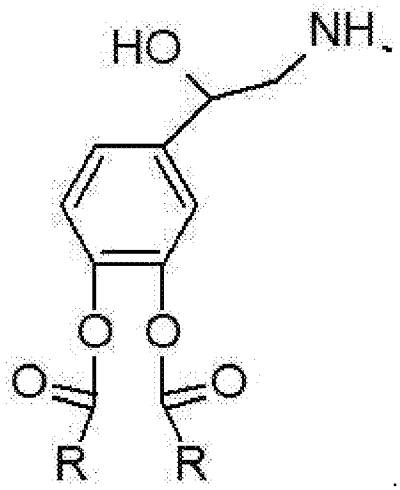
AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 080

$CH(I)CH(I)_2$, $-CH(F)CH(F)_2$, $-CH_2CHCH_2$, $-C(Cl)_2CH(Cl)_2$, $-C(I)_2CH(I)_2$, $-C(Cl)_3$, $C(I)_3$, $-CH_2COCH_3$, $-CH_2COCl$, $-CH_2CO(I)$, $-CH_2OCH_3$, $-CH(I)(CH_3)$, $-C(Cl)_2(CH_3)$, $-CH_2CH(CH3)_2$, $-CH_2CH(Cl)_2$, $-CH_2CH(I)_2$, $-CH_2C(Cl)_3$, $-CH_2C(I)_3$, $-CH(Cl)_2$, $-CH(I)_2$, $-C(CH3)_2CH(CH3)_2$, $-NH-C(CH_3)_3$, $-NH-CH(CH_3)_2$, $-NH-CH_2CH_3$, $-NH-CH_3$, $-SCH_3$, $-SCH_2CH_3$, $-SCH(CH3)_2$, $-SC(CH_3)_3$, $-CH_2C_6H_5$ and $-C_6H_5$ or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0 and more particularly in a unit dosage form as a rapidly dissolving film.

Or

Claim 19.

A compound of a Formula:



wherein R is selected from the group consisting of: CH_3, CH_2CH_3, and $CH(CH_3)_2$ wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration.

(3) Neither the Office Action nor the cited references themselves provide a reasonable expectation of success; and

(4) The 132 declaration establishes a long felt need in the industry for such a composition.

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(1) The cited references fail to disclose each and every recited claim element;

Point one: None of the cited references disclose the claimed prodrugs.

Rawas-Qalaji discloses a fast-disintegrating epinephrine tablet for buccal or sublingual administration. It should be noted that this patent application was published in 2007. Yet at present, epinephrine is delivered by an injection. The problem with epinephrine is that it is highly hydrophilic and cannot be absorbed by the GI tract. In addition, within the GI tract, it can be oxidized in the intestinal lumen and can lose its efficacy. To date, no pharmaceutical industry was able to develop and market a sublingual tablet of epinephrine simply because of the erratic absorption behavior of epinephrine observed in many of Rawas-Qalaji's published animal studies.

Bodor discloses sympathomimetic amines having anti hemorrhoidal activity.

"It has recently been suggested that epinephrine, be
cause of its vasoconstrictor action, might possibly be
useful in treating hemorrhoidal conditions. However,
this compound is relatively unstable at rectal pH, i.e.,
about 6.0 but moreover, does not have the capability to
effectively reduce swelling. The compounds of the
present invention are among other things characterized
as stable at rectal pH and slowly "cleavable' to the
parent catecholamine, which through vasoconstriction,
reduces the swelling associated with hemorrhoids. At col5 l 18
Bodor cites
Compound (7) 3-(trimethylaceloxy)-a-(methylamino)methyl
benzyl alcohol as an example.

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However, this compound is not epinephrine nor is it set out in the claims. It has only one phenolic group forming an ester with an alkyl group. The side chain $C(CH_3)_3$ is not listed in the claims. Bodor teaches compound 7 has the R group C(CH3)3. However, the R group claimed is: -CH2C(CH3)3, which is not the same compound. Thus, the disclosure in Bodor does not disclose or suggest the claimed compounds to one skilled in the art. Since the claimed compounds are not disclosed, the compounds of Bodor would not inherently have the claimed Log P value in the range of about 0.5-6.0.

2) <u>One of skill would not have been motivated to modify the disclosure in Rawas-Qalaji read in view of Bodor in order to arrive at the instantly claimed invention.</u>

It is beyond the knowledge of someone skillful in the art to combine the teachings of Rawas-Qalaji with Bodor to obtain the claimed invention. There is no scientific rationale to use Bodor's compounds for anaphylaxis as he teaches for the treatment of hemorrhoids (topical rectal application). On the other hand, Rawas-Qalaji teaches treating anaphylaxis by sublingual or buccal absorption of epinephrine. Bodor doesn't teach that any compounds included in structures I, II and III are effective for treating anaphylaxis. To the contrary, Bodor teaches that his compounds are active locally in the rectal area. Usually, Hemorrhoids are treated locally and not by oral or sublingual route (this is a medical fact). It is novel for someone to propose that Bodor's compounds can be used to treat anaphylaxis and it is beyond the knowledge of someone skillful in the art. In the present invention, epinephrine prodrugs are absorbed by sublingual tissues then cleaved in plasma in order to release epinephrine.

3) <u>Neither the Office Action nor the cited references themselves provide a reasonable expectation of success</u>.

Prompt injection of epinephrine in the mid-outer thigh (vastus lateralis muscle) using an auto-injector is the recommended first-aid treatment of anaphylaxis in community settings Many patients at risk of anaphylaxis in the community fail to carry their epinephrine auto-injectors consistently, due to their bulky shape and large size. When

anaphylaxis occurs, many patients and caregivers who have an epinephrine auto-injector available were reported to delay injecting epinephrine because of their fear of needles. There is an increasingly challenging availability and affordability issue of epinephrine autoinjectors worldwide, with pharmacy acquisition costs in North America ranging from $170 to $430 US dollars per pack [Brown, J.C.; Tuuri, R.E.; Akhter, S.; Guerra, L.D.; Goodman, I.S.; Myers, S.R.; Nozicka, C.; Manzi, S.; Long, K.; Turner, T.; et al. Lacerations and embedded needles caused by epinephrine autoinjector use in children. *Ann. Emerg. Med.* **2016**, *67*, 307–315. Yet even in view of this need and in view of prior art that is more than 40 years old, a need in the medical field exists for a noninjectable form of epinephrine. A reasonable expectation of success has not been shown because the 1) claimed prodrugs are not shown in the cited art and 2) as the cited art is unrelated to the claimed formulation for sublingual or buccal administration.

4) <u>The 132 Declaration refutes prima facie finding of obviousness.</u>

Prompt injection of epinephrine in the mid-outer thigh (vastus lateralis muscle) using an auto-injector is the recommended first-aid treatment of anaphylaxis in community settings. At present, sublingual or buccal administration of epinephrine is not available to treat patients. To date, no pharmaceutical industry was able to develop and market a sublingual tablet of epinephrine simply because of the erratic absorption behavior of epinephrine observed in many of Rawas-Qalaji's published animal studies. However, effective sublingual or buccal administration of a pharmaceutical composition to treat anaphylaxis would meet a long felt need in the medical field. 132 declaration of Dr. Kafait U. Malik

Dependent claims:

The dependent claims are not obvious as they include all of the limitations present in the independent claims which are not obvious to one skilled in the art for the aforementioned reasons. However, applicant would like to address the subject matter set out in claims 3 and 21 "The compound of claim 1 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film."

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A wafer is not a film. A wafer is a polymerized solid matrix that is surgically inserted into biological systems for long term or sustained drug release. A fast-dissolving film is a thin and flexible polymerized matrix that dissolves very quickly and releases the drug instantaneously. **Rawas-Qalaji** teaches about a wafer as an alternative approach to make sublingual tablets.

"Other known methods for manufacturing buccal or Sublingual ODTS include lyophilization (e.g., Lyoc (Farma lyoc, now Cephalon, Franzer, PA) and QuickSolv (Janssen Pharmaceutica, Beerse, Belgium). Lyoc is a porous, Solid **wafer** manufactured by lyophilizing an oil-in-water emul sion placed directly in a blister and subsequently sealed. The **wafer** can accommodate high drug dosing and disintegrates rapidly but has poor mechanical strength (see EP 0159237). QuickSolv tablets are made with a similar technology that creates a porous solid matrix by freezing an aqueous dis persion or Solution of the matrix formulation."

Rawas-Qalaji doesn't teach a wafer is a film.

Conclusion:

Rawlas-Qalaji discloses epinephrine sublingual or buccal formulations. However, to date, no pharmaceutical industry was able to develop and market a sublingual tablet of epinephrine simply because of the erratic absorption behavior of epinephrine observed in many of Rawas-Qalaji's published animal studies. Rawlas-Qalaji taken in context teaches away from the claimed subject matter. Bodor does not disclose any of the claimed pro-drugs. Thus, there is no factual basis for a prima facie case of obviousness. Even if a prima facie case of obviousness has been made, the secondary considerations discussed in the 132 declaration of Dr. Kafait U. Malik shown that in

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context in view of the long felt need in the industry and the date of publication of the references a finding of obviousness is unwarranted.

Applicant respectfully submits that the pending claims are in condition for allowance based on the patent prosecution highway request filed herewith. The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. 60-1480.

Respectfully submitted,

/Susan B Fentress/

Susan B. Fentress, Agent of Record
Reg. No. 31327
20 S Dudley, No 803
Memphis, Tennessee 38103
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Dated: January 22, 2021.

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 086

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/347,625	05/06/2019	Hassan Almoazen	24050.0001US	8118

76447 7590 12/24/2020

Susan B. Fentress
Veritay Group, IP
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Memphis, TN 38103

EXAMINER	
STRONG, TORI	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
12/24/2020	ELECTRONIC

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

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

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

eofficeaction@appcoll.com
sfentress@veritaygroup.com

Office Action Summary	Application No. 16/347,625	Applicant(s) Almoazen, Hassan	
	Examiner TORI STRONG	Art Unit 1629	AIA (FITF) Status Yes

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

Period for Reply

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

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

Status

1)☑ Responsive to communication(s) filed on 01 December 2020.

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

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

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

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

Disposition of Claims*

5) ☑ Claim(s) 1,3 and 19-21 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,3 and 19-21 is/are rejected.

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

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

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

Application Papers

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

11)☑ The drawing(s) filed on 06 May 2019 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Status of Claims

Claims 1, 3 and 19-21 are pending in the instant application; claims 2, 4-18 and 22 are previously cancelled prior to examination; claims 1, 3 and 19-21 are the subject of the Office Action below.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on May 6, 2019 and October 14, 2019 were filed on and after the mailing date of the application. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Enclosed with this Office Action are return copies of Form PTO/SB/08B with the Examiner's initials and signature indicating those references that have been considered.

Response to Election/Restrictions

In response to Restriction Requirement mailed on November 4, 2020, Applicants filed a Reply on December 1, 2020, and elected the invention of Group I, claims 1, 3 and 19-21, directed to a compound formulated for sublingual or buccual administration

of claimed formula (prodrug formulations of epinephrine). This election was made without traverse.

It is also acknowledged that the Applicants have elected the species of R is –$C(Cl)_2CH_3$, claims 1 and 3, without traverse.

Claims 14, 16 and 18, previously directed to patently distinct inventions, have been withdrawn from consideration and further cancelled. Claims 1, 3 and 19-21 are pending and are the subject of examination.

Claim Objections

Claim 18 is objected to because of the following informalities:

Claim 18 has been cancelled as being directed as a dependent method claim, yet claim 18 is further recited inadvertently. As the method claims were all cancelled, and claim 18 is a method claim and listed once as being cancelled, the examiner is treating claim 18 as being cancelled. In future amendments the text of claim 18 should be deleted. Should applicant intend claim 18 to be pending and not cancelled, it should be reinstated as a new claim numbered claim 23.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

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

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having

> ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3 and 19-21 are rejected under 35 U.S.C. 103 as being unpatentable over Rawas-Qalaji *et al.* (US 2007/0202163 A1; cited in IDS) in view of Bodor (US 4,145,441; cited in IDS).

Applicant's invention, according to **claim 1**, is directed to a compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of the depicted Formula wherein R is the elected $-C(Cl)_2CH_3$ in the alternative or $-CH_2C(CH_3)_3$ in the alternative; wherein said compound has a Log P value in the range of about 0.5 to 6.0.

It is noted by Applicant's own admission the claimed invention is directed to delivery of an epinephrine, or prodrug formulation of epinephrine, for rapid delivery through sublingual or buccal administration (see specification, p.1, [0001]). The claimed formula is a prodrug construct of epinephrine. Furthermore, the claimed limitation of Log P value is deemed inherent to the claimed structures, unless evidence to the contrary.

Rawas-Qalaji teaches formulations for fast-disintegrating epinephrine tablets which can be prepared for buccal or sublingual administration (abs). Rawas-Qalaji teaches the formulation to provide epinephrine plasma concentrations similar to those achieved by traditional injectable forms (p.3, [0025]). Rawas-Qalaji teaches as a preferred embodiment the use of epinephrine bitartrate or HCl salt, however, Rawas-Qalaji further teaches that any suitable form of epinephrine can be used for the disclosed buccal or sublingual formulation. Rawas-Qalaji does not explicitly teach the claimed species of epinephrine.

Bodor teaches prodrug epinephrine compounds, where Bodor teaches the compounds are stable and cleavable to the parent epinephrine compound (col.1, l.40-42). Bodor teaches compounds of Formula I, where R can be methyl and R_1 and R_2 can be an acyl member which is alkanoyl (col.1-2, bridging para). Bodor explicitly teaches compound (7) 3-(trimethylaceloxy)-α-[(methylamino)methyl]benzyl alcohol (col.5, l.18) which corresponds to the claimed R being $-CH_2C(CH_3)_3$. Bodor establishes the claimed species as a known epinephrine compound.

One of ordinary skill in the art would arrive at the instant claims having a reasonable expectation of success based on the combine teaching because Rawas-Qalaji establishes the use of sublingual and buccal formulations of epinephrine compounds generally where Bodor teaches epinephrine prodrugs and particularly a claimed species of epinephrine prodrug. A skilled artisan would glean from Rawas-Qalaji formulating sublingual or buccal epinephrine where it is further taught that any form of epinephrine can be used within the formulation, where Bodor establishes a known form of epinephrine. As mentioned above, the resultant function having a Log P

value in the claimed range is inherent to the structure of the compounds, unless evidence to the contrary. Therefore it was *prima facie* obvious to arrive at the instant claim based on the combined teaching of Rawas-Qalaji and Bodor.

Applicant's invention, according to **claim 3**, limits claim 1 and requires being formulated in a unit dosage form as a rapidly dissolving film.

It is noted that Applicant describes film as that active ingredient incorporated into a sheet, dried and then cut into individual doses (specification, p.3, [0005]).

Rawas-Qalaji teaches formulation in other matrix forms, such as a wafer-like formulation that is quick dissolving (p.6, [0068]) thus Rawas-Qalaji teaches that formulations can be a film that is rapidly dissolving; where a wafer is being broadly and reasonably considered a type of film. Thus the limitation is met and the instant claim remains *prima facie* obvious over the combined art.

Applicant's invention, according to **claims 19-21**, is directed to a compound of the claimed Formula wherein R is $CH(CH_3)_2$ in the alternative formulated for sublingual or buccal administration, where claim 20 requires the species in the alternative and claim 21 requires being formulated in a unit dosage form as a rapidly dissolving film.

As mentioned above Rawas-Qalaji teaches epinephrine sublingual or buccal formulations, where Bodor teaches prodrug species of epinephrine. The claimed species and the taught species by Bodor differ in methyl substitutions on the R group. The courts precedence deems that interchange of alkyl and hydrogen are obvious variants in and of itself (*Ex parte Bluestone*) and not a patentable modification absent

unexpected result (*In re Wood*), particularly where the compounds will have the same properties as the prior art compounds (*In re Dillion*). The claimed modification is provided to generate another prodrug form of epinephrine, thus having the same properties of the embodiment taught by Bodor. Furthermore, Rawas-Qalaji teaches a rapidly dissolving film for sublingual and buccal administration. Therefore the instant claims remain *prima facie* obvious over the combined art of Rawas-Qalaji and Bodor.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI STRONG whose telephone number is (571)272-6333. The examiner can normally be reached on Monday - Friday 8:00 am - 5:00 pm (EST).

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

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on (571)272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

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

/Kortney L. Klinkel/
Primary Examiner, Art Unit 1699

TORI STRONG
Examiner
Art Unit 1629

/TORI STRONG/
Examiner, Art Unit 1629

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/347,625	Almoazen, Hassan
	Examiner	Art Unit
	TORI STRONG	1629

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

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

Search Notes		
Search Notes	Date	Examiner
Review of Global Dossier	12/16/2020	TMS
Structure search performed in STNext	12/16/2020	TMS
Background search in Google	12/16/2020	TMS
Inventor search in PE2E	12/16/2020	TMS

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

/TORI STRONG/ Examiner, Art Unit 1629	

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 096

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

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	
First Named Inventor	Dr. Hassan Almoazen
Art Unit	
Examiner Name	
Attorney Docket Number	24050.0001US

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	3809714	A	1974-05-07	Hussain et al.	Entire Document
	2	3825583	A	1974-07-23	Hussain et al.	Entire Document
	3	4136145	A	1979-01-23	Fuchs et al.	Entire Document
	4	4145441	A	1979-03-20	Bodor	Entire Document
	5	4320144	A	1982-03-16	Resnick	Entire Document

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20030180357	A1	2003-09-25	Martino et al.	Entire Document

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.S/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Dr. Hassan Almoazen
	Art Unit	
	Examiner Name	
	Attorney Docket Number	24050.0001US

	2	20070202163	A1	2007-08-30	Rawas-Qalaji et al.	Entire Document

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	ARYA, A. et. al., "Fast dissolving oral films: An innovative drug delivery system and dosage form," Int. J. ChemTech Res., vol. 2, no. 1, pp. 576–583, 2010.	☐
	2	HUSSAIN, A, Journal of Pharmaceutical Sciences, Vol. 65, No. 10, October 1976, p: 1510-1512.	☐
	3	International Preliminary Report on Patentability PCT/US2017/060761 02.11.2018	☐
	4	International Search Report PCT/US2017/060761 25.01.2018	☐
	5	~~PUBCHEM-CID-70464361~~	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.S/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Dr. Hassan Almoazen
	Art Unit	
	Examiner Name	
	Attorney Docket Number	24050.0001US

	6	~~PUBCHEM-CID-888492~~	☐
	7	RAWAS-QALAJI, et al., Adrenaline (epinephrine) microcrystal sublingual tablet formulation: enhanced absorption in a preclinical model, J of Pharmacy and Pharmacology, 67.pp 20-25 (2014).	☐
	8	RAWAS-QALAJI, M. et. al, Sublingual epinephrine tablets versus intramuscular injection of epinephrine:Dose equivalence for potential treatment of anaphylaxis. J of Allergy Clin Immunol, v 117 no 2, 398 (2006)	☐
	9	SINGH, S. et. al. "Formulation and Evaluation of Rapidly Disintegrating Film of Levocetrizine Hydrochloride," Pharmacia, vol. 2, no. 2, pp. 208--220, 2010.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/TORI STRONG/	Date Considered	12/16/2020

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

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.S/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	
First Named Inventor	Dr. Hassan Almoazen
Art Unit	
Examiner Name	
Attorney Docket Number	24050.0001US

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/susan b fentress/	Date (YYYY-MM-DD)	2019-05-06
Name/Print	Susan B Fentress	Registration Number	31327

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.S/

Bibliographic Data

Application No: 16/347,625

Foreign Priority claimed: ○ Yes ◉ No

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

Verified and Acknowledged: /TORI STRONG/ Examiner's Signature | Initials

Title: PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
05/06/2019	514	1629	24050.0001US
RULE			

APPLICANTS

Iono Pharma, LLC, Bartlett, TN, UNITED STATES

INVENTORS

Hassan Almoazen, Hassan, TN, UNITED STATES

CONTINUING DATA

This application is a 371 of PCT/US2017/060761 11/09/2017

PCT/US2017/060761 has PRO of 62421316 11/13/2016

FOREIGN APPLICATIONS

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07/30/2019

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ADDRESS

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Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103
UNITED STATES

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 NEWS  2  OCT  8  Third 2019 update to Emtree(TM) now available on STN(R)
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                  Status Information.
 NEWS  5  NOV 18  German Patent Full-Text Database DEFULL enhanced
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                  Number of Annual DWPI Updates
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                  in INPADOCDB and INPAFAMDB
 NEWS 12  MAR 10  2020 Version of MEDLINE Now Available on STN(R)
 NEWS 13  MAR 11  First 2020 Update to Emtree(TM) Now Available on STN(R)
 NEWS 14  MAR 26  STN Database Updates Continue as Usual
 NEWS 15  APR  6  Advanced German Patent Full-Text Database DEFULL
                  Replaces Patdpafull
 NEWS 16  APR  6  Announcements from Patent Offices Concerning
                  Coronavirus/COVID-19
 NEWS 17  MAY 18  Patent Kind Code Changes for Korean Patents
 NEWS 18  MAY 29  Second 2020 Update to Emtree(TM) Now Available on STN(R)
 NEWS 19  JUN 26  COMPENDEX - New Fields for Author Identifier and URL
 NEWS 20  JUN 30  Numeric Property Search Added to USPATFULL and USPAT2
 NEWS 21  AUG  5  Chemical and Technology Databases RAPRA, CEABA,
                  and TEMA Add Numeric Property Search
 NEWS 22  OCT  7  EP Appeal Data from European Patent Register Added to
                  INPADOCDB and INPAFAMDB
 NEWS 23  NOV 15  Enhanced INPADOCDB and INPAFAMDB Files
 NEWS 24  NOV 23  Claims Access: WIPO, United States, and China for 1999 -
                  Present.
 NEWS 25  DEC  1  Engineering Flagship Database Inspec Reaches
                  Milestone 20 Million Total Records
 NEWS 26  DEC  1  Full-Text Patent Documents from German Democratic
                  Republic Added to DEFULL

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.18	0.18

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FILE LAST UPDATED: 14 Dec 2020 (20201214/ED)

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FULL ESTIMATED COST	1.18	1.36

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DICTIONARY FILE UPDATES: 14 DEC 2020 HIGHEST RN 2559710-34-6

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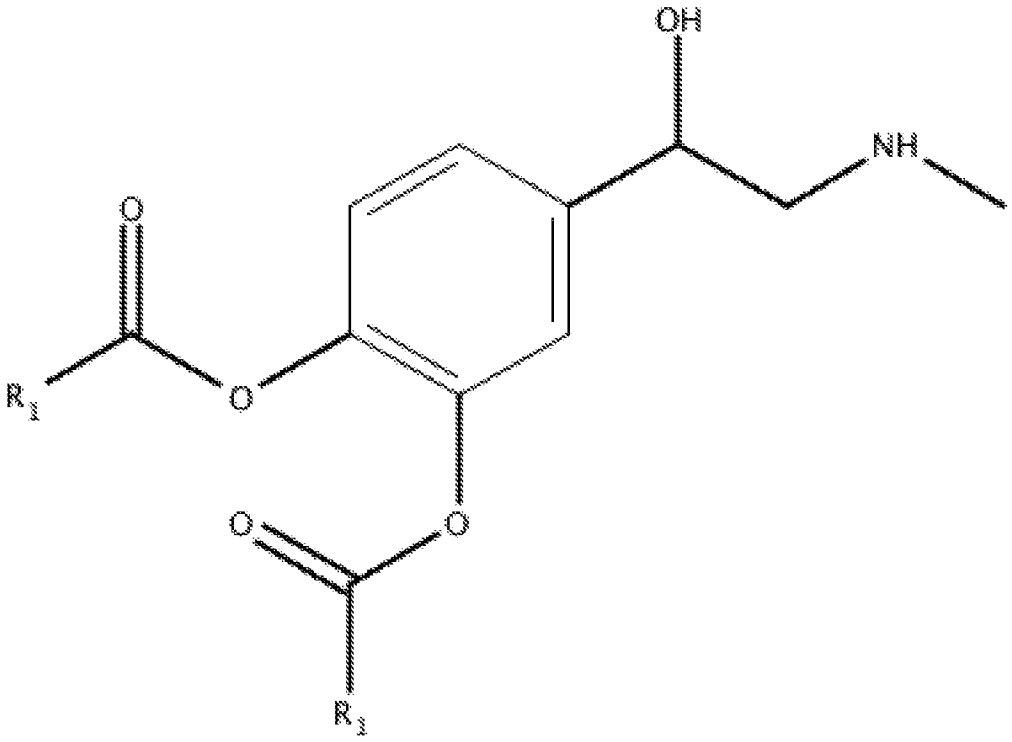
TSCA INFORMATION NOW CURRENT THROUGH March 2020.

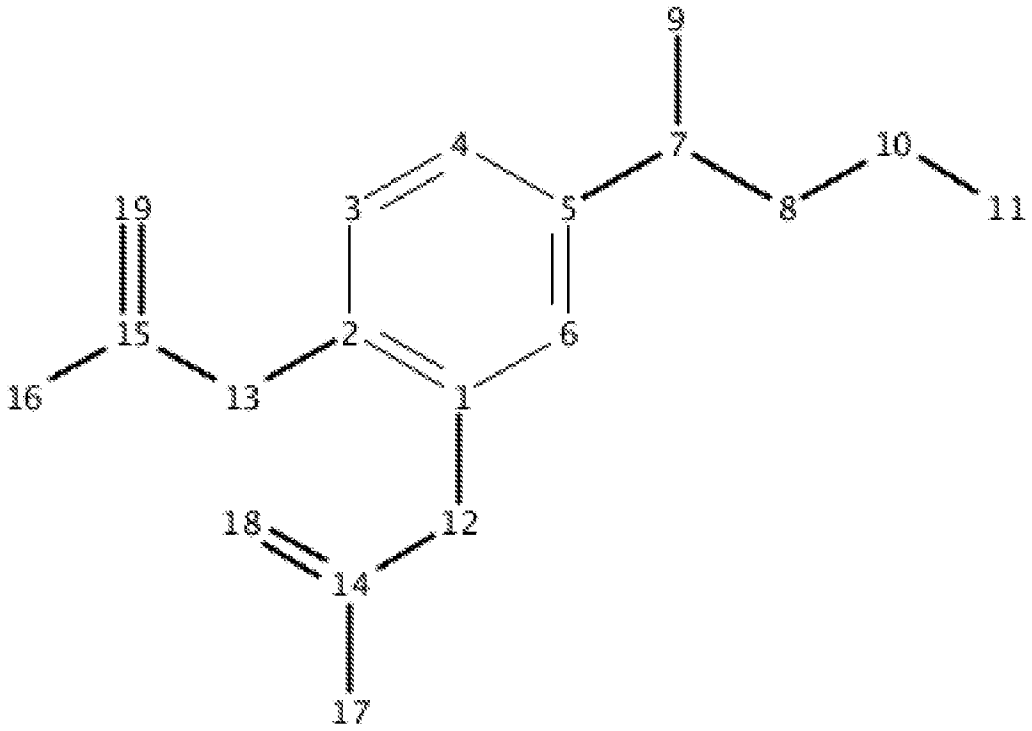
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Uploading structure file: 16347625-1


OH
NH
O
R1
O
O
O
R1



R-Group Definitions
R1: C,H,X,Ak,NH,SH,N,S,Ph
Node Attributes
Ring Nodes : 1 2 3 4 5 6
Chain Nodes : 7 8 11 12 13 14 15 18 19
Bond Attributes
Ring Bonds : 1-2 2-3 3-4 4-5 5-6 6-1
Chain Bonds : 1-12 2-13 5-7 7-8 7-9 8-10 10-11 12-14 13-15 14-17 14-18
15-16 15-19
Normalized Bonds : 1-2 2-3 3-4 4-5 5-6 6-1
Exact/Normalized Bonds : 1-12 2-13 5-7 7-8 7-9 8-10 10-11 12-14 13-15 1
4-17 14-18 15-16 15-19
Markush Attributes
Match Level (ATOM) : 1 2 3 4 5 6
Match Level (CLASS) : 7 8 9 10 11 12 13 14 15 18 19
Element Count Level (LIMITED) : 1 2 3 4 5 6 7 8 9 10 11 12 13 14 1
5 18 19

L1 STRUCTURE UPLOADED

=> s l1 sss sam

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SAMPLE SCREEN SEARCH COMPLETED - 83 TO ITERATE

100.0% PROCESSED 83 ITERATIONS 10 ANSWERS

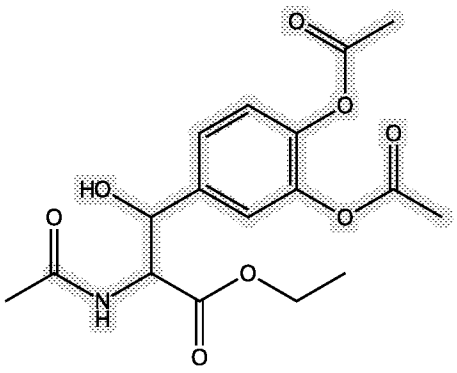
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 1114 TO 2206
PROJECTED ANSWERS: 11 TO 389

L2 10 SEA SSS SAM L1

=> d scan

L2 10 ANSWERS REGISTRY COPYRIGHT 2020 ACS on STN
IN Tyrosine, N-acetyl-3-(acetyloxy)-β-hydroxy-, ethyl ester, 4-acetate (9CI)
MF C17 H21 N O8



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> s l1 sss full

FULL SEARCH INITIATED 17:04:48 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 2072 TO ITERATE

100.0% PROCESSED 2072 ITERATIONS 301 ANSWERS

SEARCH TIME: 00.00.01

L3 301 SEA SSS FUL L1

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	464.11	465.47

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FILE LAST UPDATED: 14 Dec 2020 (20201214/ED)

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L4         433 L3

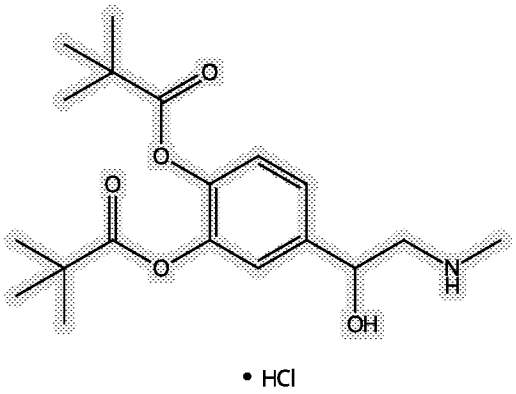
=> s l4 and (sublingual or buccal)

          11286 SUBLINGUAL
              4 SUBLINGUALS
          11287 SUBLINGUAL
                  (SUBLINGUAL OR SUBLINGUALS)
          21273 BUCCAL
              2 BUCCALS
          21273 BUCCAL
                  (BUCCAL OR BUCCALS)
L5           11 L4 AND (SUBLINGUAL OR BUCCAL)

=> d l5 1-11 ibib abs hitstr


L5   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER:        2020:2193419  CAPLUS Full-text
TITLE:                   Quinoline compound or pharmaceutically acceptable salt
                         thereof for treating giant cell tumor of bone
INVENTOR(S):             Xu, Ping; Wang, Chengqian
PATENT ASSIGNEE(S):      Chia Tai Tianqing Pharmaceutical Group Co., Ltd.,
                         Peop. Rep. China
SOURCE:                  Faming Zhuanli Shenqing, 14pp.
                         CODEN: CNXXEV
DOCUMENT TYPE:           Patent
LANGUAGE:                Chinese
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:
     PATENT NO.          KIND  DATE        APPLICATION NO.         DATE
     ---------------     ----  --------    ----------------------  --------
     CN 111840289         A    20201030    CN 2019-10348530        20190428
PRIORITY APPLN. INFO.:                    CN 2019-10348530        20190428
AB   The present invention relates to the application of a therapeutically
     effective amt. of quinoline compd. I or a pharmaceutically acceptable salt
     thereof in the prepn. of a medicament for treating giant cell tumor of
     bone, and the application of a therapeutically effective amt. of quinoline
     compd. I or a pharmaceutically acceptable salt thereof in combination with
     a second therapeutic agent in the prepn. of a combined medicine for
     treating giant cell tumor of bone.  Quinoline compd. I has a chem. name
     1-[[[4-(4-fluoro-2-methyl-1H-indol-5-yl)
     oxy-6-methoxyquinolin-7-yl]oxy]methyl]cyclopropanamine.
IT   INDEXING IN PROGRESS
IT   64019-93-8, Dipivefrin Hydrochloride
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (quinoline compd. or pharmaceutically acceptable salt thereof for
        treating giant cell tumor of bone)
RN   64019-93-8  CAPLUS
CN   Propanoic acid, 2,2-dimethyl-, 1,1'-[4-[1-hydroxy-2-(methylamino)ethyl]-
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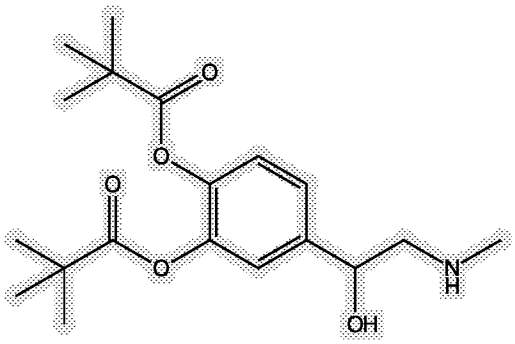
1,2-phenylene] ester, hydrochloride (1:1) (CA INDEX NAME)



L5 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER: 2019:168236 CAPLUS Full-text
DOCUMENT NUMBER: 170:237067
TITLE: Enhanced delivery epinephrine and prodrug compositions
INVENTOR(S): Schobel, Alexander Mark; Varjan, Stephanie Marie; Wargacki, Stephen Paul
PATENT ASSIGNEE(S): Aquestive Therapeutics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 59pp., Cont.-in-part of U.S. Ser. No. 791,249.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20190022023	A1	20190124	US 2018-16143821		20180927
US 20170348251	A1	20171207	US 2017-15587364		20170504
US 20180125977	A1	20180510	US 2017-15717859		20170927
US 20180104195	A1	20180419	US 2017-15791249		20171023
PRIORITY APPLN. INFO.:			US 2016-62331996	P	20160505
			US 2017-15587364	A2	20170504
			US 2017-15717859	A2	20170927
			US 2017-15791249	A2	20171023

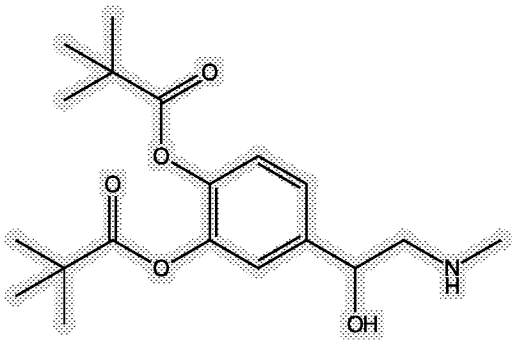
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2019:168236
AB Pharmaceutical compns. having enhanced active component permeation properties are described.
IT 52365-63-6, Dipivefrin
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhanced delivery epinephrine and prodrug compns.)
RN 52365-63-6 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 1,1'-[4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester (CA INDEX NAME)



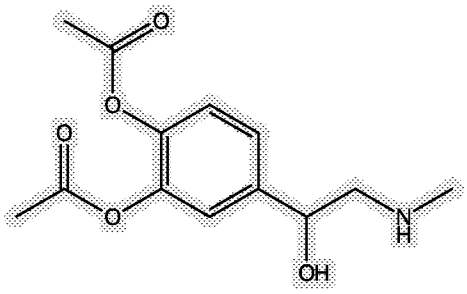
L5 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER: 2018:953917 CAPLUS Full-text
DOCUMENT NUMBER: 169:11381
TITLE: Pharmaceutical formulation for sublingual or buccal delivery of epinephrine
INVENTOR(S): Almoazen, Hassan; Haynes, Lindsay
PATENT ASSIGNEE(S): Iono Pharma, LLC, USA
SOURCE: PCT Int. Appl., 32pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2018089570	A1	20180517	WO 2017-US60761		20171109
CN 110418639	A	20191105	CN 2017-80083246		20171109
US 20190337886	A1	20191107	US 2019-16347625		20190506
PRIORITY APPLN. INFO.:			US 2016-62421316	P	20161113
			WO 2017-US60761	W	20171109

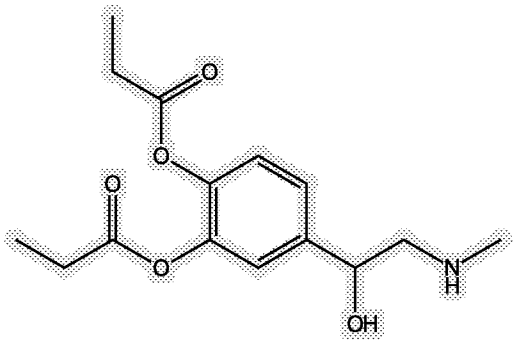
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 169:11381; CASFORMULTNS 2018:953917
AB The present invention relates to a pharmaceutical compn. for the treatment of anaphylaxis formulated for rapid delivery, in one embodiment, the delivery vehicle is a rapidly dissolvmg film. The films contain an epinephrine or a novel epinephrine pro-drag for fee rapid treatment of anaphylaxis in a patient. This invention relates to pharmaceutical compns. made by modifying the physicoehemieal properties of epinephrine in order to enhance its permeability through biol. membranes (sublingual and buccal membranes). Several prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring, by chem. reacting the two groups with several acid moieties to form an ester bond with different alkyl chains. The addn. of an alkyl group will enhance the lipophilicity of epinephrine (increase log P) and will consequently increase its permeability through the biol. membranes (sublingual and buccal tissues in the oral cavity).
IT 52365-63-6 104714-60-5 1195867-43-6
2226477-75-2
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation for sublingual or buccal delivery of epinephrine)
RN 52365-63-6 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 1,1'-[4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester (CA INDEX NAME)



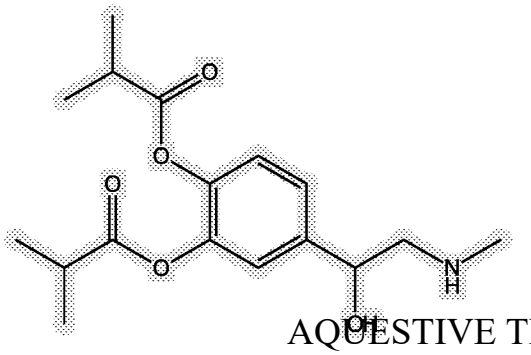
RN 104714-60-5 CAPLUS
CN 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, 1,2-diacetate (CA INDEX NAME)



RN 1195867-43-6 CAPLUS
CN 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, 1,2-dipropanoate (CA INDEX NAME)



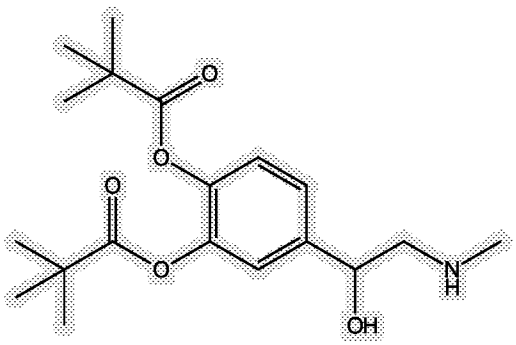
RN 2226477-75-2 CAPLUS
CN Propanoic acid, 2-methyl-, 1,1'-[4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester (CA INDEX NAME)



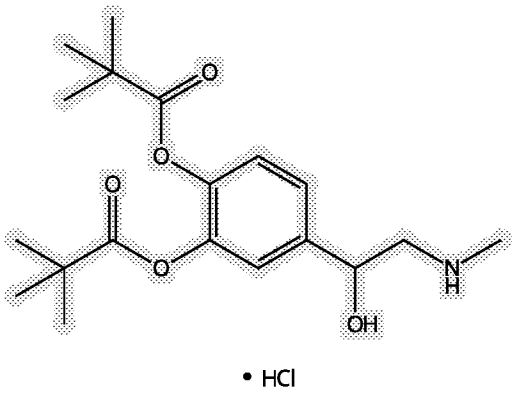
L5 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER: 2017:388962 CAPLUS Full-text
DOCUMENT NUMBER: 166:319668
TITLE: Micelles comprising hydrophilic polymers for mucoadhesive drug delivery
INVENTOR(S): Sheardown, Heather; Prosperi-Porta, Graeme; Kedzior, Stephanie; Muirhead, Benjamin
PATENT ASSIGNEE(S): McMaster University, Can.
SOURCE: PCT Int. Appl., 38pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2017035656	A1	20170309	WO 2016-CA51038		20160901
CA 2996910	A1	20170309	CA 2016-2996910		20160901
EP 3344232	A1	20180711	EP 2016-840475		20160901
JP 2018526438	T	20180913	JP 2018-529696		20160901
US 20180265694	A1	20180920	US 2018-15756758		20180301
US 10611908	B2	20200407			
PRIORITY APPLN. INFO.:			US 2015-62212784	P	20150901
			WO 2016-CA51038	W	20160901

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2017:388962
AB Biocompatible block copolymer micelles for use in mucoadhesive drug delivery are provided. The micelles comprise a degradable hydrophobic polymer, a degradable synthetic hydrophilic polymer and a mucoadhesive polymer. The micelles are particularly useful for ophthalmic uses.
IT 52365-63-6, Dipivefrin 64019-93-8, Propine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(micelles comprising hydrophilic polymers for mucoadhesive drug delivery)
RN 52365-63-6 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 1,1'-[4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester (CA INDEX NAME)



RN 64019-93-8 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 1,1'-[4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester, hydrochloride (1:1) (CA INDEX NAME)

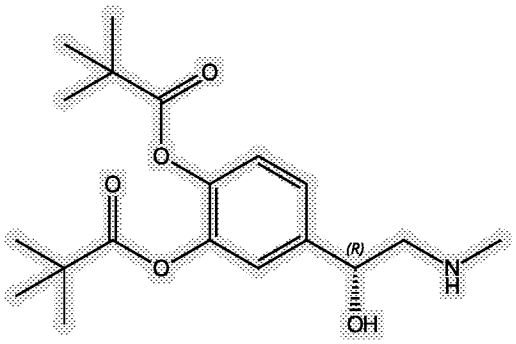


• HCl

L5 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER: 2016:1956619 CAPLUS Full-text
DOCUMENT NUMBER: 166:530773
TITLE: Treatment of effect of chemicals with their ultradilute stereoisomers
INVENTOR(S): Kuzeff, Reinhard Michael
PATENT ASSIGNEE(S): Australia
SOURCE: U.S., No pp. given
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 8071630	B2	20111206	US 2004-505956		20040827
US 20050119350	A1	20050602			
WO 2003072105	A1	20030904	WO 2003-AU219		20030228
US 20120136020	A1	20120531	US 2011-13304618		20111126
US 20130338181	A1	20131219	US 2013-13969590		20130818
PRIORITY APPLN. INFO.:			AU 2002-796	A	20020228
			AU 2002-925	A	20020306
			AU 2002-950351	A	20020722
			AU 2003-900353	A	20030124
			AU 2003-900716	A	20030219
			WO 2003-AU219	W	20030228
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			US 2011-13304618	B1	20111126

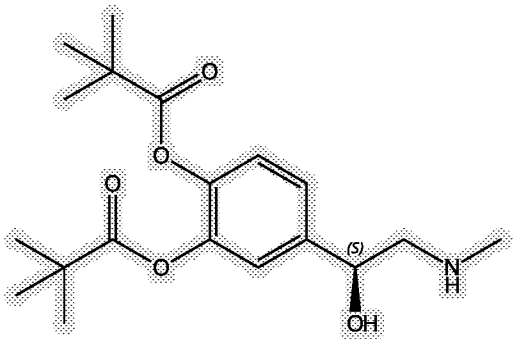
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB A method of treating an effect of a chem. agent, which agent is characterized by one or more chiral centers, by administering a diln. or an ultra-high diln. or potentised prepn. of a stereoisomer of said chem. agent.
IT 79071-01-5 133815-41-5
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of adverse effect of chems. such as drugs with their ultradilute stereoisomers)
RN 79071-01-5 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 1,1'-[4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester, hydrochloride (1:1) (CA INDEX NAME)



• HCl

Absolute stereochemistry shown

RN 133815-41-5 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 4-[(1S)-1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene ester, hydrochloride (9CI) (CA INDEX NAME)



• HCl

Absolute stereochemistry shown

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER: 2016:1847241 CAPLUS Full-text
DOCUMENT NUMBER: 166:33567
TITLE: Pharmaceutical composition of dipivefrine hydrochloride and application in biomedicine thereof
INVENTOR(S): Ding, Yuting
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 7pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 106109459	A	20161116	CN 2016-10466130	20160622

PRIORITY APPLN. INFO.: CN 2016-10466130 20160622

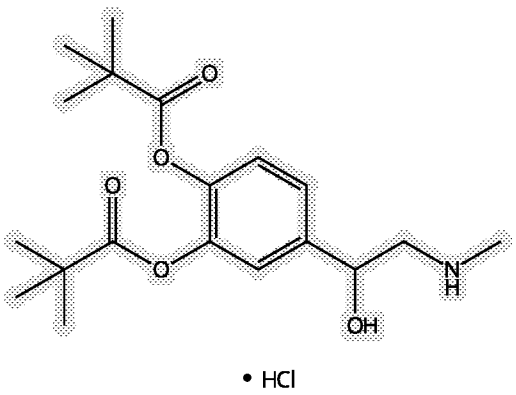
AB The present invention discloses a pharmaceutical compn. of dipivefrine hydrochloride and its use in biomedicine. The pharmaceutical compn. of the present invention provides dipivefrine hydrochloride and a novel natural compd. I, dipivefrine hydrochloride and compd. I have the therapeutic effect on the kidney-yang deficiency of mice when the compd. I

is alone. When the combination of the dipivefrine hydrochloride and the compd. I can be further developed into a drug for treating kidney-yang deficiency, which has outstanding substantive characteristics and remarkable progress compared with the prior art.

IT 64019-93-8, Dipivefrine hydrochloride
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compn. of dipivefrine hydrochloride and application in biomedicine thereof)

RN 64019-93-8 CAPLUS

CN Propanoic acid, 2,2-dimethyl-, 1,1'-[4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester, hydrochloride (1:1) (CA INDEX NAME)



L5 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2020 ACS on STN

ACCESSION NUMBER: 2006:238357 CAPLUS Full-text

DOCUMENT NUMBER: 144:318557

TITLE: Preparation, compositions and uses of mixtures of polypeptides

INVENTOR(S): Pinchasi, Irit; Dolitzky, Ben-Zion; Frenkel, Anton; Schwartz, Michal; Arnon, Ruth; Aharoni, Rina

PATENT ASSIGNEE(S): Teva Pharmaceutical Industries, Ltd., Israel; Teva Pharmaceuticals USA, Inc.; Yeda Research and Development Co. Ltd.

SOURCE: PCT Int. Appl., 197 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2006029411	A2	20060316	WO 2005-US32553		20050909
WO 2006029411	A3	20060803			
US 20060122113	A1	20060608	US 2005-223408		20050909
US 7560100	B2	20090714			
EP 1797109	A2	20070620	EP 2005-795337		20050909
EP 1797109	B1	20160224			
IL 181802	A	20120830	IL 2005-181802		20050909
ES 2572811	T3	20160602	ES 2005-795337		20050909
US 20070054857	A1	20070308	US 2006-541263		20060929
PRIORITY APPLN. INFO.:			US 2004-60608844	P	20040909
			US 2005-223408	A1	20050909
			WO 2005-US32553	W	20050909

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2006:238357

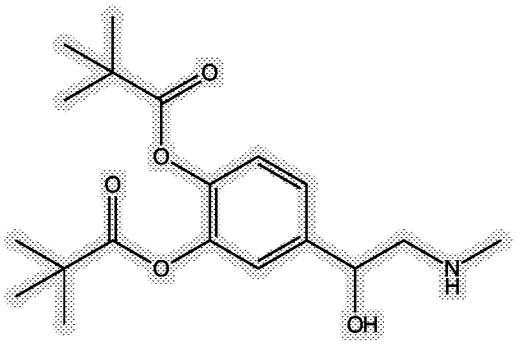
AB The invention provides a compn. comprising a mixt. of polypeptides, wherein each polypeptide (a) is a copolymer of the amino acids L-glutamic acid, L-alanine, L-tyrosine, and L-lysine, and (b) may be in the form of a pharmaceutically acceptable salt. In the mixt. (i) the polypeptides have an av. mol. wt. in the range 13,500 to 18,500 daltons, (ii) 13% to 38% of the polypeptides have a diethylamide group instead of a carboxyl group

present at one end thereof, and (iii) 68% of the polypeptides have a mol. wt. between 7000 and 41,000 daltons. The av. mol. wt. of polypeptides is 16,000 daltons. Processes for prepg. the mixt. of polypeptides and its therapeutic uses are described. For example, an injection formulation contg. the polypeptide mixt. 5 mg, mannitol 50 mg, and water for injection to 1.0 mL was prepd. and packaged in Hypak syringe. Also, the biol. activity of prepns. of different mol. wt. (MW) was evaluated by their ability to block the induction of exptl. autoimmune encephalomyelitis (EAE) in mice by reducing the no. of sick animals and lowering the severity of disease (clin. score). The results were compared to that of glatiramer acetate (GA). The effect of increase in MW on biol. activity was obsd. At the dose of 25 μg/mouse, GA blocking activity was suboptimal while prepns. with MW ranging between 15 and 20 KDa were more effective in inhibiting acute EAE. At the dose of 50 μg/mouse, GA (7.5 daltons) was not effective in inhibiting chronic myelin oligodendrocyte glycoprotein (MOG)-induced EAE, while the mixt. of polypeptides of the invention (~ 16.0 KD) had a significant inhibitory effect.

IT 52365-63-6, Dipivefrin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic combinations contg. mixts. of polypeptides comprising alanine, glutamic acid, lysine and tyrosine)

RN 52365-63-6 CAPLUS

CN Propanoic acid, 2,2-dimethyl-, 1,1'-[4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester (CA INDEX NAME)



OS.CITING REF COUNT: 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS RECORD (24 CITINGS)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2020 ACS on STN

ACCESSION NUMBER: 2005:55116 CAPLUS Full-text

DOCUMENT NUMBER: 142:141267

TITLE: Film comprising therapeutic agents

INVENTOR(S): Maibach, Todd

PATENT ASSIGNEE(S): USA

SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

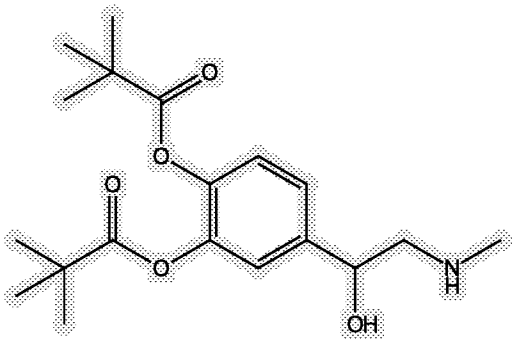
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

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WO 2005004989	A2	20050120	WO 2004-US21038		20040630
WO 2005004989	A3	20050616			
CA 2530843	A1	20050120	CA 2004-2530843		20040630
EP 1648362	A2	20060426	EP 2004-777314		20040630
CN 1829490	A	20060906	CN 2004-80022053		20040630
US 20070059346	A1	20070315	US 2006-562633		20060609
US 20120121724	A1	20120517	US 2012-13355414		20120120
PRIORITY APPLN. INFO.:			US 2003-60484009	P	20030701
			US 2003-60497426	P	20030821

	WO 2004-US21038	W	20040630
	US 2006-562633	B1	20060609

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2005:55116
AB The present invention is related to the compn. and methods of manuf. of orally-dissolvable, edible films as a vehicle for the non-invasive administration of nitroglycerin, as well as other therapeutic agents either with or without nitroglycerin, through the mucosal tissues of the oral cavity. The films include a water-sol. film-forming polymer, such as pullulan. Methods for producing the films are also disclosed.
IT 52365-63-6, Dipivefrin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(buccal tapes comprising therapeutic agents)
RN 52365-63-6 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 1,1'-[4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester (CA INDEX NAME)

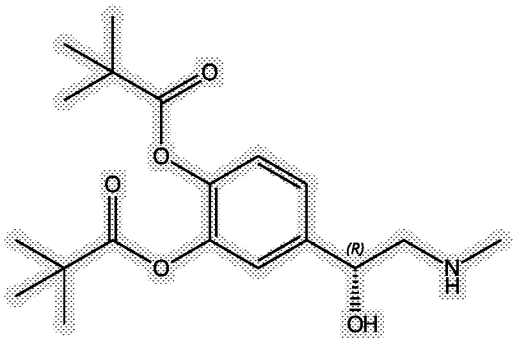


OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER: 2003:696739 CAPLUS Full-text
DOCUMENT NUMBER: 139:207830
TITLE: Treatment of effect of chemicals with their ultradilute stereoisomers
INVENTOR(S): Kuzeff, Reinhard Michael
PATENT ASSIGNEE(S): Sempach Pty. Ltd., Australia
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003072105	A1	20030904	WO 2003-AU219	20030228
CA 2505984	A1	20030904	CA 2003-2505984	20030228
AU 2003208170	A1	20030909	AU 2003-208170	20030228
AU 2003208170	B2	20061123		
EP 1487448	A1	20041222	EP 2003-706123	20030228
NZ 535654	A	20101224	NZ 2003-535654	20030228
US 8071630	B2	20111206	US 2004-505956	20040827
US 20050119350	A1	20050602		
IN 2004DN02704	A	20090403	IN 2004-DN2704	20040914
IN 246566	B	20110311		
US 20120136020	A1	20120531	US 2011-13304618	20111126
US 20130338181	A1	20131219	US 2013-13969590	20130818
PRIORITY APPLN. INFO.:			AU 2002-796 A	20020228
			AU 2002-925 A	20020306
			AU 2002-950351 A	20020722
			AU 2003-900353 A	20030124

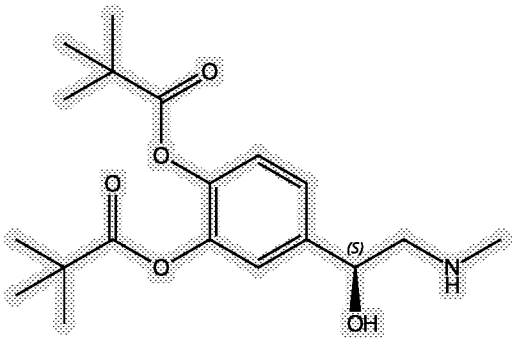
AU 2003-900716 A 20030219
WO 2003-AU219 W 20030228
US 2004-505956 A1 20040827
US 2011-13304618 B1 20111126
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2003:696739
AB A method of treating an adverse effect of a chem. agent such as a drug, which agent is characterized by one or more chiral centers, by administering a diln. or an ultra-high diln. or potentised prepn. of a stereoisomer of said chem. agent.
IT 79071-01-5 133815-41-5
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of adverse effect of chems. such as drugs with their ultradilute stereoisomers)
RN 79071-01-5 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 1,1'-[4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester, hydrochloride (1:1) (CA INDEX NAME)



• HCl

Absolute stereochemistry shown

RN 133815-41-5 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 4-[(1S)-1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene ester, hydrochloride (9CI) (CA INDEX NAME)



• HCl

Absolute stereochemistry shown

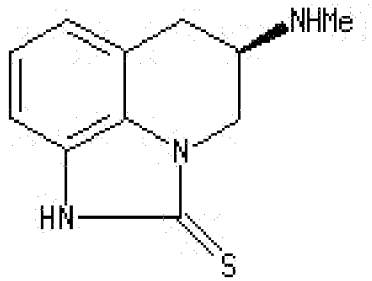
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2020 ACS on STN

ACCESSION NUMBER: 2003:633448 CAPLUS Full-text
DOCUMENT NUMBER: 139:185666
TITLE: Coated pharmaceutical tablets with speckled appearance
INVENTOR(S): Martino, Alice C.; Noack, Robert M.; Pierman, Steven A.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

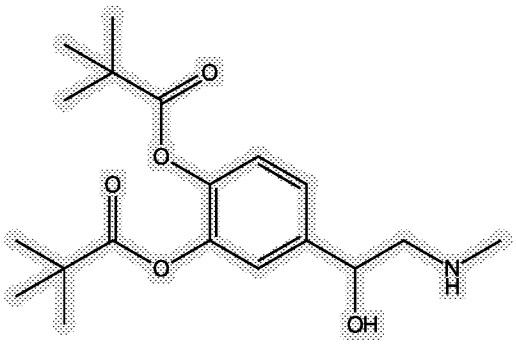
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003066030	A2	20030814	WO 2003-US3837		20030206
WO 2003066030	A3	20031016			
CA 2474921	A1	20030814	CA 2003-2474921		20030206
AU 2003210930	A1	20030902	AU 2003-210930		20030206
AU 2003210930	B2	20070104			
US 20030180357	A1	20030925	US 2003-359939		20030206
EP 1480624	A2	20041201	EP 2003-737712		20030206
EP 1480624	B1	20061129			
BR 2003007593	A	20050201	BR 2003-7593		20030206
JP 2005517693	T	20050616	JP 2003-565454		20030206
JP 4174426	B2	20081029			
CN 1630512	A	20050622	CN 2003-803580		20030206
CN 1267087	C	20060802			
NZ 533957	A	20060224	NZ 2003-533957		20030206
RU 2273473	C2	20060410	RU 2004-124065		20030206
AT 346591	T	20061215	AT 2003-737712		20030206
ES 2274248	T3	20070516	ES 2003-737712		20030206
MX 2004006799	A	20041206	MX 2004-6799		20040713
ZA 2004005556	A	20050810	ZA 2004-5556		20040713
IN 2004DN02122	A	20071019	IN 2004-DN2122		20040722
IN 219622	B	20080627			
CO 5611097	A2	20060228	CO 2004-77266		20040809
NO 2004003716	A	20040906	NO 2004-3716		20040906
HK 1074581	A1	20061020	HK 2005-106918		20050811
PRIORITY APPLN. INFO.:			US 2002-60355705	P	20020207
			WO 2003-US3837	W	20030206

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 139:185666; CASFORMULTNS 2003:633448
GI



AB A pharmaceutical tablet is provide comprising a core and a coating adherent thereto, wherein (a) the core comprises solid particles of a water-sol. dye distributed in a matrix and (b) the coating comprises gellan gum. The tablet is suitable for peroral or intraoral administration, for example for delivery of a drug contained in the core of the tablet to a subject. The tablet has a speckled appearance that renders the tablet readily identifiable.
IT 52365-63-6, Dipivefrin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(active ingredients for coated pharmaceutical tablets with speckled appearance)

RN 52365-63-6 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 1,1'-[4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester (CA INDEX NAME)

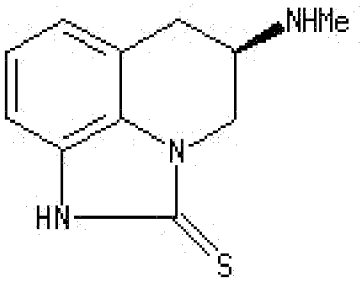


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REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER: 2003:633447 CAPLUS Full-text
DOCUMENT NUMBER: 139:185665
TITLE: Pharmaceutical dosage form for mucosal delivery
INVENTOR(S): Martino, Alice C.; Pierman, Steven A.; Noack, Robert M.; Britten, Nancy
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003066029	A2	20030814	WO 2003-US3836		20030206
WO 2003066029	A3	20031016			
CA 2474190	A1	20030814	CA 2003-2474190		20030206
AU 2003215110	A1	20030902	AU 2003-215110		20030206
AU 2003215110	B2	20071129			
US 20030235617	A1	20031225	US 2003-360167		20030206
EP 1471890	A2	20041103	EP 2003-710927		20030206
EP 1471890	B1	20060927			
BR 2003007473	A	20041109	BR 2003-7473		20030206
CN 1627938	A	20050615	CN 2003-803419		20030206
CN 100346832	C	20071107			
JP 2005519924	T	20050707	JP 2003-565453		20030206
NZ 534340	A	20060428	NZ 2003-534340		20030206
AT 340565	T	20061015	AT 2003-710927		20030206
RU 2285520	C2	20061020	RU 2004-124057		20030206
PT 1471890	E	20070131	PT 2003-710927		20030206
ES 2271542	T3	20070416	ES 2003-710927		20030206
ZA 2004005614	A	20050627	ZA 2004-5614		20040714
IN 2004DN02055	A	20090313	IN 2004-DN2055		20040716
CO 5611096	A2	20060228	CO 2004-76758		20040806
MX 2004007728	A	20041110	MX 2004-7728		20040809
NO 2004003723	A	20040906	NO 2004-3723		20040906
PRIORITY APPLN. INFO.:			US 2002-60355703	P	20020207
			WO 2003-US3836	W	20030206

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 139:185665; CASFORMULTNS 2003:633447
GI

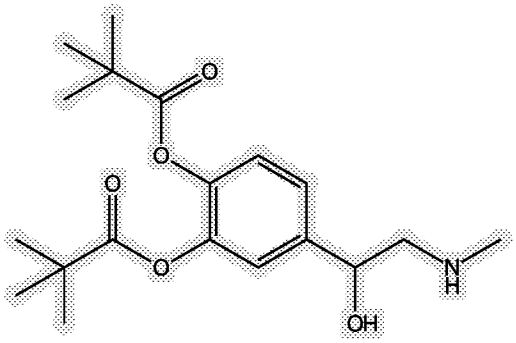


AB A pharmaceutical tablet is provided comprising an intraorally disintegratable core and an excipient coating adherent thereto, wherein the coating comprises gellan gum. The tablet is suitable for intraoral administration, for example for delivery of a drug contained in the core of the tablet to a subject, at least in part by absorption of the drug via oral mucosa of the subject.

IT 52365-63-6, Dipivefrin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(active ingredients for coated sublingual tablets)

RN 52365-63-6 CAPLUS

CN Propanoic acid, 2,2-dimethyl-, 1,1'-[4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester (CA INDEX NAME)



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L3 301 S L1 SSS FULL

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L5 11 S L4 AND (SUBLINGUAL OR BUCCAL)

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file reg

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FULL ESTIMATED COST                                       0.18       0.18

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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
COPYRIGHT (C) 2020 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   14 DEC 2020  HIGHEST RN 2559710-34-6
DICTIONARY FILE UPDATES:  14 DEC 2020  HIGHEST RN 2559710-34-6

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http://www.cas.org/legal/infopolicy

TSCA INFORMATION NOW CURRENT THROUGH March 2020.

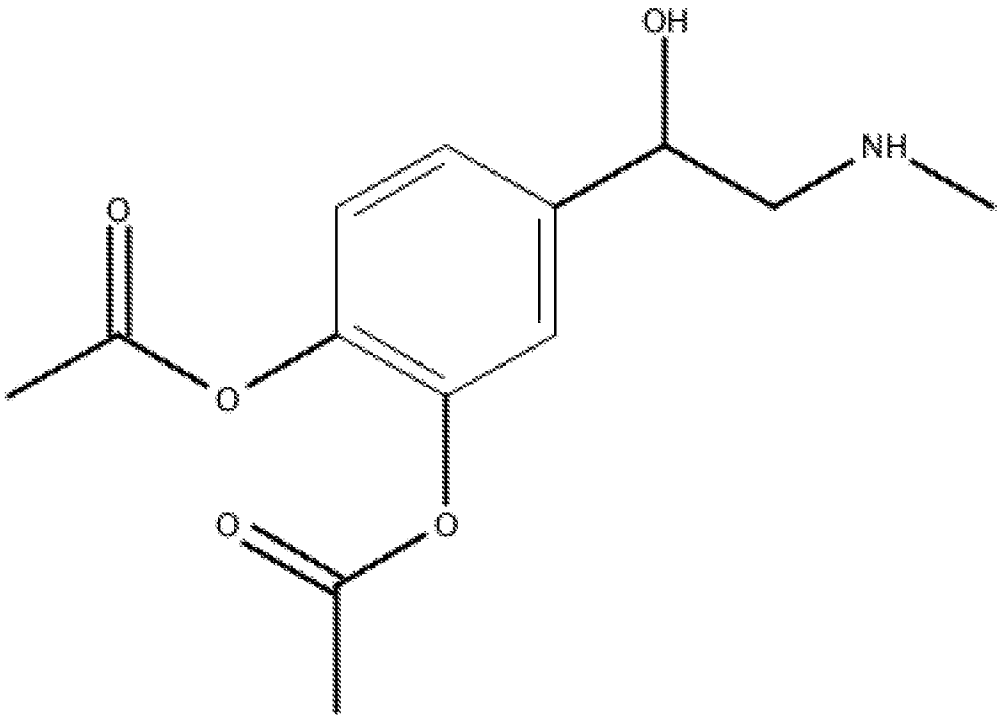
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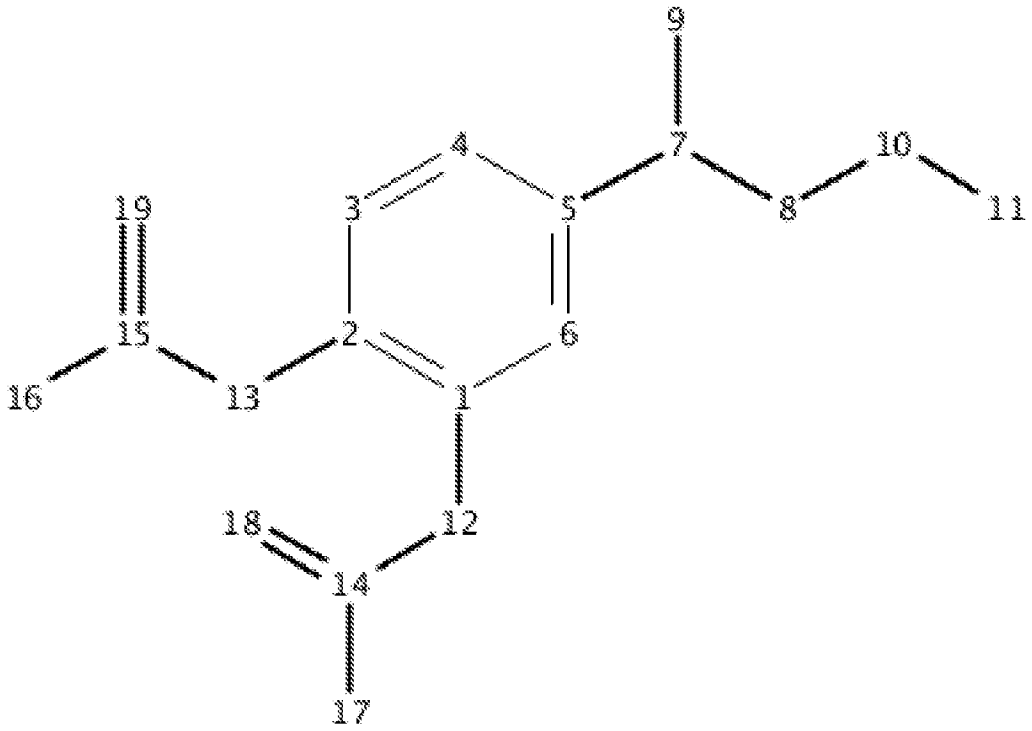
REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:



http://www.cas.org/training/stn/database-specific

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O
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Chain Nodes : 7 8 11 12 13 14 15 16 17 18 19
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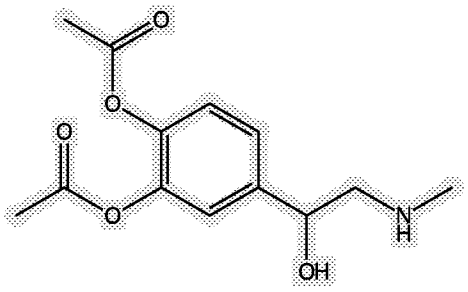
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PROJECTED ITERATIONS: 2 TO   124
PROJECTED ANSWERS: 1 TO   80

L2   1 SEA EXA SAM L1

=> d scan

L2   1 ANSWERS   REGISTRY COPYRIGHT 2020 ACS on STN
IN   1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, 1,2-diacetate
MF   C13 H17 N O5
CI   COM



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

=> s l1 exact full

FULL SEARCH INITIATED 20:37:09 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   4 TO ITERATE

100.0% PROCESSED   4 ITERATIONS   2 ANSWERS

SEARCH TIME: 00.00.01

L3   2 SEA EXA FUL L1

=> file caplus

COST IN U.S. DOLLARS   SINCE FILE   TOTAL
                                                         ENTRY   SESSION
FULL ESTIMATED COST   158.71   158.89

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FILE COVERS 1907 - 16 Dec 2020 VOL 174 ISS 1
FILE LAST UPDATED: 15 Dec 2020 (20201215/ED)

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

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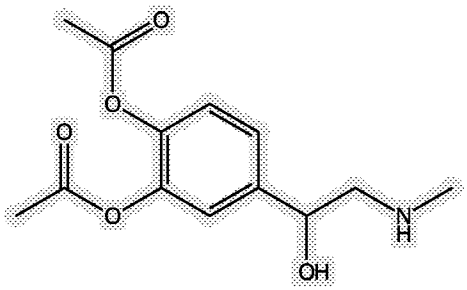
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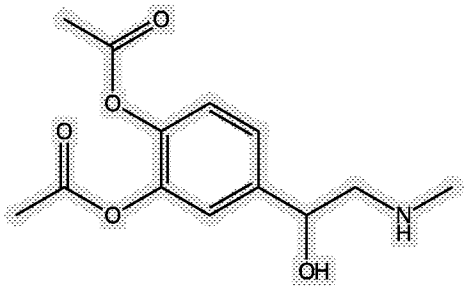
L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER: 2018:953917 CAPLUS Full-text
DOCUMENT NUMBER: 169:11381
TITLE: Pharmaceutical formulation for sublingual or buccal delivery of epinephrine
INVENTOR(S): Almoazen, Hassan; Haynes, Lindsay
PATENT ASSIGNEE(S): Iono Pharma, LLC, USA
SOURCE: PCT Int. Appl., 32pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2018089570	A1	20180517	WO 2017-US60761		20171109
CN 110418639	A	20191105	CN 2017-80083246		20171109
US 20190337886	A1	20191107	US 2019-16347625		20190506
PRIORITY APPLN. INFO.:			US 2016-62421316	P	20161113
			WO 2017-US60761	W	20171109

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 169:11381; CASFORMULTNS 2018:953917
AB The present invention relates to a pharmaceutical compn. for the treatment of anaphylaxis formulated for rapid delivery, in one embodiment, the delivery vehicle is a rapidly dissolvmg film. The films contain an epinephrine or a novel epinephrine pro-drag for fee rapid treatment of anaphylaxis in a patient. This invention relates to pharmaceutical compns. made by modifying the physicoehemieal properties of epinephrine in order to enhance its permeability through biol. membranes (sublingual and buccal membranes). Several prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring, by chem. reacting the two groups with several acid moieties to form an ester bond with different alkyl chains. The addn. of an alkyl group will enhance the lipophilicity of epinephrine (increase log P) and will consequently increase its permeability through the biol. membranes (sublingual and buccal tissues in the oral cavity).
IT 104714-60-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation for sublingual or buccal delivery of epinephrine)
RN 104714-60-5 CAPLUS
CN 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, 1,2-diacetate (CA INDEX NAME)



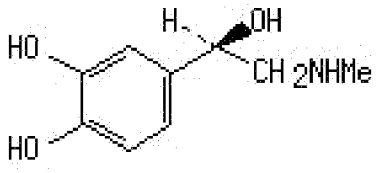
L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER: 1986:572151 CAPLUS Full-text
DOCUMENT NUMBER: 105:172151
ORIGINAL REFERENCE NO.: 105:27733a,27736a
TITLE: Improved synthesis of adrenaline
AUTHOR(S): Yang, Paw Wang; Huang, Ya Yung
CORPORATE SOURCE: Dep. Chem., Natl. Taiwan Univ., Taipei, Taiwan
SOURCE: Huaxue (1985), 43(1), 19-29
CODEN: HUHSA2; ISSN: 0441-3768
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB The synthesis and resoln. of dl-adrenaline [dl-3,4-(OH)2C6H3CH(OH)CH2NHMe (I)] and dl-noradrenaline [dl-3,4-(OH)2C6H3CH(OH)CH2NH2 (II)] were reviewed and modified. I was prepd. in 84% overall yield from o-C6H4(OH)2 via acylation with ClCH2CO2H and amination with MeNH2 followed by catalytic hydrogenation. II was prepd. from 3,4-(MeO)HOC6H3CHO via demethylation, bisacetylation, addn. reaction with MeNO2 to give 3,4-(AcO)2C6H3CH(OH)CH2NO2, followed by catalytic hydrogenation.
IT 104714-60-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and hydrolysis of)
RN 104714-60-5 CAPLUS
CN 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, 1,2-diacetate (CA INDEX NAME)



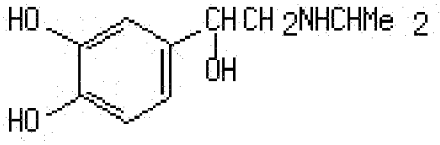
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER: 1978:58723 CAPLUS Full-text
DOCUMENT NUMBER: 88:58723
ORIGINAL REFERENCE NO.: 88:9223a,9226a
TITLE: Aerosolized or intravenous catecholamines: cardiovascular effects in awake rats
AUTHOR(S): Bunag, Ruben D.; Riley, Elinor; Walaszek, Edward J.
CORPORATE SOURCE: Coll. Health Sci., Univ. Kansas Med. Cent., Kansas City, KS, USA
SOURCE: General Pharmacology (1977), 8(4), 269-73

CODEN: GEPHDP; ISSN: 0306-3623
DIGITAL OBJECT ID: 10.1016/0306-3623(77)90025-8
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



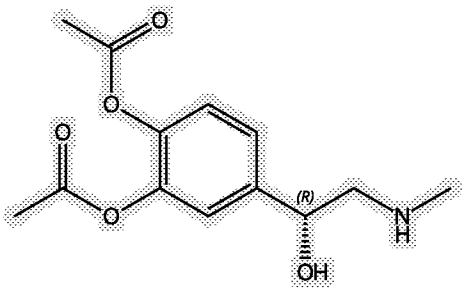
I



II

AB To compare the cardiovascular effects of epinephrine (I) [51-43-4] and isoproterenol (II) [7683-59-2] derivs., drugs were injected i.v. or given as aerosols while aortic pressures and heart rates were recorded continuously in unanesthetized rats. Cardiovascular responses to aerosols always started later but lasted longer than those to i.v. injections. I derivs. invariably elevated aortic pressure whereas II derivs. lowered it. Heart rate responses varied from decreases by I, irregular effects by diacetylepinephrine [65279-36-9], to increases by dipivalylepinephrine [56298-24-9]; by contrast, II derivs. consistently increased heart rate and for i.v. doses this effect was dose-dependent. Since diacetylisoproterenol [35553-62-9] and dipivalylisoproterenol [65114-85-4] were both weaker than II in causing tachycardia, chronotropic side-effects may be lessened when these drugs are used for treating bronchial asthma.

IT 65279-36-9
RL: PRP (Properties)
(cardiovascular effects of)
RN 65279-36-9 CAPLUS
CN 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, 1,2-diacetate, (R)- (9CI) (CA INDEX NAME)



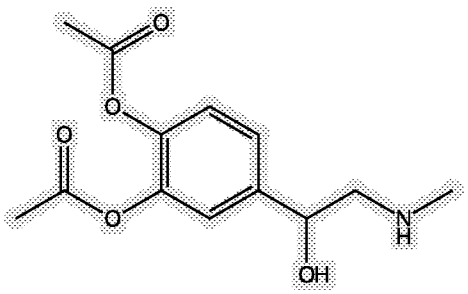
Absolute stereochemistry shown

L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER: 1929:45024 CAPLUS Full-text
DOCUMENT NUMBER: 23:45024
ORIGINAL REFERENCE NO.: 23:5162b-f
TITLE: Alkamines. III
AUTHOR(S): Kanao, S.
SOURCE: Yakugaku Zasshi (1929), 49, 238-46
CODEN: YKKZAJ; ISSN: 0031-6903
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

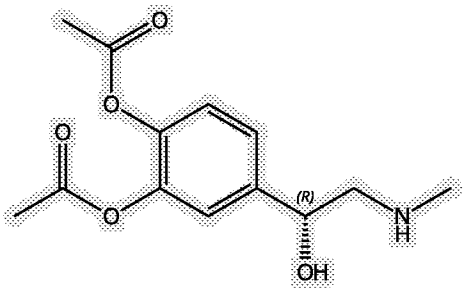
AB cf. C. A. 23, 4205. During the condensation of nitroparaffin and aromatic aldehyde, the phenol hydroxyl radical often causes the retardation. This is more so when an aldehyde possesses two OH radicals, such as resorcylaldehyde, gentisinaldehyde and protocatechualdehyde (Ber. 46,

1034(1913)). In order to lessen this retardation CH3CO2 or some other radical was substituted for OH radical. 3,4-Dihydroxybenzaldehyde (I) (100 g.), CH3CO2Na (100 g.) in AcOH (170 g.) gave diacetyl deriv. (II) m. 55° (yield 90%). Reduction of II (10 g.) with CH3NO2 (4 g.) in KHCO3 gave 3,4-diacetoxyphenylnitroethanol (III), m. 155° (yield 80-90%). III (5 g.) in alc. (20 cc.) treated on the water bath with concd. acid gave 3,4-dihydroxy-Ω-nitrostyrene (IV) (8 g.), m. 146-7° (yield 97%). IV (3 g.) AcOH (5 g.) in the cold treated with 30% KCl (6-7 g.) gave 3,4-diacetoxy-ωnitrostyrene, m. 118°. Reduction of III (5 g.) with 30% AcOH (60 cc.) and Zn dust gave 1-(3,4-diacetoxyphenyl)-2-aminoethanol (yield 2.2 g.), dioxalate, m. 153°. Reduction of III (5 g.) with 35% HCHO (1.5 g.), Zn dust and AcOH gave 1-(3,4-diacetoxyphenyl)-2-methylaminoethanol, m. 168°, HCl salt m. 155-6°. Reduction of III (3 g.) with CH3(CH2)5CHO (1.2 g) by usual method gave 1-(3,4-diacetoxyphenyl)-2-heptylaminoethanol (yield 1.1 g.), dioxalate, m. 175° III (5 g.) and PhCHO by usual method gave 1-(3,4-diacetoxyphenyl)-2-(benzylideneoximino) ethanol (V) (yield 1 g.), m. 161-2°. Reduction of V by usual method gave 1-(3,4-diacetoxyphenyl)-2-benzylaminoethanol, dioxalate, m. 168°. Reduction of III (6 g.) with (CH2O2)C6H3CHO (3.2 g.) by usual method gave 1-(3,4-diacetoxyphenyl)-2-piperonylaminoethanol, dioxalate, m. 192° (yield 2.6 g.). III (6 g.), 3,4-(CH3CO2)2C6H3CHO (4.8 g.), AcOH and Zn dust treated as before gave 1-(3,4-diacetoxyphenyl)-2-(3,4-dihydroxybenzyl) aminoethanol, dioxalate, m. 201° (yield 4 g.). III (6 g.) and acetylvanillin (2.3 g.) treated as before gave 1-(3,4-diacetoxyphenyl)-2-(3-methoxy-4-acetoxybenzyl) aminoethanol, dioxalate, m. 210° (yield 2 g.). Reduction of III (6 g.) with furfurol (2.6 g.) as before gave 1-(3,4-diacetoxyphenyl-2-furylaminoethanol, dioxalate, m. 162-3° (yield 2 g.).

IT 104714-60-5P
RL: SPN (Synthetic preparation); PRP (Properties); PREP (Preparation)
(Alkamines. III)
RN 104714-60-5 CAPLUS
CN 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, 1,2-diacetate (CA INDEX NAME)



IT 65279-36-9P, Adrenaline, 3,4-diacetate
RL: PREP (Preparation)
(prepn. of)
RN 65279-36-9 CAPLUS
CN 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, 1,2-diacetate, (R)-(9CI) (CA INDEX NAME)



Absolute stereochemistry shown

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=> file reg

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      54.10     212.99

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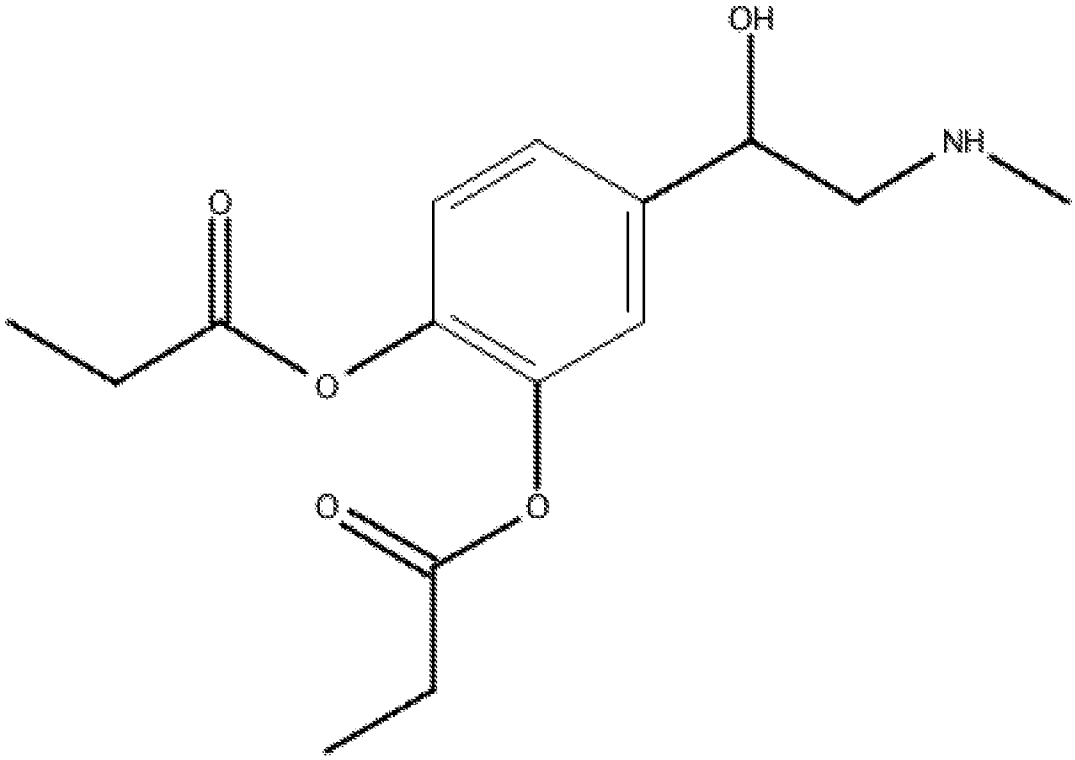
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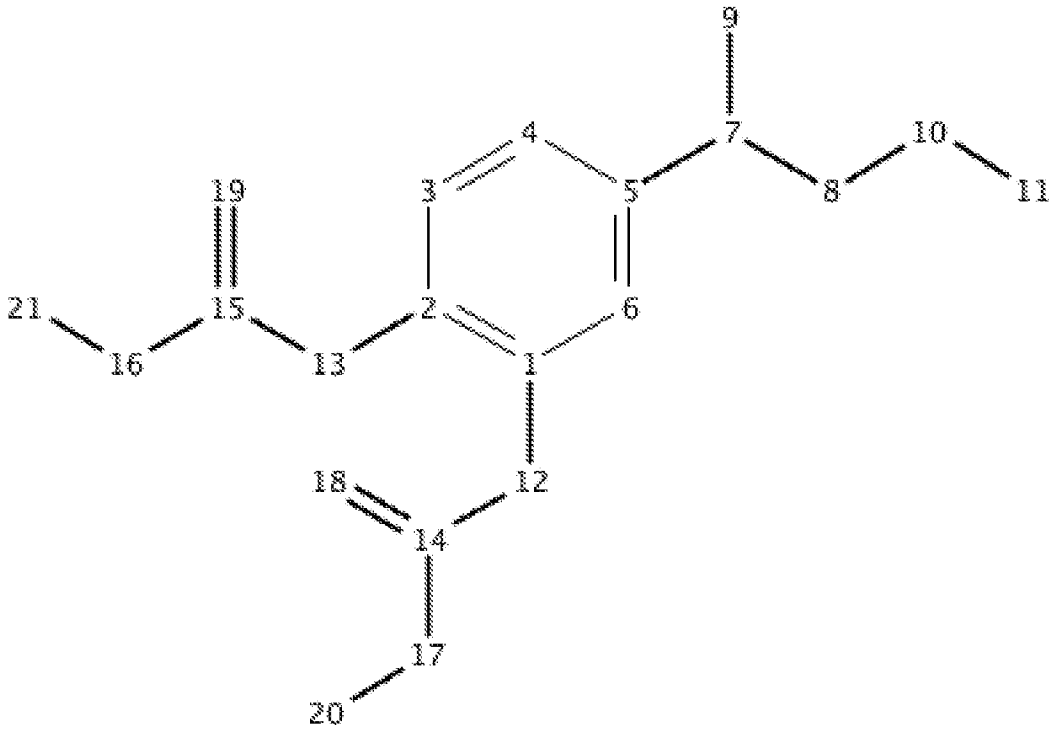
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http://www.cas.org/training/stn/database-specific

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L5      STRUCTURE UPLOADED

=> s l5 exact sam

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SAMPLE SCREEN SEARCH COMPLETED -        0 TO ITERATE

100.0% PROCESSED          0 ITERATIONS                                0 ANSWERS
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SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            0 TO        0
PROJECTED ANSWERS:               0 TO        0

L6            0 SEA EXA SAM L5

=> s l5 exact full

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100.0% PROCESSED          3 ITERATIONS                                1 ANSWERS

SEARCH TIME: 00.00.01

L7            1 SEA EXA FUL L5

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     158.71     371.70

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FILE LAST UPDATED: 15 Dec 2020 (20201215/ED)

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L8            1 L7

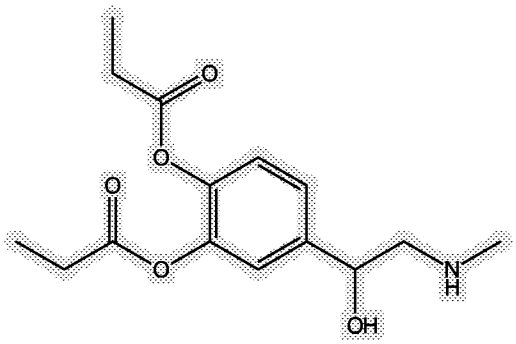
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L8   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER:         2018:953917  CAPLUS Full-text
DOCUMENT NUMBER:          169:11381
TITLE:                    Pharmaceutical formulation for sublingual or buccal
                          delivery of epinephrine
INVENTOR(S):              Almoazen, Hassan; Haynes, Lindsay
PATENT ASSIGNEE(S):       Iono Pharma, LLC, USA
SOURCE:                   PCT Int. Appl., 32pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
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LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2018089570	A1	20180517	WO 2017-US60761		20171109
CN 110418639	A	20191105	CN 2017-80083246		20171109
US 20190337886	A1	20191107	US 2019-16347625		20190506
PRIORITY APPLN. INFO.:			US 2016-62421316	P	20161113
			WO 2017-US60761	W	20171109

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 169:11381; CASFORMULTNS 2018:953917
AB The present invention relates to a pharmaceutical compn. for the treatment of anaphylaxis formulated for rapid delivery, in one embodiment, the delivery vehicle is a rapidly dissolvmg film. The films contain an epinephrine or a novel epinephrine pro-drag for fee rapid treatment of anaphylaxis in a patient. This invention relates to pharmaceutical compns. made by modifying the physicoehemieal properties of epinephrine in order to enhance its permeability through biol. membranes (sublingual and buccal membranes). Several prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring, by chem. reacting the two groups with several acid moieties to form an ester bond with different alkyl chains. The addn. of an alkyl group will enhance the lipophilicity of epinephrine (increase log P) and will consequently increase its permeability through the biol. membranes (sublingual and buccal tissues in the oral cavity).
IT 1195867-43-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation for sublingual or buccal delivery of epinephrine)
RN 1195867-43-6 CAPLUS
CN 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, 1,2-dipropanoate (CA INDEX NAME)



=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	14.41	386.11

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DICTIONARY FILE UPDATES: 14 DEC 2020 HIGHEST RN 2559710-34-6

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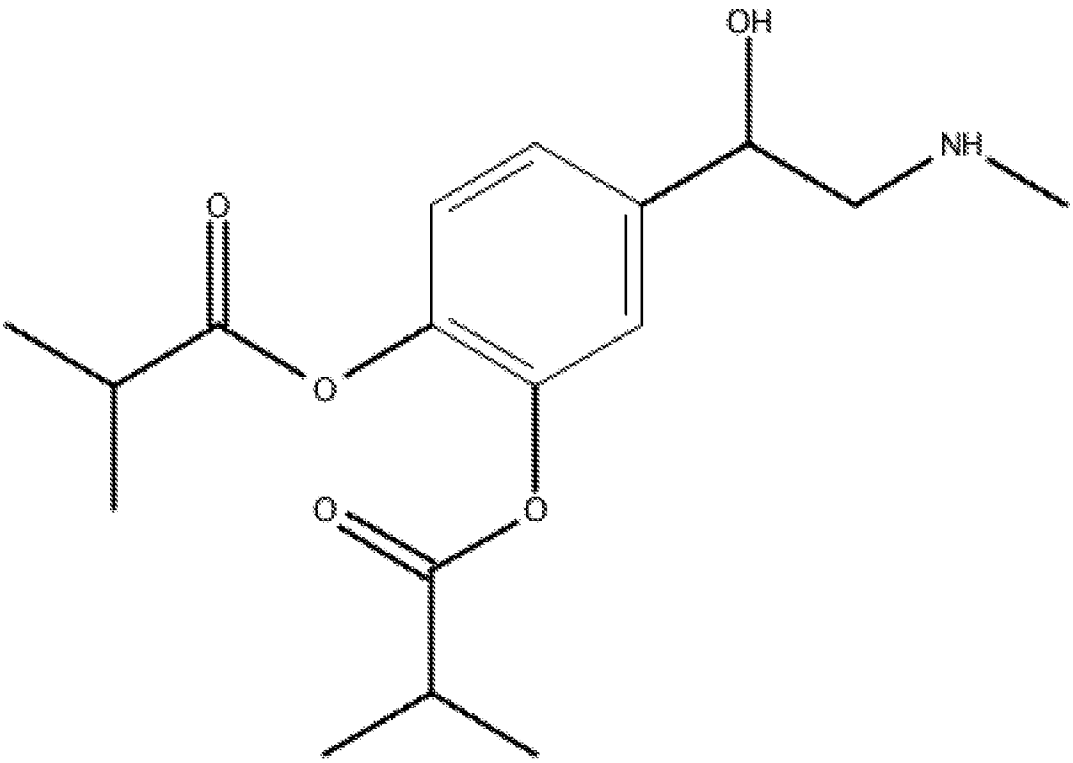
TSCA INFORMATION NOW CURRENT THROUGH March 2020.

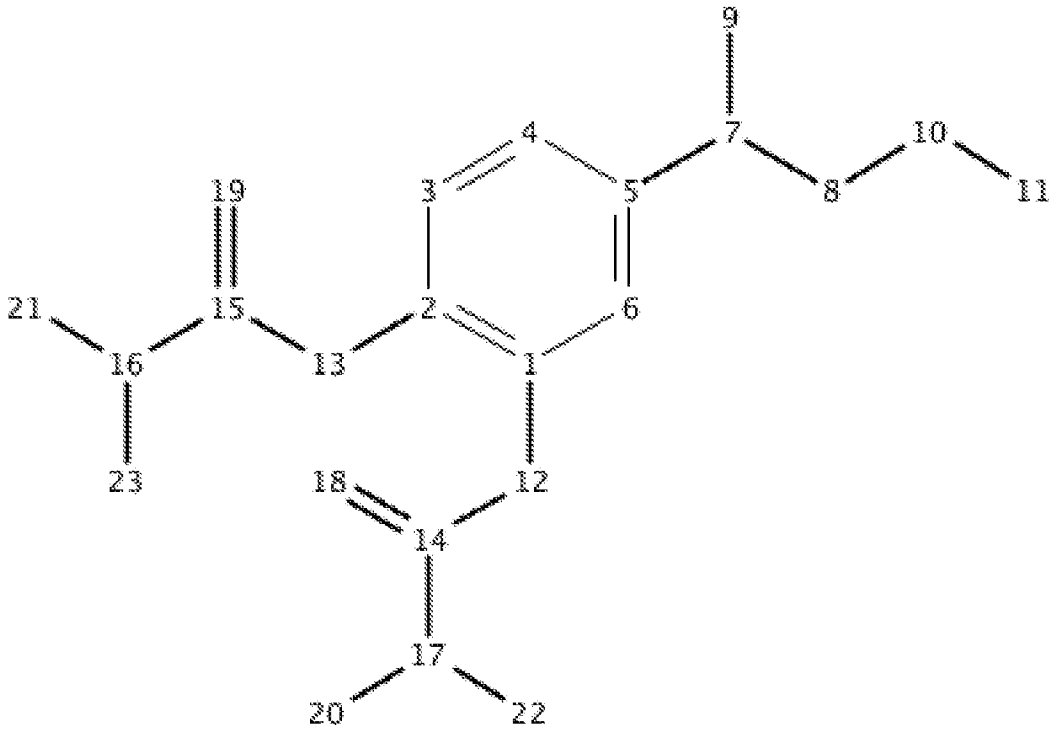
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Exact/Normalized Bonds : 1-12  2-13  7-9  8-10  10-11  12-14  13-15  14-18  15-1
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L9      STRUCTURE UPLOADED

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SAMPLE SCREEN SEARCH COMPLETED -        0 TO ITERATE
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100.0% PROCESSED          0 ITERATIONS                                0 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            0 TO        0
PROJECTED ANSWERS:               0 TO        0

L10           0 SEA EXA SAM L9

=> s l9 exact full

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FULL SCREEN SEARCH COMPLETED -        5 TO ITERATE

100.0% PROCESSED          5 ITERATIONS                                1 ANSWERS

SEARCH TIME: 00.00.01

L11           1 SEA EXA FUL L9

=> file caplus

COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   158.71     544.82

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

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L12           1 L11

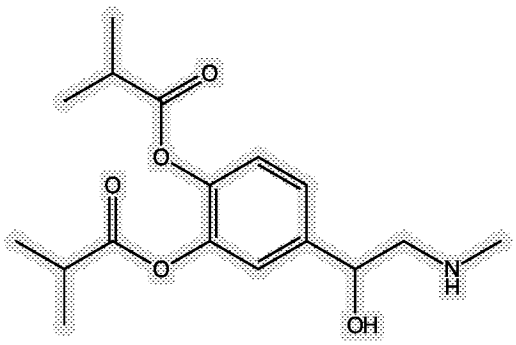
=> d l12 ibib abs hitstr


L12  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2020 ACS on STN
ACCESSION NUMBER:         2018:953917  CAPLUS Full-text
DOCUMENT NUMBER:          169:11381
TITLE:                    Pharmaceutical formulation for sublingual or buccal
                          delivery of epinephrine
INVENTOR(S):              Almoazen, Hassan; Haynes, Lindsay
PATENT ASSIGNEE(S):       Iono Pharma, LLC, USA
SOURCE:                   PCT Int. Appl., 32pp.
                          CODEN: PIXXD2
```

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2018089570	A1	20180517	WO 2017-US60761		20171109
CN 110418639	A	20191105	CN 2017-80083246		20171109
US 20190337886	A1	20191107	US 2019-16347625		20190506
PRIORITY APPLN. INFO.:			US 2016-62421316	P	20161113
			WO 2017-US60761	W	20171109

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 169:11381; CASFORMULTNS 2018:953917
AB The present invention relates to a pharmaceutical compn. for the treatment of anaphylaxis formulated for rapid delivery, in one embodiment, the delivery vehicle is a rapidly dissolvmg film. The films contain an epinephrine or a novel epinephrine pro-drag for fee rapid treatment of anaphylaxis in a patient. This invention relates to pharmaceutical compns. made by modifying the physicoehemieal properties of epinephrine in order to enhance its permeability through biol. membranes (sublingual and buccal membranes). Several prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring, by chem. reacting the two groups with several acid moieties to form an ester bond with different alkyl chains. The addn. of an alkyl group will enhance the lipophilicity of epinephrine (increase log P) and will consequently increase its permeability through the biol. membranes (sublingual and buccal tissues in the oral cavity).
IT 2226477-75-2
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation for sublingual or buccal delivery of epinephrine)
RN 2226477-75-2 CAPLUS
CN Propanoic acid, 2-methyl-, 1,1'-[4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene] ester (CA INDEX NAME)



=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	14.41	559.23

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DICTIONARY FILE UPDATES: 14 DEC 2020 HIGHEST RN 2559710-34-6

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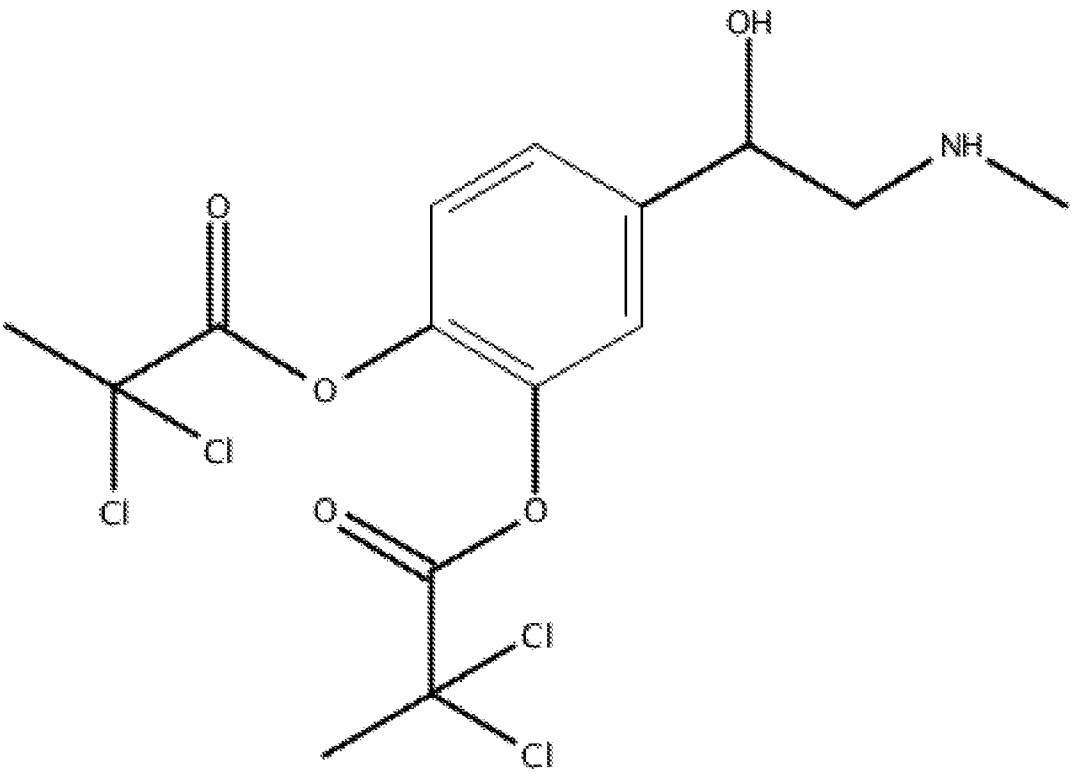
TSCA INFORMATION NOW CURRENT THROUGH March 2020.

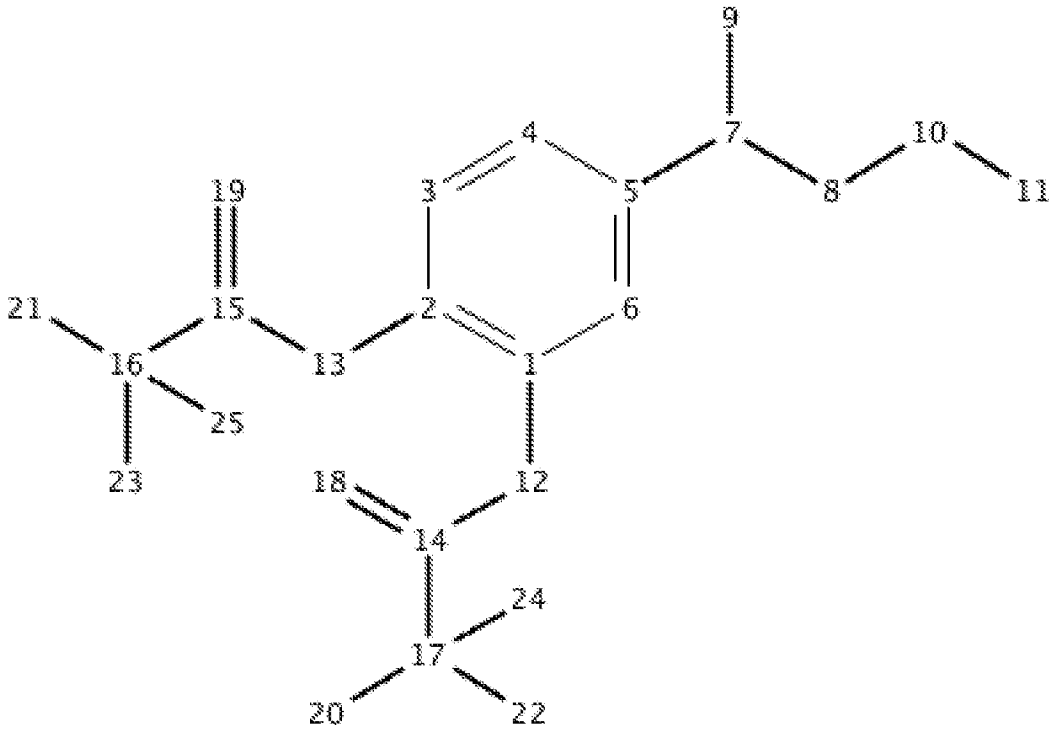
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Chain Bonds : 1-12  2-13  5-7  7-8  7-9  8-10  10-11  12-14  13-15  14-17  14-18
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L13     STRUCTURE UPLOADED

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SAMPLE SCREEN SEARCH COMPLETED -        0 TO ITERATE
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SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
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PROJECTED ANSWERS:               0 TO        0

L14           0 SEA EXA SAM L13

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100.0% PROCESSED          1 ITERATIONS                                    0 ANSWERS

SEARCH TIME: 00.00.01

L15           0 SEA EXA FUL L13

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L3            2 S L1 EXACT FULL

     FILE 'CAPLUS' ENTERED AT 20:37:15 ON 16 DEC 2020
L4            4 S L3

     FILE 'REGISTRY' ENTERED AT 20:38:03 ON 16 DEC 2020
L5              STRUCTURE UPLOADED
L6            0 S L5 EXACT SAM
L7            1 S L5 EXACT FULL

     FILE 'CAPLUS' ENTERED AT 20:38:53 ON 16 DEC 2020
L8            1 S L7

     FILE 'REGISTRY' ENTERED AT 20:39:19 ON 16 DEC 2020
L9              STRUCTURE UPLOADED
L10           0 S L9 EXACT SAM
L11           1 S L9 EXACT FULL

     FILE 'CAPLUS' ENTERED AT 20:40:03 ON 16 DEC 2020
L12           1 S L11

     FILE 'REGISTRY' ENTERED AT 20:40:16 ON 16 DEC 2020
L13             STRUCTURE UPLOADED
L14           0 S L13 EXACT SAM
L15           0 S L13 EXACT FULL

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

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16347625
Filing Date	2019-05-07
First Named Inventor	Dr. Hassan Almoazen
Art Unit	
Examiner Name	
Attorney Docket Number	24050.0001US

U.S.PATENTS

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

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20190022023	A1	2019-01-24	Schobel et al.	Entire Document

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.S/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16347625
	Filing Date	2019-05-07
	First Named Inventor	Dr. Hassan Almoazen
	Art Unit	
	Examiner Name	
	Attorney Docket Number	24050.0001US

	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/TORI STRONG/	Date Considered	12/16/2020

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

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16347625
	Filing Date	2019-05-07
	First Named Inventor	Dr. Hassan Almoazen
	Art Unit	
	Examiner Name	
	Attorney Docket Number	24050.0001US

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/susan fentress/	Date (YYYY-MM-DD)	2019-10-14
Name/Print	susan fentress	Registration Number	31327

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/347,625	Filing Date 05/06/2019	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	12/01/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
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	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

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

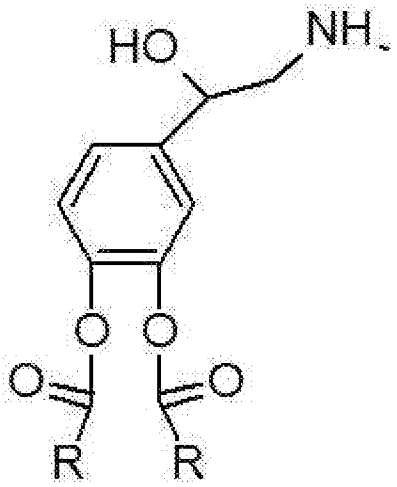
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/VICTORIA JOHNSON/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest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

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

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

AMENDMENTS TO THE CLAIMS

1. (previously presented) A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:



wherein R is selected from the group consisting of: $-CHCH_2$, $-CHCHCH_3$, $-CH_2-CH_2-Cl$, $-CHCH_2I$, $-CH(Cl)CH_2$ (Cl), $-CH(I)CH_2(I)$, $-CH(CH_3)CH_2(CH_3)$, $-CH_2C(CH_3)_3$, $-CH_2CH_2CH_3$, $-CH_2Cl$, $-CH_2I$, $-CH_2F$, H, Cl, I, F, $-CH(CH_3)CH(CH_3)_2$, $-CH(Cl)CH(Cl)_2$, $-CH(I)CH(I)_2$, $-CH(F)CH(F)_2$, $-CH_2CHCH_2$, $-C(Cl)_2CH(Cl)_2$, $-C(I)_2CH(I)_2$, $-C(Cl)_3$, $C(I)_3$, $-CH_2COCH_3$, $-CH_2COCl$, $-CH_2CO(I)$, $-CH_2OCH_3$, $-CH(I)(CH_3)$, $-C(Cl)_2(CH_3)$, $-CH_2CH(CH3)_2$, $-CH_2CH(Cl)_2$, $-CH_2CH(I)_2$, $-CH_2C(Cl)_3$, $-CH_2C(I)_3$, $-CH(Cl)_2$, $-CH(I)_2$, $-C(CH3)_2CH(CH3)_2$, $-NH-C(CH_3)_3$, $-NH-CH(CH_3)_2$, $-NH-CH_2CH_3$, $-NH-CH_3$, $-SCH_3$, $-SCH_2CH_3$, $-SCH(CH3)_2$, $-SC(CH_3)_3$, $-CH_2C_6H_5$ and $-C_6H_5$ or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0.

2. (cancelled)

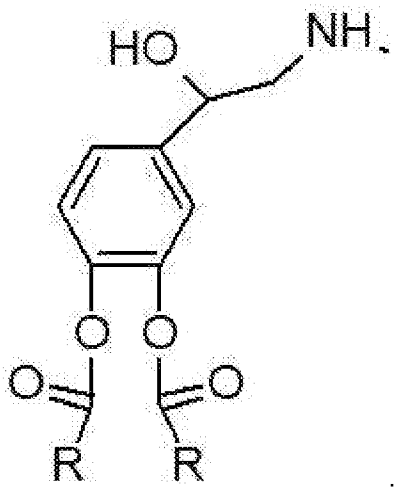
3. (previously presented) The compound of claim 1 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

4.-18 (cancelled)

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 145

18. (original) The method of claim 14 further comprising: providing said prodrug of epinephrine in a unit dosage form to a patient in need of anaphylactic treatment.

19. (previously presented) A compound of a Formula:



wherein R is selected from the group consisting of: CH_3, CH_2CH_3, and $CH(CH_3)_2$ wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration.

20. (previously presented) The compound of claim 19, wherein the compound is selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

21 (original) The compound of claim 19, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

22. (cancelled).

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 146

Electronic Acknowledgement Receipt

EFS ID:	41256945
Application Number:	16347625
International Application Number:	
Confirmation Number:	8118
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	Hassan Almoazen
Customer Number:	76447
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001US
Receipt Date:	01-DEC-2020
Filing Date:	06-MAY-2019
Time Stamp:	11:05:49
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response to Election / Restriction Filed	amendmentrrupdated.pdf	198574 1c0edfb2c62ade7360537e12308d8d88e302b184	no	2

Warnings:

Information:					
2	Claims	rrclaimsupdated.pdf	170843 f8d109787d572f9fc94ad81bba3b2b1ec35b0944	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	369417		

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CONFIRMATION NO.:	8188
APPLICATION NO.:	16/347,625
FILED:	05/06/2019
ART UNIT:	1629
TITLE:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

AMENDMENT

Dear Sir:

In response to the restriction requirement, please amend the above-identified applications as follows:

Amendments to the Specification: none

Amendments to the Abstract: none.

Amendments to the Claims: begin on page 3 of this paper.

Amendments to the Drawings: None.

Remarks/Arguments: begin on page 6 of this pager.

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 149

Remarks:

This application is a § 371 National Stage Application of PCT/US17/60761 application filed 11-09-2017.

In response to the restriction requirement applicant elects group 1 and has canceled claims in group II without traverse. In response to the requirement to elect a species applicant notes that claims 1. 3-14,16,18-22 were found in the International Preliminary Report on Patentability (as amended by article 34) to be novel, non-obvious and have technical merit. This application being the subject of a granted petition to make special under the Global/IP5 PPH based on the prior review by the PCT. USPTO record dated 07/26/2019. The PPH program allows the examiner at the USPTO to rely on the search and examination results from another participating country in which similar claims were deemed allowable, or from a favorable international search report (*i.e.*, a report indicating that at least one claim has novelty, inventive step, and industrial applicability)

However to expedite review applicant elects the molecule which has the side group R = $-C(Cl)_2CH_3$. Support for this election is shown in table 1, claims 1 and 19.

Applicant respectfully submits that the pending claims are in condition for allowance based on the patent prosecution highway request filed herewith. The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. 60-1480.

Respectfully submitted,

/Susan B Fentress/

Susan B. Fentress, Agent of Record
Reg. No. 31327
20 S Dudley, No 803
Memphis, Tennessee 38103
Telephone No. (901) 525-1455
Dated: DEC 12, 2020

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 150

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/347,625	05/06/2019	Hassan Almoazen	24050.0001US	8118

76447 7590 11/04/2020

Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

EXAMINER	
STRONG, TORI	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
11/04/2020	ELECTRONIC

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

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

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

eofficeaction@appcoll.com
sfentress@veritaygroup.com

Office Action Summary	Application No. 16/347,625	Applicant(s) Almoazen, Hassan	
	Examiner TORI STRONG	Art Unit 1629	AIA (FITF) Status Yes

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☑ Responsive to communication(s) filed on 16 August 2019.

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

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

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

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

Disposition of Claims*

5) ☑ Claim(s) 1,3,14,16 and 18-21 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

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

9) ☑ Claim(s) 1,3,14,16 and 18-21 are subject to restriction and/or election requirement

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Election/Restriction

REQUIREMENT FOR UNITY OF INVENTION

As provided in 37 CFR 1.475(a), a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in a national stage application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. See 37 CFR 1.475(e).

When Claims Are Directed to Multiple Categories of Inventions:

As provided in 37 CFR 1.475 (b), a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or

(2) A product and a process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

Otherwise, unity of invention might not be present. See 37 CFR 1.475 (c).

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 1, 3 and 19-21, drawn to a compound formulated for sublingual or buccal administration of claimed formula (prodrug formulations of epinephrine).

Group II, claims 14, 16 and 18, drawn to a method of delivering a prodrug of epinephrine that is formulated for sublingual or buccal administration.

Election of Species

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

A) species of Formula or prodrug of epinephrine – Applicant is required to elect a single species of the Formula or prodrug of epinephrine, delineating the specific R groups for the elected species.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise require all the limitations of an allowed generic claim. Currently, the following claim(s) are generic: claims 3, 14, 16, 18 and 21

Lack of Unity of Invention

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I and II lack unity of invention because even though the inventions of these groups require the technical feature of a sublingual or buccal formulation of epinephrine, this technical feature is not a special technical feature as it does not make a contribution over the prior art in view of Rawas-Qalaji *et al.* (US 2007/0202163 A1; cited in ISR). Rawas-Qalaji teaches formulations for fast-disintegrating epinephrine tablets for buccal or sublingual administration (abs) thus providing the same technical feature. Therefore the instant claims lack a special technical feature and thus lacks unity.

Considerations for Rejoinder of Product and Method Inventions

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper

restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI STRONG whose telephone number is (571)272-6333. The examiner can normally be reached on Monday - Friday 8:00 am - 5:00 pm (EST).

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

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on (571)272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Kortney L. Klinkel/
Primary Examiner, Art Unit 1699

TORI STRONG
Examiner
Art Unit 1629

/TORI STRONG/
Examiner, Art Unit 1629

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/347,625	05/06/2019	Hassan Almoazen	24050.0001US

CONFIRMATION NO. 8118

76447
Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

PUBLICATION NOTICE



Title:PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

Publication No.US-2019-0337886-A1
Publication Date:11/07/2019

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16347625
Filing Date	2019-05-07
First Named Inventor	Dr. Hassan Almoazen
Art Unit	
Examiner Name	
Attorney Docket Number	24050.0001US

U.S.PATENTS

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

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20190022023	A1	2019-01-24	Schobel et al.	Entire Document

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16347625
	Filing Date	2019-05-07
	First Named Inventor	Dr. Hassan Almoazen
	Art Unit	
	Examiner Name	
	Attorney Docket Number	24050.0001US

	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16347626
	Filing Date	2019-05-07
	First Named Inventor	Dr. Hassan Almoazen
	Art Unit	
	Examiner Name	
	Attorney Docket Number	24050.0001US

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/susan fentress/	Date (YYYY-MM-DD)	2019-10-14
Name/Print	susan fentress	Registration Number	31327

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Electronic Acknowledgement Receipt

EFS ID:	37444390
Application Number:	16347625
International Application Number:	
Confirmation Number:	8118
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	Hassan Almoazen
Customer Number:	76447
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001US
Receipt Date:	14-OCT-2019
Filing Date:	06-MAY-2019
Time Stamp:	11:17:20
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	Scan_0036.pdf	1124464 3f9fc329de2c5a3a3cbfa37c0752bd9e650418aa	no	3

Warnings:

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/347,625	Filing Date 05/06/2019	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	08/16/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

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

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

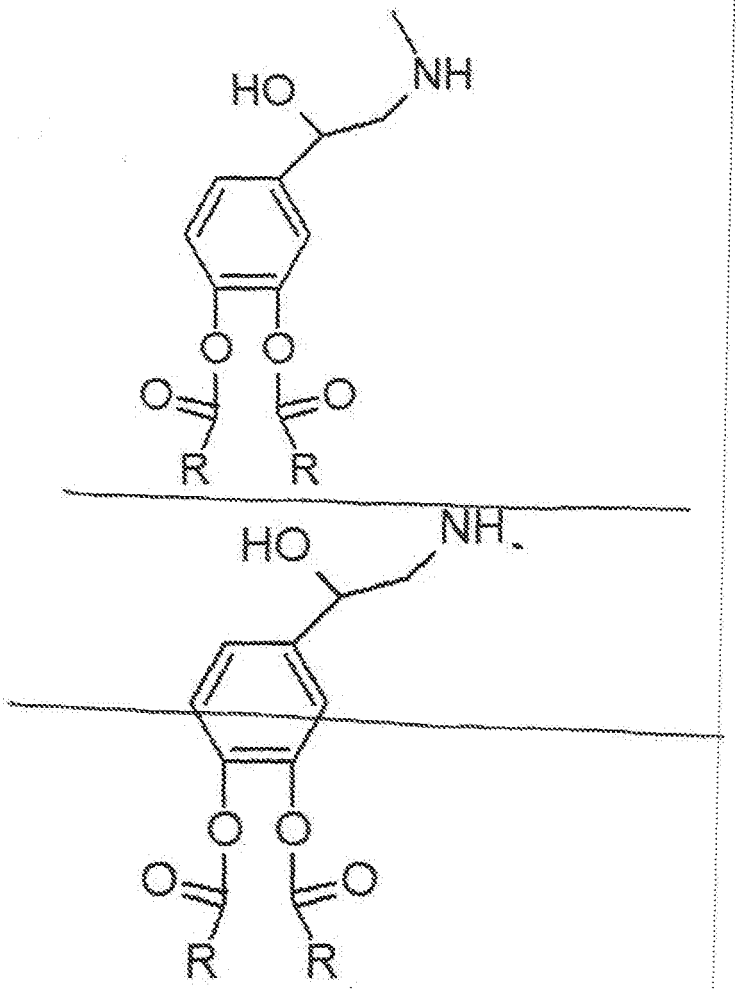
This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes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

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

I claim:

CLAIMS

1.(currently amended) A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:



wherein R is selected from the group consisting of: $-CHCH_2$, $-CHCHCH_3$, $-CH_2-CH_2-Cl$, $-CHCH_2I$, $-CH(Cl)CH_2$ (Cl), $-CH(I)CH_2(I)$, $-CH(CH_3)CH_2(CH_3)$, $-CH_2C(CH_3)_3$, $-CH_2CH_2CH_3$, $-CH_2Cl$, $-CH_2I$, $-CH_2F$, H, Cl, I, F, $-CH(CH_3)CH(CH_3)_2$, $-CH(Cl)CH(Cl)_2$, $-CH(I)CH(I)_2$, $-CH(F)CH(F)_2$, $-CH_2CHCH_2$, $-C(Cl)_2CH(Cl)_2$, $-C(I)_2CH(I)_2$, $-C(Cl)_3$, $C(I)_3$, $-CH_2COCH_3$, $-CH_2COCl$, $-CH_2CO(I)$, $-CH_2OCH_3$, $-CH(I)(CH_3)$, $-C(Cl)_2(CH_3)$, $-CH_2CH(CH3)_2$, $-CH_2CH(Cl)_2$, $-CH_2CH(I)_2$, $-CH_2C(Cl)_3$, $-CH_2C(I)_3$, $-CH(Cl)_2$, $-CH(I)_2$, $-C(CH3)_2CH(CH3)_2$, $-NH-C(CH_3)_3$, $-NH-CH(CH_3)_2$, $-NH-CH_2CH_3$, $-NH-CH_3$, $-SCH_3$, -

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 166

SCH_2CH_3, -$SCH(CH3)_2$, -$SC(CH_3)_3$, -$CH_2C_6H_5$ and -C_6H_5 or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0.

2. (cancelled).

3. (previously presented) The compound of claim 1 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

4.-13 (canceled)

14. (currently amended) A method to deliver a prodrug of epinephrine comprising: the steps of: providing the prodrug of epinephrine in a unit dosage form, formulated for sublingual or buccal administration, wherein the unit dosage form is a rapidly dissolving film, to a patient in need of treatment thereof, wherein the prodrugs of epinephrine has a Log P value in the range of about 0.5-6.0.

15. (cancelled).

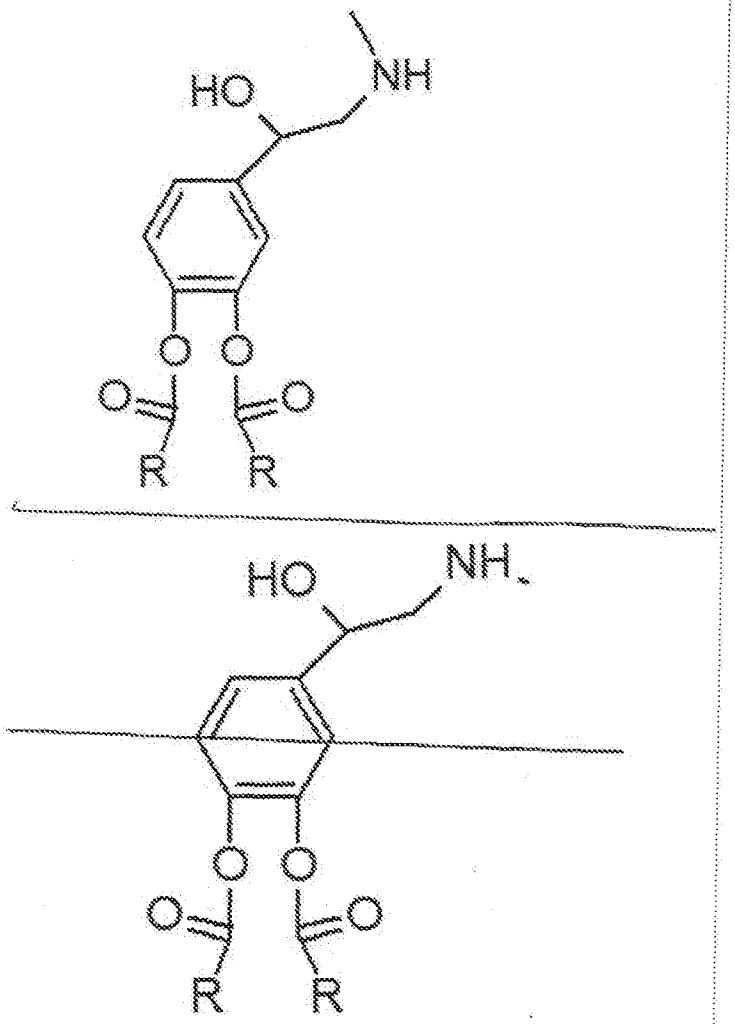
16. (original) The method of claim 14 wherein the prodrugs of epinephrine has a Log P value in the range of about 1.0-5.0.

17. (cancelled).

18. (original) The method of claim 14 further comprising: providing said prodrug of epinephrine in a unit dosage form to a patient in need of anaphylactic treatment.

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 167

19. (currently amended) A compound of a Formula:



wherein R is selected from the group consisting of: CH_3, CH_2CH_3, and $CH(CH_3)_2$ wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration.

20. (previously presented) The compound of claim 19, wherein the compound is selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 168

21.(original) The compound of claim 19, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

22. (canceled).

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Electronic Acknowledgement Receipt

EFS ID:	36896842
Application Number:	16347625
International Application Number:	
Confirmation Number:	8118
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	Hassan Almoazen
Customer Number:	76447
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001US
Receipt Date:	16-AUG-2019
Filing Date:	06-MAY-2019
Time Stamp:	12:42:27
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Preliminary Amendment	prelimamendment.pdf	305445 737e7499e32b0206f81bd8e080f366dd0976f492	no	2

Warnings:

Information:					
2	Claims	prelimaryamendedclaims.pdf	754740 e2c2718120d58f99996cb2e516870f82d73e1280	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	1060185		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Appl. No.	:	16/347,625	Confirmation No: 8118
Applicant	:	Almoazen	
Filed	:	05-06-2018	
TC/A.U.	:	TBA	
Examiner	:	TBA	
Docket No.	:	24050.0001US	
Customer No.	:	76447	

Preliminary Amendment

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

Dear Sir of Madam:

Amendments to the Specification: none.

Amendments to the Claims: page 2-4

Amendments to the Drawings: None.

Remarks/Arguments: begin on page 5 of this paper.

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 172

Remarks/Arguments:

Applicant hereby files amendments to the claims to correct the nomenclature of certain compounds as suggested in Box no VIII of the Preliminary Report on Patentability dated November 13, 2018 during the PCT proceeding.

If additional corrections or changes are required, Applicant requests that the Examiner contact the Applicant.

Respectfully submitted,

By: /Susan B. Fentress /

Susan B. Fentress, Esq., Reg. No. 31,327
20 South Dudley, Suite 601
Memphis, Tennessee 38103
Telephone No. (901) 371-6664
Email: sfentress@veritaygroup.com

August 16, 2019

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 173

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
16347625	

Applicant(s) Hassan Almoazen

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
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Total Indep	3		3		0	
Total Depend	19	↵	5	↵	0	↵
Total Claims	22		8		0	

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	Indep	Depend	Indep	Depend	Indep	Depend
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/347,625

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	150		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	0.00		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	0.00		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	8 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x 230 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	150		TOTAL	

APPLICATION AS AMENDED - PART II

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

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

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

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/347,625	05/06/2019		150	24050.0001US	8	3

CONFIRMATION NO. 8118

FILING RECEIPT

76447
Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

OC000000110026732

Date Mailed: 07/31/2019

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, 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 corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction 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 provided that the request is grantable.

Inventor(s)

Hassan Almoazen, Hassan, TN;

Applicant(s)

Iono Pharma, LLC, Bartlett, TN;

Assignment For Published Patent Application

Iono Pharma, LLC, Bartlett, TN

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US2017/060761 11/09/2017
which claims benefit of 62/421,316 11/13/2016

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

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 176

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: 07/30/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/347,625**

Projected Publication Date: 11/07/2019

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

Preliminary Class

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

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 177

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 AssetsControl, 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).

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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

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www.uspto.gov

U.S. APPLICATION NO.	FIRST NAMED INVENTOR	ATTY. DOCKET NO.
16/347,625	Hassan Almoazen	24050.0001US

76447
Susan B. Fentress
Veritay Group, IP
20 Dudley St
Suite 803
Memphis, TN 38103

INTERNATIONAL APPLICATION NO.	
PCT/US2017/060761	
I.A. FILING DATE	PRIORITY DATE
11/09/2017	11/13/2016

CONFIRMATION NO. 8118
371 ACCEPTANCE LETTER

OC000000110026733

Date Mailed: 07/31/2019

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office, in its capacity as a Designated / Elected Office (37 CFR 1.495), has ACCEPTED the above identified international application for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above. A Filing Receipt will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE "FILING DATE or 371(c) DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1) and (c)(2) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN BELOW.** The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363)

05/06/2019
DATE OF RECEIPT OF 35 U.S.C.
371(c)(1) and (c)(2) REQUIREMENTS

The following items have been received:

- Indication of Small Entity Status
- Copy of the International Application filed on 05/06/2019
- Copy of the International Search Report filed on 05/06/2019
- Preliminary Amendments filed on 05/06/2019
- Information Disclosure Statements filed on 05/06/2019
- Inventor's Oath or Declaration filed on 05/07/2019
- Request for Immediate Examination filed on 05/06/2019
- U.S. Basic National Fees filed on 05/06/2019
- Assignment filed on 05/07/2019
- Assignee Statement for PGPUB filed on 05/06/2019
- Authorize Access to Search Results filed on 05/06/2019
- Priority Documents filed on 05/06/2019
- Authorization to Permit Access filed on 05/06/2019
- Application Data Sheet (37 CFR 1.76) filed on 05/06/2019

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 180

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

ROSA M WEST

Telephone: (571) 272-1019

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 181

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/347,625		Hassan Almoazen	24050.0001US	8118

76447 7590 07/26/2019

Susan B. Fentress
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20 Dudley St
Suite 803
Memphis, TN 38103

EXAMINER	
ART UNIT	PAPER NUMBER

NOTIFICATION DATE	DELIVERY MODE
07/26/2019	ELECTRONIC

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

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

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

eofficeaction@appcoll.com
sfentress@veritaygroup.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

In re Application of	:	
Almoazen, Hassan	:	
Application No. 16/347,625	:	
Deposited: 06 May 2019	:	DECISION ON PETITION
For PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF	:	

This is a decision on the request to participate in the Patent Prosecution Highway (PPH) program and the petition under 37 CFR. § 1.102(a), filed 06 May 2019, to make the above-identified application special.

The request and petition under 37 CFR § 1.102(a) are **GRANTED**.

DISCUSSION

A grantable request to participate in the PPH pilot program and petition to make special require:

1. The U.S. application for which participation in the Global/IP5 PPH pilot program is requested must have the same earliest date, whether this is the priority date or filing date, as that of a corresponding national or regional application filed with another Global/IP5 PPH participating office or a corresponding PCT international application for which one of the Global/IP5 PPH participating offices was the International Searching Authority (ISA) or the International Preliminary Examining Authority (IPEA);

2. Applicant must:
   a. Ensure all the claims in the U.S. application must sufficiently correspond or be amended to sufficiently correspond to the allowable/patentable claim(s) in the corresponding Office of Earlier Examination (OEE) application and
   b. Submit a claims correspondence table in English;

3. Examination on the merits of the U.S. application has not begun;

4. Applicant must submit:

a. Documentation of prior office action:
   i. a copy of the office action(s) just prior to the "Decision to Grant a Patent" from each of the Global/IP5 PPH participating office application(s) containing the allowable/patentable claim(s) or
   ii. if the allowable/patentable claims(s) are from a "Notification of Reasons for Refusal" then the Notification of Reasons for Refusal or
   iii. if the Global/IP5 PPH participating office application is a first action allowance then no office action from the Global/IP5 PPH participating office is necessary should be indicated on the request/petition form or
   iv. the latest work product in the international phase of the OEE PCT application;

b. An English language translation of the Global/IP5 PPH participating office action or work product from (4)(a)(i)-(ii) or (iv) above; and

5. Applicant must submit:
   a. An IDS listing the documents cited by the Global/IP5 PPH participating office examiner in the Global/IP5 PPH participating office action or work product (unless already submitted in this application) and
   b. Copies of the documents except U.S. patents or U.S. patent application publications (unless already submitted in this application).

The request to participate in the PPH pilot program and petition comply with the above requirements. Accordingly, the above-identified application has been accorded "special" status.

Telephone inquiries concerning this decision should be directed to JoAnne Burke whose telephone number is (571) 272-4584.

All other inquiries concerning the examination or status of the application are accessible in the PAIR system at http://portal.uspto.gov/.

This application will be forwarded to the examiner for action on the merits commensurate with this decision once this application's formality reviews have been completed.

/JOANNE L BURKE/
Lead Paralegal Specialist, OPET

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

EPAS ID: PAT5510036

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
DR HASSAN ALMOAZEN	05/06/2019

RECEIVING PARTY DATA

Name:	IONO PHARMA, LLC
Street Address:	3133 HILL LAKE DRIVE
City:	BARTLETT
State/Country:	TENNESSEE
Postal Code:	38135

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	16347625

CORRESPONDENCE DATA

Fax Number:

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.

Phone: 9013716664
Email: susanbfentress@gmail.com
Correspondent Name: SUSAN B FENTRESS
Address Line 1: 20 DUDLEY ST SUITE 601
Address Line 4: MEMPHIS, TENNESSEE 38103

ATTORNEY DOCKET NUMBER:	24050.0001US
NAME OF SUBMITTER:	SUSAN B FENTRESS
SIGNATURE:	/susan b fentress/
DATE SIGNED:	05/07/2019
	This document serves as an Oath/Declaration (37 CFR 1.63).

Total Attachments: 2
source=assignmenthalmoazen2019#page1.tif
source=assignmenthalmoazen2019#page2.tif

ASSIGNMENT FOR APPLICATION FOR PATENT

WHEREAS,

Hassan Almoazen

(hereinafter referred to as "Assignors") have invented a certain invention (the "Invention") entitled:

PHARMACEUTICAL FORMULATION FOR RAPID DELIVERY OF EPINEPHRINE

for which application (the "Application") for Letters Patent in the United States has been filed; and

WHEREAS, the Application was filed on May 6, 2019 and has been assigned Serial No. 16/347,625 of the same title; and

WHEREAS, it is the intention of Assignors that patent rights in and to the invention, and any and all improvement thereto, shall belong to:

Iono Pharma, LLC
3133 Hill Lake Drive
Bartlett, TN 38135

(hereinafter referred to as "Assignee"); and

WHEREAS, Assignee desires to acquire the entire right, title and interest in and to the Application, and the Invention, and in and to all embodiments of the Invention heretofore conceived, made or discovered by Assignors, and in and to any and all patents (including but not limited to continuation applications, CIP applications and reissue patents), inventor's certificates and other forms of protection (hereinafter referred to as "Patents") thereon granted in any and all countries and group of countries; and

WHEREAS, Assignors intend to assign said rights.

NOW, THEREFORE, in consideration of One Dollar ($1.00) and other good and valuable consideration, acknowledged by said Assignors to have been received in full from Assignee:

1. Said Assignors hereby sell, assign, transfer and convey to Assignee the full and exclusive right, title and interest (a) in and to the Application and the Invention; (b) in and to all rights to apply for patents on the Inventions in any and all countries pursuant

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 186

to the International Convention for the Protection of Industrial Property or otherwise; (c) in and to any and all Application filed and any and all Patent granted on the Inventions in any and all countries, including each and every Application filed and each and every Patent granted on any application which is a division, substitution, continuation or CIP of said Application; and (d) in and to each and every reissue or extension of any said Patents.

2. Assignors covenant and agree to cooperate with Assignee to enable Assignee to enjoy to the fullest extent the right, title and interest to the Invention herein conveyed in any and all countries and groups of countries. Such cooperation by Assignors shall include prompt production of pertinent facts and documents, giving testimony, execution of petitions, oaths, specifications, declarations or other papers, and other assistance all to the extent deemed necessary or desirable by Assignee (a) for perfecting in Assignee the right, title and interest herein conveyed; (b) for prosecuting any of the Applications; (c) for filing and prosecuting substitute, divisional, continuing or additional applications covering the Invention; (d) for filing and prosecuting applications for reissuance of any of the Patents; (e) for interference or other priority proceedings involving said Inventions; and (f) for legal proceedings involving said Inventions and any application therefore and any Patents granted thereon, including without limitation opposition proceedings, cancellation proceedings, priority contests, public use proceedings, infringement actions and court actions; provided, however, that the reasonable travel, business and legal expenses incurred by Assignors in providing such cooperation shall be paid by Assignee.

3. The terms and covenants of this Agreement shall inure to the benefit of Assignee, its successors, assigns and other legal representatives, and shall be binding upon Assignors, and Assignors' respective heirs, legal representatives and assigns.

4. Assignors hereby warrant and represent that Assignors have not entered into and will not enter into any assignment, contract, or understanding in conflict herewith.

Assignors have executed and delivered this instrument to Assignee on the date indicated below.

Assignor's Signature: Hassan ALMOAZEN Date: 5-6-2019

Hassan Almoazen

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 187

PTO/SB/20PCT-US (09-10)
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U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST FOR PARTICIPATION IN THE PATENT COOPERATION TREATY – PATENT PROSECUTION HIGHWAY (PCT-PPH) PILOT PROGRAM IN A U.S. APPLICATION WHERE THE USPTO WAS THE ISA OR IPEA

Application No.:		First Named Inventor:	Hassan Almoazen
Filing Date:		Attorney Docket No.:	24050.0001US
Title of the Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF		

THIS REQUEST FOR PARTICIPATION IN THE PCT-PPH PILOT PROGRAM ALONG WITH THE REQUIRED DOCUMENTS MUST BE SUBMITTED VIA EFS-WEB. INFORMATION REGARDING EFS-WEB IS AVAILABLE AT HTTP://WWW.USPTO.GOV/EBC/EFS_HELP.HTML.

APPLICANT HEREBY REQUESTS PARTICIPATION IN THE PCT-PPH PILOT PROGRAM AND PETITIONS TO MAKE THE ABOVE-IDENTIFIED APPLICATION SPECIAL UNDER THE PCT-PPH PILOT PROGRAM.

The above-identified application is (1) a national stage entry of the corresponding PCT application, or (2) a national stage entry of another PCT application which claims priority to the corresponding PCT application, or (3) a national application that claims domestic/ foreign priority to the corresponding PCT application, or (4) a national application which forms the basis for the priority claim in the corresponding PCT application, or (5) a continuing application of a U.S. application that satisfies one of (1) to (4) above, or (6) a U.S. application that claims domestic benefit to a U.S. provisional application which forms the basis for the priority claim in the corresponding PCT application.

The corresponding PCT application number(s) is/are: PCT/US17/60761

The international filing date of the corresponding PCT application(s) is/are: 11-09-2017

I. List of Required Documents:

a. **A copy of the latest international work product (WO/ISA, WO/IPEA, or IPER) in the above-identified corresponding PCT application(s)**

☑ is attached.

☐ is not attached because the document is already in the U.S. application.

b. **A copy of all claims which were indicated as having novelty, inventive step and industrial applicability in the above-identified corresponding PCT application(s)**

☑ is attached.

☐ is not attached because the document is already in the U.S. application.

c. **English translations of the documents in a. and b. above are attached (if the documents are not in the English language). A statement that the English translation is accurate is attached for the document in b. above.**

d. **(1) An information disclosure statement listing the documents cited in the international work products (ISR, WO/ISA, WO/IPEA, IPER) of the corresponding PCT application.**

☑ is attached.

☐ has already been filed in the above-identified U.S. application on _____

(2) Copies of all documents (except for U.S. patents or U.S. patent application publications)

☑ are attached.

☐ have already been filed in the above-identified U.S. application on _____

This collection of information is required by 35 U.S.C. 119, 37 CFR 1.55, and 37 CFR 1.102(d). 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 2 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.

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REQUEST FOR PARTICIPATION IN THE PCT-PPH PILOT PROGRAM IN A U.S. APPLICATION WHERE THE USPTO WAS THE ISA OR IPEA

(continued)

Application No.:		First Named Inventor:	Hassan Almoazen

II. Claims Correspondence Table:

Claims in US Application	Patentable Claims in the corresponding PCT application	Explanation regarding the correspondence
1	1	same
3	3	same
14	14	same
16	16	same
18	18	same
19	19	same
20	20	same
21	21	same

III. All the claims in the US application sufficiently correspond to the patentable claims in the corresponding PCT application.

Signature /susan b fentress/	Date May 6, 2019
Name (Print/Typed) Susan B Fentress	Registration Number 31327

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference **24050.0001PCT**	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT/US2017/060761**	International filing date *(day/month/year)* **09 November 2017 (09.11.2017)**	Priority date *(day/month/year)* **13 November 2016 (13.11.2016)**
International Patent Classification (IPC) or both national classification and IPC IPC: A61K 31/137 CPC: A61K 9/0056, A61J 7/0053, A61J 1/035, A61K 9/006		
Applicant **Inon Phama, LLC**		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 39 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions).
      ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4*bis*, 70.2(e), 70.16 and 91.2).
      ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)).
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3*ter* of Annex C of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☑ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☑ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☑ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20 April 2018 (20.04.2018)	**29 October 2018 (29.10.2018)**
Name and mailing address of the IPEA/US **Commissioner for Patents** **Mail Stop PCT, Attn: IPEA/US** **P.O. Box 1450** **Alexandria, VA 22313-1450** Facsimile No. **(571)273-8300**	Authorized officer **SAJJADI, Fereydoun G** Telephone No. **572-272-3311**

Form PCT/IPEA/409 (cover sheet) (January 2015)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2017/060761

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:
   - [x] the international application in the language in which it was filed.
   - [ ] a translation of the international application into _____ which is the language of a translation furnished for the purposes of:
     - [ ] international search (Rules 12.3(a) and 23.1(b))
     - [ ] publication of the international application (Rule 12.4(a))
     - [ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:
   - [ ] the international application as originally filed/furnished, or
   - [x] the description:
     pages **none** as originally filed/furnished.
     pages* **none** received by this Authority on **(..)**
     pages* **1-17** received by this Authority on **20 April 2018 (20.04.2018)**
   - [x] the claims:
     Nos. _____ as originally filed/furnished.
     Nos.* _____ as amended (together with any statement) under Article 19
     Nos.* **1-22** received by this Authority on **20 April 2018 (20.04.2018)**
   - [x] the drawings:
     pages **none** as originally filed/furnished.
     pages* **none** received by this Authority on **(..)**
     pages* **1/9-9/9** received by this Authority on **20 April 2018 (20.04.2018)**
   - [ ] a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages _____
   - [ ] the claims, Nos. _____
   - [ ] the drawings, sheets/figs _____
   - [ ] the sequence listing *(specify)*: _____
4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-*bis*)):
   - [ ] the description, pages _____
   - [ ] the claims, Nos. _____
   - [ ] the drawings, sheets/figs _____
   - [ ] the sequence listing *(specify)*: _____
5. [ ] This report has been established:
   - [ ] taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-*bis*) and 70.2(e)).
   - [ ] without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4*bis* and 70.2(e)).
6. With regard to top-up searches (Rules 66.1*ter* and 70.2(f)):
   - [x] A top-up search was carried out by this Authority on **29 October 2018 (29.10.2018)**
     - [ ] Additional relevant documents have been discovered during the top-up search.
   - [ ] No top-up search was carried out by this Authority because it would serve no useful purpose.
7. [ ] Supplementary international search report(s) from Authority(ies) _____ has/ have been received and taken into account in establishing this report (Rule 45*bis*.8(b) and (c)).

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Form PCT/IPEA/409 (Box No. I) (January 2015)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2017/060761

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1, 3-14, 16, 18-22	YES
	Claims		NO
Inventive step (IS)	Claims	1, 3-14, 16, 18-22	YES
	Claims		NO
Industrial applicability (IA)	Claims	1, 3-14, 16, 18-22	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Claims 1, 3-14, 16, 18-22 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the 2-methylamino-1-hydroxyethyl side chain nor their.use to treat said alilments.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2017/060761

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 1 compound Formula has a structure that is unclear with respect to the primary nitrogen atom substituents. The group is represented as NH, but there appears to be a partial character at the base of the H on NH. This could represent a subscript number or an incomplete bond. The instant specification indicates that N has a methyl substituent in several Key examples (see Fig 1-2) so that the nitrogen atom has an H and a methyl substituent and therefore the structure was interpreted in that way for the purposes of the search and the opinion.

For the purposes of the search and the opinion, the group CH2CHCH2 was interpreted to mean -CH2CH=CH2 , the substituent group CHCH2 was interpreted to mean CH=CH2, the substituent group CHCHCH2was interpreted to mean CH=CHCH2,

Attorney Docket Number
24050.0001PCT

REPLACEMENT SHEET

TITLE OF THE INVENTION: PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF A PRO-DRUG OF EPINEPHRINE

Field of the Invention

[0001] The present invention relates to pharmaceutical compositions for the treatment of anaphylaxis formulated for rapid sublingual or buccal delivery, *i.e.*, compounds that dissolves in the oral cavity. In one embodiment, the delivery vehicle is a rapidly dissolving film. The films contain a novel epinephrine pro-drug formulated for the rapid delivery of the drug to a patient in need of treatment, such as for example, a patient in need of treatment for anaphylaxis.

Description of Related Art Including Information

[0002] Epinephrine is considered the primary choice for the treatment of anaphylaxis which is a life threatening allergic reaction that might lead to death if untreated especially in children. A study reported that one in every 10,000 children has an anaphylactic attack per year. Epinephrine is the drug of choice for the treatment of anaphylactic shock in children and adults. It is highly soluble in water, highly hydrophilic (log P -0.68) and can be oxidized readily. Based on the current physicochemical properties of epinephrine, the only delivery available in the market is intramuscular injection. The administration of proper therapeutic agents, such as, epinephrine must be prompt. This is usually performed through the usage of auto-injectors such as EPIPEN (MYLAN) or TWINJECT (SHIONOGI PHARMA, INC.) that deliver the required dose in the mid-outer thigh either subcutaneously or intramuscularly. However, many disadvantages are reported with the usage of these injectors such as high cost, inaccurate administration, short half-life, patient's fear of needles, accidental injections, and unavailability of a sufficient number of fixed prefilled doses.

[0003] These shortcomings affect greatly the patient compliance and adherence to these injectors. In addition, it is very challenging to adjust the dose to different children ages as there are only two premeasured fixed epinephrine doses (0.15 and 0.3 mg). Recent study showed that only 17% of pediatric patients who have experienced anaphylactic symptoms have used prescribed auto injectors.

Other available delivery systems such as syringes or inhalers are also underused due to their lack of rapid and accurate dosing. Therefore, there is growing interest in the development of an alternative non-invasive delivery system that can easily provide accurate doses of epinephrine.

[0004] Anwar A. Hussain and James E. Truelove were granted patents related to the synthesis of novel esters of [(methylamino)methyl] benzyl alcohol which is epinephrine. The purpose of the Hussain's *et. al.* invention was to develop a prodrug of epinephrine HCl with superior lipid solubility to enhance penetration through the cornea of the eye to treat glaucoma. Hussain *et. al.* synthesized four different prodrugs for this purpose (see structures 7A, 7B, 7C, 7D). These four molecules were tested in human, rabbit and horse plasmas and found that 3, 4 – dipivalyl-α-[(methylamino) methyl] benzyl alcohol hydrochloride (structure 7D) shows the best penetration profile into the eye. Hussain's et. al. didn't evaluate the log P of these molecules nor did they evaluate the sublingual or buccal permeability or absorption. Their main focus was to develop a prodrug specifically for the eye. Since the initial publishing of Anwar's patents in 1974 and 1975, no one has followed up or even published any new data on structures 7A, 7B, and 7C. Dipivalyl-α-[(methylamino)] benzyl alcohol hydrochloride (7D) was further developed into a drug delivery system for glaucoma (Dipivefrin or Propine). Hussain and Truelove selected this prodrug for further development because of several physicochemical and biological qualities. The first quality was estimating the delay before onset of seizure for this prodrug was about 8-10 minutes, the second quality was the rate of hydrolysis expressed as $t_{1/2}$ in human plasma was about 1,800 seconds and the third quality was the $t_{1/2}$ hydrolysis and oxidation *in vitro* was 700 and 300 days respectively. In a separate publication (Journal of Pharmaceutical Sciences, Vol. 65, No. 10, October 1976, p: 1510-1512), Hussain *et. al.* shared the graphs for the *in vitro* hydrolysis of this particular prodrug using rabbit eye homogenate and compared the hydrolysis among three different plasmas (human, rabbit, rabbit eye homogenate).

[0005] Films that incorporate a pharmaceutically active ingredient are disclosed in U.S. Pat. No. 4,136,145 to Fuchs, *et al.* ("Fuchs"). These films can be formed into a sheet, dried and then cut into individual doses. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body,

including the mouth, rectal, vaginal, nasal and ear areas. A drug delivery vehicle must provide a high level of uniformity with respect to the dosage delivered.

BRIEF SUMMARY OF THE INVENTION

[0006] This invention relates to pharmaceutical compositions made by modifying the physicochemical properties of epinephrine in order to enhance its permeability through biological membranes (sublingual and buccal membranes). Several prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring, by chemically reacting the two groups with several acid moieties to form an ester bond with different alkyl chains. The addition of an alkyl group will enhance the lipophilicity of epinephrine (increase log P) and will consequently increase its permeability through the biological membranes (sublingual and buccal tissues in the oral cavity). The 3 and 4 positions represent meta and para locations with respect to the carbon in position 1 on the phenolic ring of epinephrine. Once the prodrug penetrates biological membranes (sublingual and buccal), the biological enzyme carboxyesterase will degrade the ester bond and release epinephrine for therapeutic activity. A prodrug is a biologically inactive compound that can be metabolized in the body to produce a drug. On characteristic of the selected prodrug compounds is fast hydrolysis in plasma.

[0007] In another embodiment, the subject matter includes a method to deliver epinephrine involving the steps of: providing epinephrine in a unit dosage form formulated for sublingual or buccal administration, wherein the unit dosage form is a rapidly dissolving film and the unit dosage form provides the pharmaceutical pro-drug of epinephrine. More specifically, this method involves providing pharmaceutical pro-drug compositions epinephrine in a unit dosage form to patients in need of anaphylactic treatment.

[0008] The subject matter includes a pharmaceutical formulation made of: a compound as depicted in a formula A and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula B and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula C and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient,

REPLACEMENT SHEET

wherein R_4 is selected for the group consisting of: Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula D and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula 4E and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula 4F and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula G and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: H, I, Cl, $CH_2CH_2CH_3$ & $CH_2CH_2CH_2CH_3$, CH_2Cl, CH_2I and CH_2F A pharmaceutical formulation made of: a compound as depicted in a formula H and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula 6I and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: Cl, I and CH_3. The compound is formulated in a unit dosage form as a rapidly dissolving film. The invention further provides use of the pharmaceutical formulation in a patient in need of anaphylactic treatment.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWING(S):

[00010] The invention can be best understood by those having ordinary skill in the art by reference to the following detailed description when considered in conjunction with the accompanying drawings in which:

[00011] **FIG. 1** shows the generic chemical structure of a biologically inactive compound of this invention.

[00012] **FIGS. 2A-D** show exemplary compounds of the present invention, formula A shown as **FIG. 2A**, a species of formula A as **FIG. 2B**, formula B shown as **FIG. 2C** and a species of formula B as shown as **FIG. 2D**.

[00013] **FIGS. 3 A-D** show exemplary compounds of the present invention, formula C as **FIG. 3A**, a species of formula C as **FIG. 3B**, formula D shown as **FIG. 3C** and a species of formula D as shown as **FIG. 3D**.

REPLACEMENT SHEET

[00014] **FIGS. 4 A-D** show exemplary compounds of the present invention, formula E as **FIG. 4A**, a species of formula E as **FIG. 4B**, formula F shown as **FIG. 4C** and a species of formula F as shown as **FIG. 4D**.

[00015] **FIGS. 5 A-D** show exemplary compounds of the present invention, formula G shown as **FIG. 5A**, a species of formula G as shown as **FIG.5B**, a species of formula G as shown as **FIG. 5C and** a species of formula G as shown as **FIG. 5D**.

[00016] **FIGS. 6 A-D** show exemplary compounds of the present invention formula H shown as **FIG. 6A**, a species of formula H as **FIG. 6B**, formula I shown as **FIG. 6C** and a species of formula I as shown as **FIG. 6D**

[00017] **FIGS. 7 A-D** show Anwar A. Hussain and James E. Truelove compounds.

[00018] **FIG. 8** shows a stress-strain profile of the optimized epinephrine fast dissolving film.

[00019] **FIG. 9** shows a release profile of the epinephrine from the optimized fast dissolving film in 500 ml Simulated Saliva at 37 °C.

DETAILED DESCRIPTION OF THE INVENTION:

[00020] The present invention may be understood more readily by reference to the following detailed description of the invention. It is to be understood that this invention is not limited to the specific devices, methods, conditions or parameters described herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed invention. Also, as used in the specification including the appended claims, the singular forms "a," "an," and "the" include the plural, and reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise. Ranges may be expressed herein as from "about" or "approximately" one particular value and/or to "about" or "approximately" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment.

[00021] These and other aspects, features and advantages of the invention will be understood with reference to the detailed description herein, and will be realized

by means of the various elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description of the invention are exemplary and explanatory of preferred embodiments of the inventions, and are not restrictive of the invention as claimed. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Reference will now be made in detail to the presently preferred embodiments of the invention, examples of which are illustrated in the accompanying drawings. Throughout the following detailed description, the same reference numerals refer to the same elements in all figures.

[00022] The present invention provides a novel biologically inactive compound that can be metabolized in the body to produce a drug that has the biological activity of epinephrine. Epinephrine acts on nearly all body tissues. Its actions vary by tissue type and tissue expression of adrenergic receptors. For example, high levels of epinephrine cause smooth muscle relaxation in the airways but cause contraction of the smooth muscle that lines most arterioles. The present subject matter relates to modifying the physicochemical properties of epinephrine in order to enhance its permeability through biological membranes (sublingual and buccal membranes. FIG. 1 shows the generic chemical structure of a biologically inactive compound of this invention, while Table 1 shows exemplary prodrugs of epinephrine made by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring along with Log P values or a pharmaceutically acceptable salt thereof. The prodrugs of epinephrine preferably have a Log P value in the range of about 0.5-6.0. and more preferably between 1.0-5.0. This range was listed as a table of marketed sublingual tablets and films in Ashraf et. al "Considerations in developing sublingual tablets-An overview", Pharmaceutical Technology, 2014, 38(11). Log P is the logarithmic value of the ratio of two concentrations of a compound in a mixture of two immiscible liquids such as water and octanol at equilibrium. Log P values can be calculated mathematically by the use of PERCEPTA PLATFORM software (ACD Labs, Toronto, Ontario, Canada).

TABLE 1

R	Log P	R	Log P
R= $CHCH_2$	-0.20	R= CH_2COCH_3	-1.44
R= $CHCHCH_3$	+0.84	R= CH_2COCl	-0.21
R= $CHCH_2Cl$	+0.05	R= CH_2COI	+1.10
R= $CHCH_2I$	+1.36	R= CH_2OCH_3	-1.29
R= $CHClCH_2Cl$	+0.78	R= $CHICH_3$	+1.82
R= $CHICH_2I$	+4.0	R= $CClClCH_3$	+1.36
R= $CHCH_3CH_2CH_3$	+1.85	R= $CH_2CHCH_3CH_3$	+1.85
R= $CH_2CCH_3CH_3CH_3$	+2.55	R= $CH_2CHClCl$	+1.06
R= $CH_2CH_2CH_3$	+0.8	R= CH_2CHII	+4.09
R= CH_2Cl	-0.51	R= $CH_2CClClCl$	+2.97
R= CH_2I	+1.12	R= CH_2CIII	+7.68
R= CH_2F	-0.85	R= $CHClCl$	+0.66
R= $CIII$	+8.13	R= $CHII$	+4.03
R= Cl	+1.24	R= $CCH_3CH_3CHCH_3CH_3$	+3.24
R= I	+2.55	R= $NHCCH_3CH_3CH_3$	+1.63
R= F	+0.72	R= $NHCHCH_3CH_3$	+1.28
R= $CHCH_3CHCH_3CH_3$	+2.54	R= $NHCH_2CH_3$	+0.93
R= $CHClCHClCl$	+2.08	R= $NHCH_3$	+0.40
R= $CHICHII$	+7.09	R= SCH_3	+1.92
R= $CHFCHFF$	+0.80	R=SCH_2CH_3	+2.45
R= CH_2CHCH_2	+0.07	R=$SCHCH_3CH_3$	+2.80
R= $CClClCHClCl$	+4.18	R= $SCCH_3CH_3CH_3$	+3.15
R= $ClICHII$	+11.29	R= $CH_2C_6H_5$	+2.52
R= $CClClCl$	+2.90	R= C_6H_5	+3.10

[00023] A pro-drug is a derivative of epinephrine selected for fast permeability through sub-lingual and buccal membranes (*ie* a compound that dissolves in the oral cavity) and fast hydrolysis (half-life $t_{1/2}$ range from 1-6 minutes) by plasma enzymes to form epinephrine when delivered. These characteristics are physical properties of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film. Now referring to **FIG. 2**, derivatives of epinephrine are shown. **FIG. 2A**, showing structure **A** represents di-ester derivatives of epinephrine where the R_1 can be a short alkyl chain of CH_3, CH_2CH_3, $CH_2CH_2CH_3$, or $CH_2CH_2CH_2CH_3$, Cl or I. A representative molecule of this group compounds is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3-methylbutanoate) having a CLogP: 2.0114 shown as **FIG. 2B**. **FIG. 2C**, showing structure **B** represents derivatives of

epinephrine where R_2 = CH_3, Cl or I. A representative molecule of this group of compounds is 4-(1-hydroxy-2-(methylamino) ethyl)-1,2-phenylene bis(3,3-dimethylbutanoate) having a CLogP: 2.8094 shown as **FIG. 2D**. Adding H, CH_3, Cl or I change the Log P of the prodrug and adds a non-toxic moiety to the molecule. The rate of hydrolysis of each ester can increase or decrease depending on how the atom in position R_4 influences the ester group

[00024] Now referring to **FIG. 3**, derivatives of epinephrine are shown. **FIG. 3A**, showing structure **C** represents a derivative of epinephrine where R_3 = Cl or I. A representative molecule of the group is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dichloroacetate) having a CLogP: 1.4494 shown as **FIG. 3B**. **FIG. 3C**, showing structure **D** represents a derivative of epinephrine where R_4 = Cl or I. A representative molecule of the groups is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,2-trichloroacetae) having a CLogP: 2.8554 shown as **FIG. 3D**. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

[00025] Now referring to **FIG. 4** derivatives of epinephrine are shown. **FIG. 4A**, showing structure **E** represents a derivative of epinephrine where R1 = CH_3, Cl or I. A representative molecule is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-dimethylbutanoate) having a CLogP: 2.6294 shown as **FIG. 4B**. **FIG. 4C**, showing structure **F** represents a derivative of epinephrine where R_2 = CH_3, Cl or I. A representative molecule is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,3-trimethylbutanoate) having a CLogP: 3.4274 shown as **FIG. 4D**. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

[00026] Now referring to **FIG. 5**, derivatives of epinephrine are shown. **FIG. 5A**, showing structure **G** represents a derivative epinephrine where R_1 = H, I, Cl , $CH_2CH_2CH_3$ & $CH_2CH_2CH_2CH_3$, CH_2Cl, CH_2I or CH_2F. Representative molecules are: **5G** 4- (1-hydroxy-2-(methylamino) ethyl) 1,2-phenylene dicarboniodidate having a Clog: 1.084 (**FIG. 5B**);. **5G'** 4-(1-hydroxy-2-(methylamino-ethyl)-1,2-phenylene bis (2-iodoacetate) having a CLogP: 0.3834 (**FIG. 5C**) and Structure **5G"** 4-(1-hydroxy-2-methylamino)ethyl)-1,2-phenylene dibutyrate) having a CLogP: 1.2134 (**FIG. 5D**).

[00027] Now referring to **FIG. 6**, a derivative epinephrine is shown. **FIG. 6A**, showing structure **H** represents a derivative of epinephrine where R_2 = H, CH_3, Cl or I. A representative example is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene (2*E*,2'*E*)-bis(but-2-enoate) having a CLogP: 1.2054 shown as **FIG. 6B**. **FIG. 6C**, showing [[S]structure **I** represents a derivative of epinephrine where R_3 = Cl, I or CH_3. A representative example is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylbutanoate) having a CLogP: 1.8314 shown as **FIG. 6D**

[00028] Now referring to **FIG. 7**, the compounds of the invention as shown in US patent 3,809,714 and US patent 3,825,583 hereby incorporated by reference. Representative molecules include: **7A** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene diacetate having a DLogP: -0.9026. **7B** 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate) having a CLogP: 0.773300. **7C** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate having a CLogP: 0.1554. **7D** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate) having a CLogP: 1.5714. If these molecules show fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme (half-life 1-6 minutes) a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film. The subject matter includes: uses of a pharmaceutical formulation in a patient in need of anaphylactic treatment, wherein the pharmaceutical formulation is made of a compound selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient. A pharmaceutical formulation made of a compound selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

TABLE 2

R	Log P
Structure 7A R= CH_3	-0.97
Structure 7C R= CH_2CH_3	+0.09
Structure 7B R= $CHCH_3CH_3$	+0.79
Structure 7D R= $CCH_3CH_3CH_3$	+1.49

[00029] The present invention further provides a pharmaceutical composition made of at least one compound or mixture of compounds of the invention in a pharmaceutically acceptable carrier thereof. The invention features a pharmaceutical composition in unit dosage form formulated for sublingual or buccal administration. The delivery systems include: fast dissolving films, oral dissolving tablets, inhalation, and nasal delivery. In one embodiment, the unit dosage form of the present invention is a film for the delivery of epinephrine hydrochloride, as an anaphylactic treatment in a patient, such as for a pediatric or geriatric patient. A typical rapidly dissolving film is made of a drug, a water-soluble polymer, a plasticizer, a saliva stimulating agent, a surfactant and other fillers such as sweetening agents and flavors in case of bitter taste drugs. *See e.g.* A. Arya, A. Chandra, V. Sharma, and K. Pathak, "Fast dissolving oral films: An innovative drug delivery system and dosage form," *Int. J. ChemTech Res.*, vol. 2, no. 1, pp. 576–583, 2010.D. P. Lettre, "Formulation and Evaluation of Rapidly Disintegrating Film of Levocetrizine Hydrochloride," *Pharmacia*, vol. 2, no. 2, pp. 208–220, 2010.

[00030] For the present invention, the drug is epinephrine, a prodrug of epinephrine or a salt thereof. The typical dose of epinephrine for anaphylactic treatment is 0.3 to 0.5 mg in adults and 0.01 mg/kg up to a maximum of 0.3 mg in children administered through intramuscular route. In this study, 13mg/9 cm^2 of epinephrine (5.9 % w/w) are used as the dose size. This quantity is calculated for 6-7-year-old child according to Clark's rule Pediatric dose = Adult dose x (child's weight/150).

[000031] A typical dose of 40 mg was based on a study in rabbits that showed a dose bioequivalence between a 40mg epinephrine tablet administered sublingually

and 0.3 mg epinephrine administered intramuscularly using Epi pen, Injectors, Rawas-Qalaji et. al. Biopharm Drug Dispos. 27: 427-435 (2006). Furthermore, the time to reach maximum epinephrine concentration after a 0.3 mg EPIPEN (Mylan Specialty L.P.) injection in children is reported at 8±2 minutes. In another study, maximum plasma epinephrine concentration is reached within 34±14 minutes using 0.01 mg/kg dose injection of epinephrine subcutaneously in the deltoid region.

[00032] The polymer and the optimal amount of polymer are selected to obtain a non-sticky and functional film. A film-forming polymer should have good wetting property, high spread ability, good feeling in the mouth and should be safe and non-irritant. Many studies have showed that polymer content of at least 10 -15 % is needed in order to formulate proper film of proper thickness after drying in order to peel the film off from the release line. In one exemplary embodiment, the polymer is a water soluble modified hydroxypropyl starch that is specifically manufactured for aqueous film coating in immediate release solid oral dosage forms.

[00033] A plasticizer is used to form the rapidly dissolving film. The plasticizer enhances the flow of the polymer and improve the tensile strength and elongation of the fill. Several plasticizers are commonly used in rapidly dissolving film preparation such as glycerol, di-butylphthalate, and polyethylene glycols and they are usually used up to 20 % concentration of dry polymer weight.

[00034] The function of the surfactant is to facilitate the solubilization or wetting of the film and subsequently causing the film to disintegrate quickly, releasing the drug to be absorbed through the buccal cavity. Surfactants can include Tween 80, which is a complex mixture of polyoxyethylene ethers used as emulsifiers or dispersing agents in pharmaceuticals.

[00035] A saliva stimulating agent used to facilitate the delivery of the drug using a rapidly dissolving film to the patient. Other fillers, such as sweetening agents and flavors in case of bitter taste drugs and colors are added to the rapidly dissolving film to facilitate the delivery of the drug using a rapidly dissolving film to the patient. Typically, acids such as citric acid, malic acid, lactic acid and ascorbic acid are used as chemical stimulants of saliva secretion. However, citric acid is the most preferred among them. Xylitol and Tutti Frutti flavor are used for taste masking. Xylitol is an effective sweetening agent which has equal sweetness to sucrose.

[00037] Examples:Four formulations are prepared in this example. Epinephrine is soluble in Lycoat 720 (modified hydroxypropyl starch) water mixture. This hydrophilic polymer solubilizes epinephrine HCl, form a high viscosity gel that spreads well as we cast the film and lead to a non-sticky dry film after water evaporation. This polymer doesn't have any oxyethylene groups that can promote the oxidation of epinephrine nor it has glucose units that promotes water adsorption. The other ingredients added such as tween, glycerin decreased the rigidity of the film and improved elasticity. sodium metabisulfite was added to prevent and long-term oxidation of epinephrine HCl in the film. The citric acid brings the pH of the gel to the maximum stability range for epinephrine. The percentages of the polymer are shown in (Table 3). The polymer percentages are (20, 25, 27 and 30 %) of the total formulation weights. The polymer used in this example is LYCOAT (Ferromet). LYCOAT is a water soluble modified hydroxypropyl starch that is specifically manufactured for aqueous film coating in immediate release solid oral dosage forms.

[00038] **Table 3: List of the compositions of the four FDFs formulations.**

Ingredient (% w/w)	Use	F1	F2	F3	F4
Epinephrine HCl	Drug	5.9	5.9	5.9	5.9
Sodium Metabisulfite	Antioxidant	5.9	5.9	5.9	5.9
Lycoat 720 (hydroxypropyl starch)	Film-forming polymer	20	25	27	30
Glycerin	Plasticizer	3	3	3	3
Tween 80	Surfactant	2	2	2	2
Citric Acid Monohydrate	Buffer; increases absorption in oral cavity	0.5	0.5	0.5	0.5
Sodium Citrate Monobasic	Buffer	0.5	0.5	0.5	0.5

Xylitol	Sweetener	10	10	10	10
Tutti Frutti	Flavor	6	6	6	6
Water		46.2	41.2	39.2	36.2

[00039] Glycerin is used as a plasticizer to provide the proper elasticity for the film (Table 1). A plasticizer imparts a certain level of flexibility to the film by decreasing its brittleness. Films in this example are prepared using 3% glycerol which is equivalent to 10-15 % of the amount of polymer used.

[00040] Tween 80 is used as a surfactant (Table 2). Citric acid is used to adjust the pH and can be used in rapidly dissolving film as a saliva simulating agent to increase the secretion rate of saliva which will further improve the disintegration time of the film. Finally, the addition of an antioxidant is very important for the stability of epinephrine. Prompt oxidation of epinephrine in aqueous solutions results in a colored inactive product which has been reported. Therefore, different types of antioxidants are used in the commercial injectors such as sodium metabisulfite, EDTA and ascorbic acid achieving shelf life of two years. In this exemplary embodiment, the addition of sodium metabisuflite stabilizes the film.

[00041] However, films formed by formulations 1, 2 and 3 are too sticky after drying rendering them unusable. Formulation 4, having 30 % polymer content, formed a smooth, transparent, flexible and uniform film and therefore it is selected for further testing. The difference in stickiness is clearly related to the variation of the polymer content. This comes in agreement with a previous study that showed that using 22.5% of LYCOAT polymer formed a thin and flexible but sticky film at that concentration concluding that a higher percentage of polymer is needed.

[00042] Physical properties of the film prepared by formulation 4 are evaluated such as elastic modulus, thickness, content uniformity and dissolution time. Assessing these parameters is essential to determine the efficiency and usability of the film by patients. Elastic modulus is first studied as it represents a clear measure of the stiffness level of the film. It is calculated as the ratio of the applied stress over strain on a specific section.

[00043] Elastic's modulus= (Force at corresponding strain/cross section area) ×1/ (corresponding strain).

[00044] Now referring to **FIG. 8**, the profile of the film is illustrated showing a small increase in the applied strain to the film causes a quick increase in stress reaching a value of 0.1 MPa at 20 % strain level. As the strain increases further above 20 %, the increase magnitude in stress decreases gradually until it reaches a semi-plateau at value 0.16 MPa where % stress is 80 %. The value of elastic modulus is determined at 1.325 MPa which is an indication of very good flexibility of the film (Table 3).

[00045] **Table 4: List of physical properties of the optimized film**

Test	Results
Elastic Modulus	1.325±0.2 MPa
Thickness	0.29±0.01 mm
Content Uniformity	93% ± 10%

[00046] The thickness of the film at different locations is measured at 0.29 mm with very small margin of variability which is an indication of the high uniformity of the film (Table 4). A maximum thickness variation of 5 % is permitted in the preparation of the rapidly dissolving film. A uniform thickness across the film as it directly correlates with the accuracy of the dose in the film. Drug content in film is measured at 93 % ±10 indicating high level of consistency of epinephrine dose within the film (Table 2), as a limit of 85 -115 % of content uniformity is acceptable according to USP.

[00047] Now referring to **FIG. 9**, the dissolution profile of epinephrine from the film in terms of rate and extent in simulated saliva is determined on six samples of the optimized film. More than 90 % of epinephrine is released from the film within 7.2 minutes.

[00048] Taste and disintegration time of the optimized film are evaluated on 6 volunteers (Table 3). The disintegration time is the time when the film starts to break

or disintegrates. Volunteers reported 10 -30 seconds disintegration time (Table 3). This complies with the regulations set by United State Pharmecopeia (USP) for disintegration time of oral films (not exceeding 30 seconds). Bitterness of epinephrine is masked efficiently according to volunteer's comments (Table 5). Four volunteers sensed no bitterness of the film while the other two volunteers reported slight to very slight sensation of bitterness. Moreover, no tongue constriction is reported by any of the volunteers. This data presents clear proof of the efficiency of rapidly dissolving film in taste masking the bitterness of epinephrine and an indication of strong potential for using a rapidly dissolving film as a replacement therapy of epinephrine injections for children.

[00049] **Table 5**: *In vivo* taste and disintegration time evaluation of the optimized epinephrine FDF.

Volunteer	Bitterness	Tongue Constriction	Disintegration Time
1	None	None	~10 seconds
2	None	None	~10 seconds
3	Slight	None	~20 seconds
4	None	None	~30 seconds
5	Very slight	None	~20 seconds
6	None	None	~30 seconds

[00050] Materials--Epinpherine hydrochloride, sodium metabisulfite, citric acid monohydrate and sodium citrate monobasic are purchased from Sigma Aldrich (St. Louis, MO). Lycoat® RS720 is obtained from Roquette (Lestrem, France). Glycerin and tween 80 are purchased from Fisher Chemicals (Pittsburg, PA). Xylitol is purchased from Gallipot (St. Paul, MN). Tutti Frutti is obtained from LorAnn Oils (Lansing, MI). Film Preparation--Several rapidly dissolving films are prepared by a solvent casting technique to choose the optimum film formulation. The formulation

compositions of the rapidly dissolving film are mentioned in Table 3. LYCOAT and Xylitol are dissolved in warm water. The solution is then placed in a sonicator for two hours and then the solution is left overnight to ensure the removal of all entrapped air bubbles. Other excipients and Epinephrine HCl are added to the solution on the next day at room temperature. The mixture is then placed again in a sonicator for 40 minutes. The mixture is then spread onto a checkered paper covered by plastic sheet using a stainless-steel bar applicator. The film is left to dry overnight and is cut into 9 mm^2 small film strips.

[00053] Physical properties-The thickness and elastic modulus of the optimized film is evaluated using Dynamic Mechanical Analyzer (Q800 DMA, TA instruments, New Castle, DE). This is important to evaluate tensile properties of the films. Three strips of the optimized films are tested at 25 °C according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02). Each film is positioned between the grips of the instrument. The preload force is set at 0.01 N and the final force at 15N. The initial grip separation is set to 60 mm and crosshead speed is set to 500 mm/min. The test is terminated when the film breaks. Elastic modulus is determined as the slope of the straight-line part of the stress-strain curve and it is expressed in force per unit area (MPa).

[00054] Drug content uniformity: Specific areas are cut from six different films and weighted to calculate the estimated amount of drug in each area. Films are then dissolved in 100 ml of citric acid buffer. The media are stirred and then filtered using 0.45 um filters (Millipore Corporation, Millipore, Vimodron, Italy) and epinephrine content is assessed using UVmini-1240 UV-Vis Spectrophotometer (Shimadzu, Japan) at wavelength 280 nm. Epinephrine content is determined by calculating the percentage of the measured epinephrine to the estimated amount in each film.

[00055] *In vitro* dissolution test: For the dissolution test, rapidly dissolving film are evaluated using USP dissolution apparatus II, paddle (Distek Evolution 6100, North Brunswick, NJ). Six strips are placed in different 1 L vessels containing 500 ml Simulated Saliva. The temperature of the dissolution media is set to 37 C and rpm is set to 50 rpm. Samples are taken at different time points throughout the time of the experiment (15 mins), and the amount of epinephrine released in the media is determined by UVmini-1240 UV-Vis Spectrophotometer (Shimadzu, Japan) at 280 nm.

[00056] Human taste panel--To evaluate the palatability of optimized epinephrine film, a taste evaluation study is performed on six healthy volunteers. The study is carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), and all volunteers are informed in advance of the related details and the goal of the study and their consents are obtained. Volunteers are asked to place the film on the interior surface of their buccal cavity until the film is fully disintegrated. Volunteers then rinsed their mouths with drinking water. Volunteers have to report their findings of the presence of bitterness or not, any tongue restriction and how long it took for full disintegration of the film.

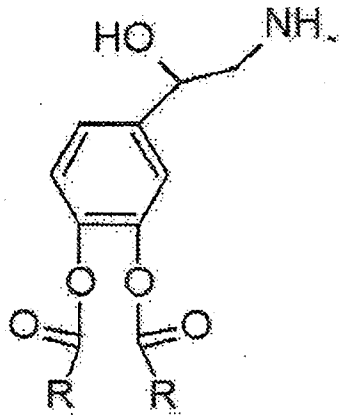
[00057] Equivalent elements can be substituted for the ones set forth above such that they perform in substantially the same manner in substantially the same way for achieving substantially the same result. It is believed that the system and method of the present invention and many of its attendant advantages will be understood by the foregoing description. It is also believed that it will be apparent that various changes may be made in the form, construction and arrangement of the components thereof without departing from the scope and spirit of the invention or without sacrificing all of its material advantages. The form herein before described being merely exemplary and explanatory embodiment thereof. It is the intention of the following claims to encompass and include such changes.

Attorney Docket Number
24050.0001PCT

REPLACEMENT SHEET

CLAIMS

1. A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:



wherein R is selected from the group consisting of: $-CHCH_2$, $-CHCHCH_3$, $-CH_2-CH_2-Cl$, $-CHCH_2I$, $-CH(Cl)CH_2(Cl)$, $-CH(I)CH_2(I)$, $-CH(CH_3)CH_2(CH_3)$, $-CH_2C(CH_3)_3$, $-CH_2CH_2CH_3$, $-CH_2Cl$, $-CH_2I$, $-CH_2F$, H, Cl, I, F, $-CH(CH_3)CH(CH_3)_2$, $-CH(Cl)CH(Cl)_2$, $-CH(I)CH(I)_2$, $-CH(F)CH(F)_2$, $-CH_2CHCH_2$, $-C(Cl)_2CH(Cl)_2$, $-C(I)_2CH(I)_2$, $-C(Cl)_3$, $C(I)_3$, $-CH_2COCH_3$, $-CH_2COCl$, $-CH_2CO(I)$, $-CH_2OCH_3$, $-CH(I)(CH_3)$, $-C(Cl)_2(CH_3)$, $-CH_2CH(CH3)_2$, $-CH_2CH(Cl)_2$, $-CH_2CH(I)_2$, $-CH_2C(Cl)_3$, $-CH_2C(I)_3$, $-CH(Cl)_2$, $-CH(I)_2$, $-C(CH3)_2CH(CH3)_2$, $-NH-C(CH_3)_3$, $-NH-CH(CH_3)_2$, $-NH-CH_2CH_3$, $-NH-CH_3$, $-SCH_3$, $-SCH_2CH_3$, $-SCH(CH3)_2$, $-SC(CH_3)_3$, $-CH_2C_6H_5$ and $-C_6H_5$ or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0.

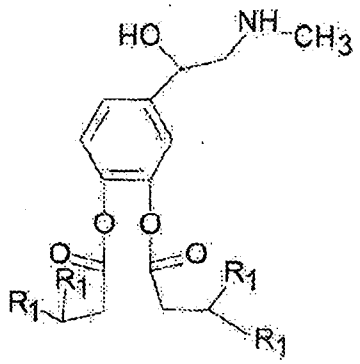
2.

3. The compound of claim 1 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

4. Use of the pharmaceutical composition of claims 1 or 3 in a patient in need of anaphylactic treatment.

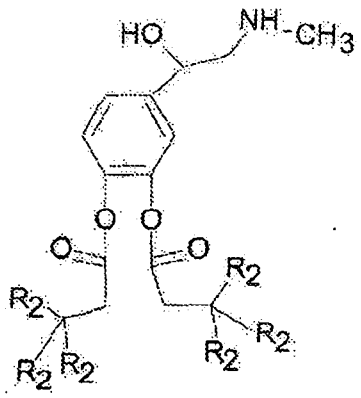
REPLACEMENT SHEET

5. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, Cl and I.

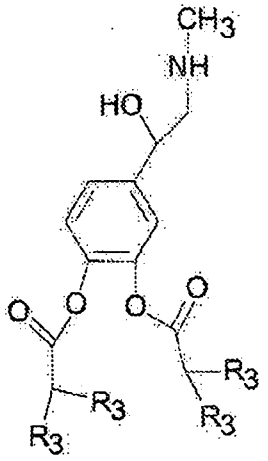
6. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: CH_3, Cl and I.

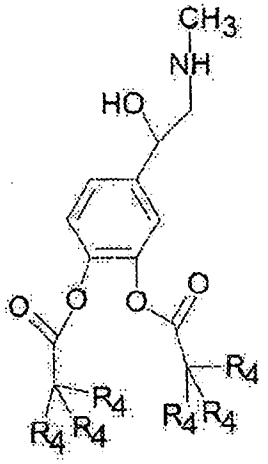
REPLACEMENT SHEET

7. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: Cl and I.

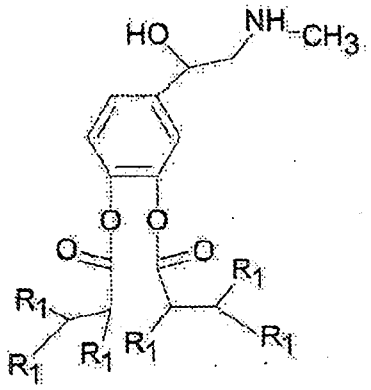
8. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_4 is selected for the group consisting of: Cl and I.

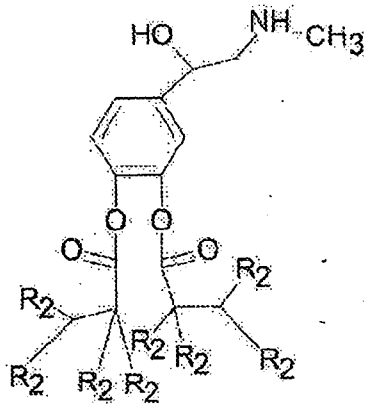
REPLACEMENT SHEET

9. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, Cl and I.

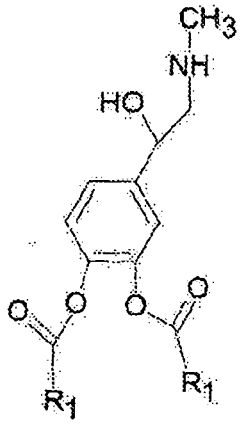
10. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: CH_3, Cl and I.

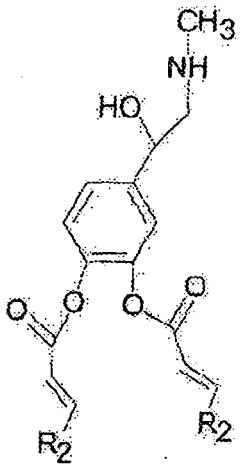
REPLACEMENT SHEET

11. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: H, I, Cl, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, CH_2Cl, CH_2I and CH_2F.

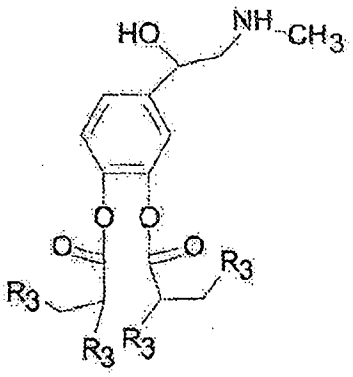
12. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3, Cl and I.

REPLACEMENT SHEET

13. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: Cl, I and CH_3

14. A method to deliver a prodrug of epinephrine comprising: the steps of: providing epinephrine in a unit dosage form, formulated for sublingual or buccal administration, wherein the unit dosage form is a rapidly dissolving film, to a patient in need of treatment thereof, wherein the prodrugs of epinephrine has a Log P value in the range of about 0.5-6.0.

15.

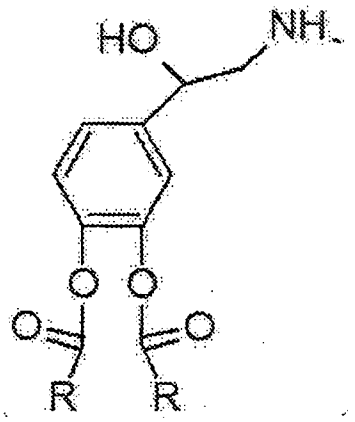
16. The method of claim 14 wherein the prodrugs of epinephrine has a Log P value in the range of about 1.0-5.0.

17.

18. The method of claim 14 further comprising: providing said prodrug of epinephrine in a unit dosage form to a patient in need of anaphylactic treatment.

REPLACEMENT SHEET

19. A compound of a Formula:



wherein R is selected from the group consisting of: CH_3, CH_2CH_3, and $CH(CH_3)_2$; wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration.

20. The compound of claim 19, wherein the compound is selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

21. The compound of claim 19, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

22. Use of the pharmaceutical formulation of claims 19 and 21 in a patient in need of anaphylactic treatment.

Replacement Sheet

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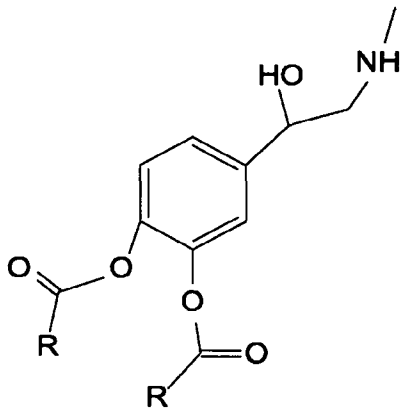
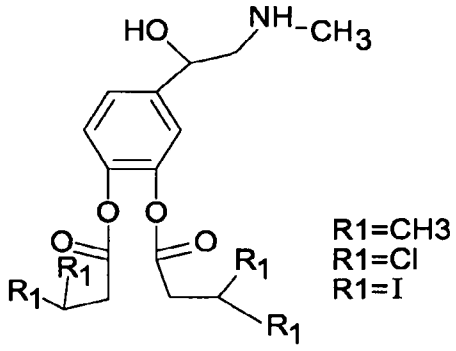


FIG. 1

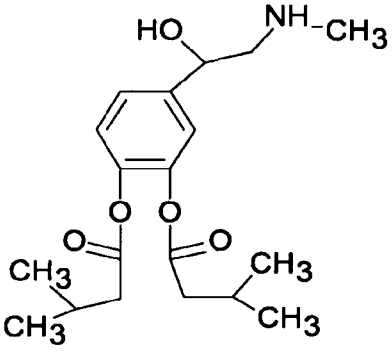
Replacement Sheet

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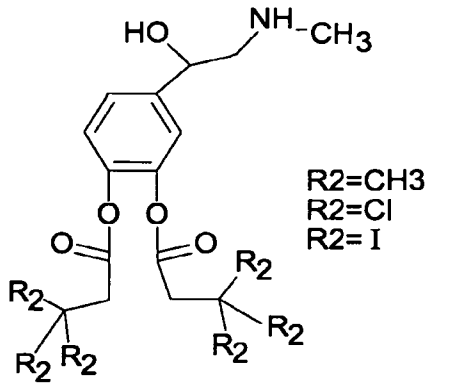
Formula A

FIG. 2A



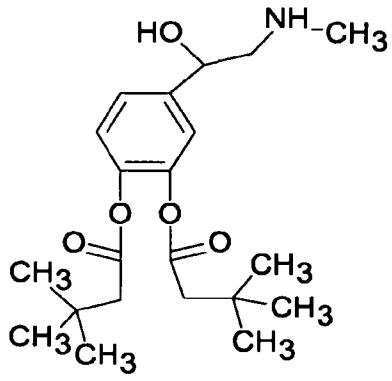
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3-methylbutanoate)
CLogP: 2.0114

FIG. 2B



Formula B

FIG. 2C

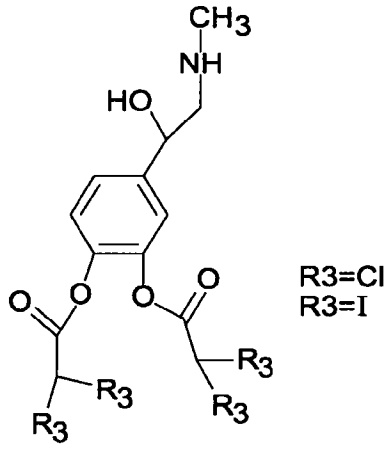


4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3,3-dimethylbutanoate)
CLogP: 2.8094

FIG. 2D

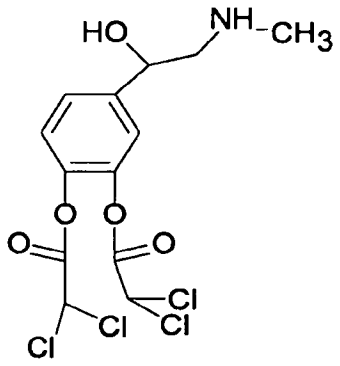
Replacement Sheet

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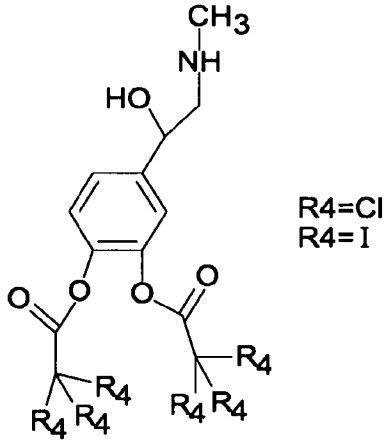
Formula C

FIG. 3A



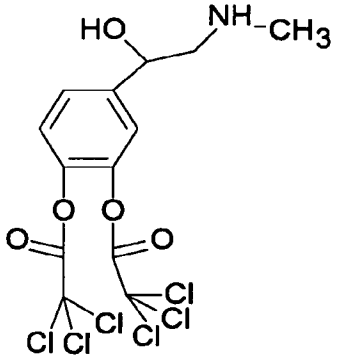
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dichloroacetate)
CLogP: 1.4494

FIG. 3B



Formula D

FIG. 3C

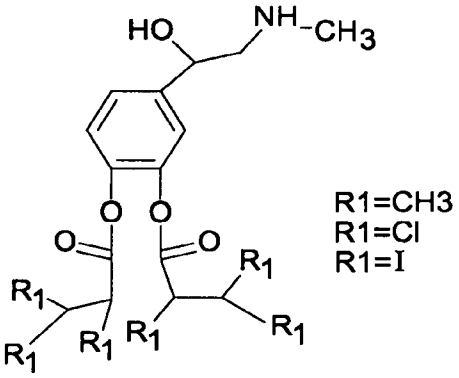


4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,2-trichloroacetate)
CLogP: 2.8554

FIG. 3D

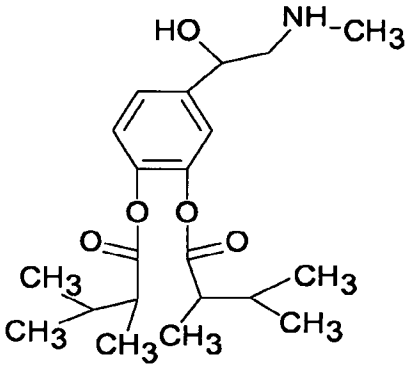
Replacement Sheet

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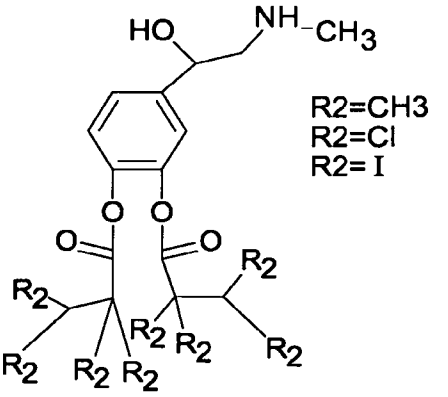
Formula E

FIG. 4A



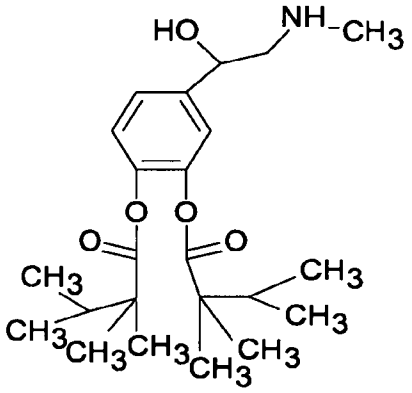
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-dimethylbutanoate)
CLogP: 2.6294

FIG. 4B



Formula F

FIG. 4C

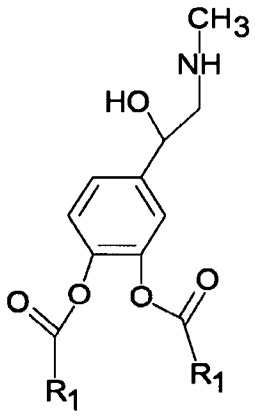


4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3,3-trimethylbutanoate)
CLogP: 3.4274

FIG. 4D

Replacement Sheet

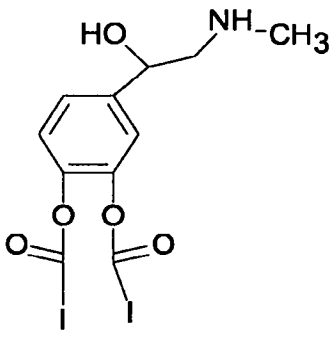
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R1=H
R1= I
R1=Cl
R1=CH2CH2CH3
R1=CH2CH2CH2CH3
R1=CH2Cl
R1=CH2I
R1=CH2F

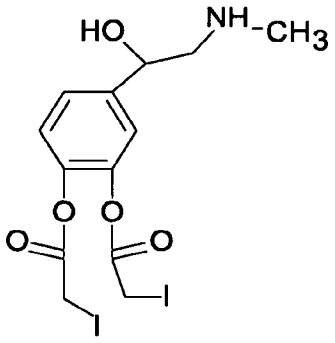
Formula G

FIG. 5A



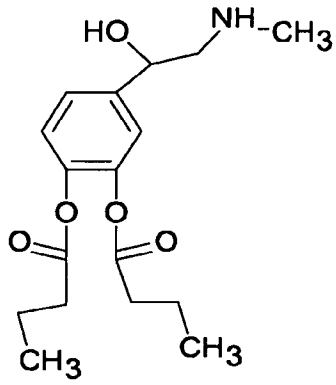
4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene dicarboniodidate
CLogP: 1.0854

FIG. 5B



4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene bis(2-iodoacetate)
CLogP: 0.3834

FIG. 5C

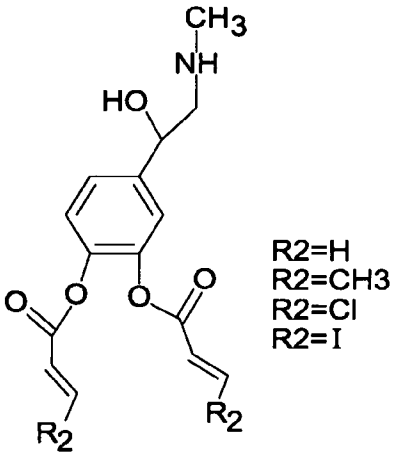


4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene dibutyrate
CLogP: 1.2134

FIG. 5D

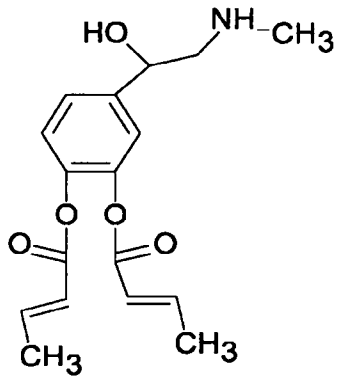
Replacement Sheet

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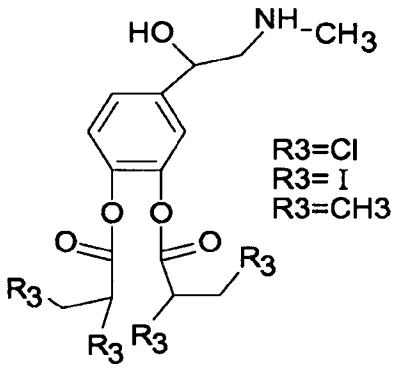
Formula H

FIG. 6A



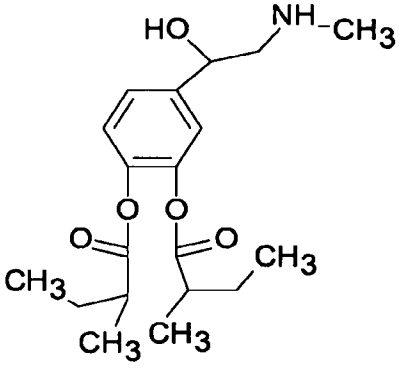
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene (2*E*,2'*E*)-bis(but-2-enoate)
CLogP: 1.2054

FIG. 6B



Formula I

FIG. 6C



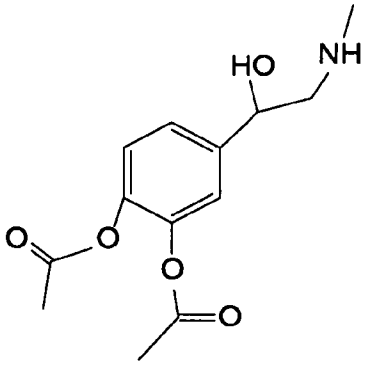
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylbutanoate)
CLogP: 1.8314

FIG. 6D

AMENDED SHEET - IPEA/US

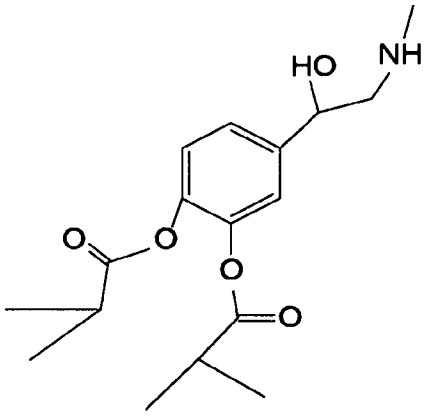
Replacement Sheet

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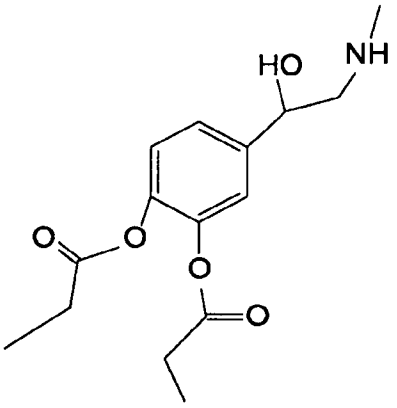
4-(1-hydroxy-2-(methylamino)ethyl)-1, 2-phenylene diacetate
CLogP: -0.9026

FIG. 7A



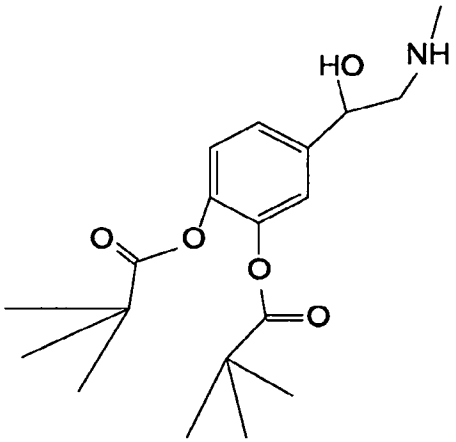
4-(1-hydroxy-2-(methylamino)ethyl)-1, 2-phenylene bis(2-methylpropanoate)
CLogP: 0.7733

FIG. 7B



4-(1-hydroxy-2-(methylamino)ethyl)-1, 2-phenylene dipropanoate
CLogP: 0.1554

FIG. 7C



4-(1-hydroxy-2-(methylamino)ethyl)-1, 2-phenylene bis(2,2-dimethylpropanoate)
CLogP: 1.5714

FIG. 7D

Replacement Sheet

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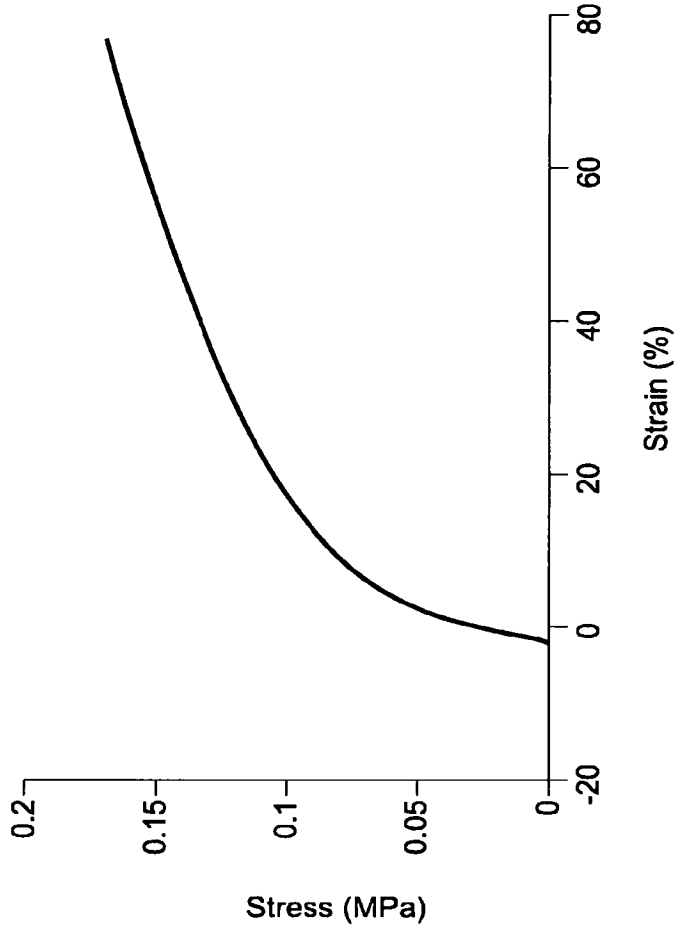


FIG. 8

Replacement Sheet

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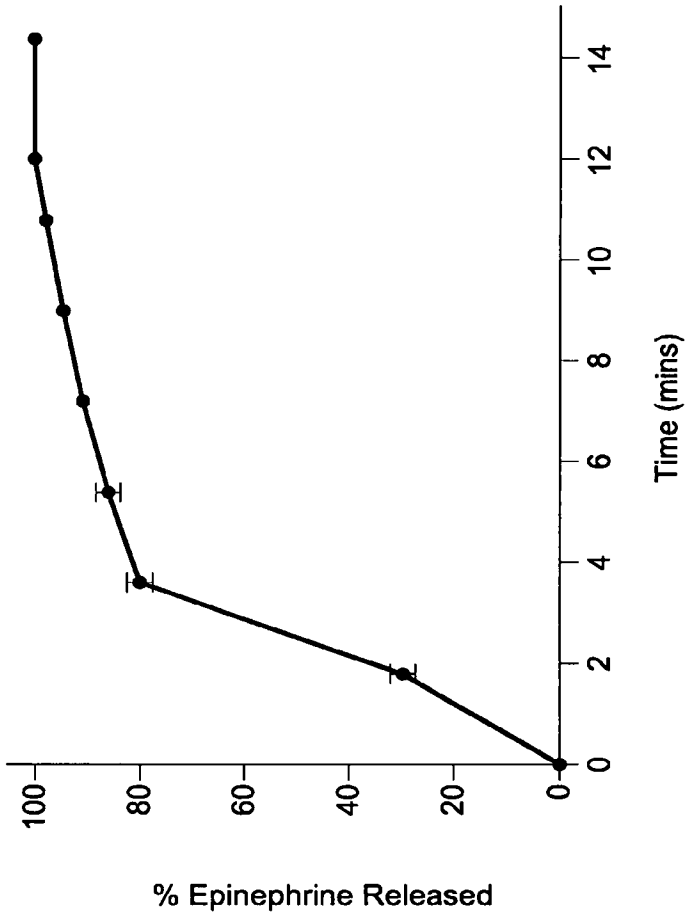


FIG. 9

APPL. NO.: PCT/US2017/060761

APPLICANT: Iono Phama, LLC

FILED: 09 NOV 2017

TITLE: PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

Article 34 Letter

Dear Sirs:

REPLACMENT FIGURES 2-6 are herewith submitted to correct confusion caused by the renumbering of the drawing per the PCT requirement. The original figures referred to structure numbers, while the replacement figures were numerically sequential, thus causing confusion regarding the structure number.

The specification has been updated to remove the confusion between structure reference and figure numbers that was inadvertently caused by the submission of renumbered figures. No new matter is added. The reference paragraphs are to the replacement specification as filed herewith.

Claim 1 has been amended to standardize the nomenclature according to the suggestion of the examiner and to incorporate the subject matter of claim 2 and 15.

Claims 2 canceled.

Claim 3 amended to depend on claim 1.

Claim 4 amended to depend on claims 1 and 3.

Claim 5 is amended to be an independent claim and to add the compound of formula A. Support **FIG. 2** and [0012] and [0023] and to limit the R group to: wherein R_1 is selected for the group consisting of: CH_3, Cl and I.

Claim 6 is amended to be an independent claim and to add the compound of formula B. Support **FIG. 2** and [0012] and [0023] and the r group CH_3

Claim 7 is amended to be an independent claim and to add the compound of formula C. Support FIG. 3 and [0013] and [0024].

Claim 8 is amended to be an independent claim and to add the compound of formula D. Support FIG. 3 and [0013] and [0024].

Claim 9 is amended to be an independent claim and to add the compound of formula E. Support FIG. 4 and [0014] and [0025]and the r group CH_3

Claim 10 is amended to be an independent claim and to add the compound of formula F. Support FIG. 4 and [0014] and [0025] and the r group CH_3

Claim 11 is amended to be an independent claim and to add the compound of formula G. Support FIG. 5 and [0015] and [0025].

Claim 12 is amended to be an independent claim and to add the compound of formula H. Support FIG. 6 and [0016] and [0026].

Claim 13 is amended to be an independent claim and to add the compound of formula I. Support FIG. 6 and [0016] and [0027].

Claim 14 epinephrine was deleted and the Log P value in the range of about 0.5-6.0 for the prodrug from claim 15 was added.

Claim 15 cancelled.

Claim 16 original.

Claim 17 cancelled.

Claim 18 original.

Claim 19 reformat ~~$CHCH_3CH_3$~~ to $CH(CH_3)_2$ and delete structure: ~~$CCH_3CH_3CH_3$~~,

Claim 20 structure ~~4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate).~~

Claim 21 original.

Claim 22 amended to depend on claim 19

Comments:

It is noted that claim 1 is anticipated by a compound at col 5, designated as compound 7. Bodor teaches compound 7 has the R group -C(CH3)3. However, the R group claimed is: -CH2C(CH3)3, which is not the same compound. The applicant has selected the claimed R group based on log P values (as claimed) and not on any other physical chemical factors. Thus, the disclosure in Bodor does not disclose or suggest the claimed compounds to one skilled in the art. The same argument applies to the obviousness of claims 5, 11 and 13.

Regarding claims 1-4, it is beyond the knowledge of someone skillful in the art to combine the teachings of Rawas-Qalaji and Bodor to come up with the concept of modifying Bodor's compounds in structure I (a general formula for epinephrine prodrug derivatives), which he teaches for the treatment of hemorrhoids as a topical rectal application and then apply Rawas-Qalaji teachings to modify the application in order to treat anaphylactic shock by sublingual or buccal absorption. Bodor's compounds structure II and III are not epinephrine derivatives and are not effective to treat anaphylactic shock. It is beyond the knowledge of someone skillful in the art to combine the teachings of Rawas-Qalaji with Bodor to obtain the claimed invention. There is no scientific rationale to use Bodor's compounds for anaphylaxis as he teaches for the treatment of hemorrhoids (topical rectal application). On the other hand, Rawas-Qalaji teach about treating anaphylaxis by sublingual or buccal absorption of epinephrine. Bodor doesn't teach that any compounds included in structures I, II and III are effective for treating anaphylaxis. To the contrary, Bodor teaches that his compounds are active locally in the rectal area. Usually, Hemorrhoids are treated locally and not by oral or sublingual route (this is a medical fact). It is novel for someone to propose that Bodor's compounds can be used to

treat anaphylaxis and it is beyond the knowledge of someone skillful in the art. In the present invention epinephrine prodrugs are absorbed by sublingual tissues then cleaved in plasma in order to release epinephrine.

Claim 1 has been amendment: "A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration"

Regarding claim 5, Bodor teaches compound 17 which has R group -CHCHCH2CHCH2; however, this compound is not set out in any of the pending claims. Bodor's compound 17 has two side chains of six carbons each with two double bonds while the compound in 2A [0023] has two side chains of 4 carbons each with no double bonds. We disagree with the comment "but the compound of Bodor doesn't have the propyl substituent branching off the third carbon of the hexadienoyl moiety."

Regarding claim 11, in compound 5G [00026] we have listed R1 as -CH2CH2CH3 or -CH2CH2CH2CH3. Bodor teaches away from R1 as -CH2CH2CH3 or -CH2CH2CH2CH3. In fact, compound 17 in Bodor patent has R listed as CHCHCH2CHCH2. This R group is not listed in any of claims. The fifth substituent listed for compound 5G is -CH2CH2CH2CH3. In compound 17, Bodor teaches away from R1 as -CH2CH2CH2CH3. In fact, compound 17 in Bodor patent has R group listed as CHCHCH2CHCH2 with two double bonds. This R group is not listed in any of our claims and doesn't bear any similarity to compound 5G with R1 -CH2CH2CH2CH3. It is noted that: "but the compound of Bodor doesn't teach any of the substituents exactly" which is a true comment. Our argument, why would someone skilled in the art look at Bodor's compound 17 and reduce the number of side chains to 4 and saturate two double bonds?

Regarding claim 13, compound 6l para [0027] when the R is CH3 in formula I we get a side chain -CH1(CH3)CH2(CH3) and not -CH2(CH3)CH2(CH3) and not as recited in the opinion on patentability R3 -CH2CH2CH2CH3. In compound 17, Bodor teaches away from the claimed subgroup. In compound 17 Bodor teaches R as -CHCHCH2CHCH2 with two double bonds. There are no double bonds in compound 6l. When the R3 group in compound 6l is CH3, the ester side chain will become CH2(CH3)CH2(CH3) and not as shown by the reviewer R3 -CH2CH2CH2CH3. Claim 13 does not claim CH2(CH3)CH2(CH3) as an R group.

In compound 17, Bodor teaches away from this subgroup. In compound 17, Bodor teaches for -CHCHCH2CHCH2 with two double bonds and no side branching. Since there are no double bonds in compound 6l, and considering the reviewer's comment "but the compound of Bodor doesn't teach the branching of R3 group or any of the R3 substituent directly", we find the comparison between Bodor compound 17 and compound 6l not clearly justified

Regarding claims 14 and 18 since Rawas-Qalaji teaches away from the use of any prodrugs in fast dissolving tablets or films, we have amended the claim to include the Log P value in the range of about 0.5-6.0 of a prodrug in the claim and omit epinephrine. The problem with epinephrine is that it has a very low log P (highly hydrophilic) and cannot be absorbed by the GI tract. In addition, within the GI tract, it can be oxidized in the intestinal lumen and can lose its efficacy. Bodor teaches about using epinephrine prodrugs rectally to treat hemorrhoids and to overcome the stability problem. Bodor does not teach about the **systemic absorption** of epinephrine prodrugs. On the other hand, Rawas-Qalaji teaches about the use of epinephrine in fast dissolving tablets but does not teach about using Log P to evaluate epinephrine or the design of new prodrugs to improve systemic

absorption. Neither Rawas-Qalaji and Bodor do not teach about enhancing the membrane permeability by increasing lipophilicity of the prodrug molecules. It is highly unlikely for someone skillful in the art to combine the teachings of Rawas-Qalaji and Bodor with log P and propose that increasing log P between 0.5-6 can increase sublingual permeability. Consequently, the presently formatted claims are not disclosed or suggested in the prior art.

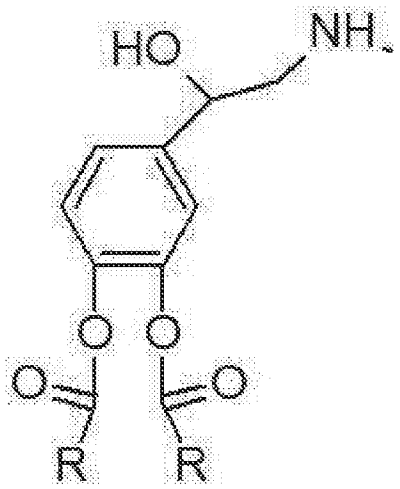
Claims 19-22 structure 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate was deleted. The remaining compounds are not disclosed or suggested in the cited art.

Applicant respectfully suggest that the pending claims are novel, non-obvious and have technical applicability.

Respectfully Submitted
/Susan B Fentress/
Susan B. Fentress, Agent of record 31327
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Telephone No. 901-371-6664
Email: sfentress@veritaygroup.com
Dated: April 20, 2018

AMENDMENTS TO THE CLAIMS

1. (previously presented) A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:



wherein R is selected from the group consisting of: -$CHCH_2$, -$CHCHCH_3$, -CH_2-CH_2-Cl, -$CHCH_2$I, -$CH(Cl)CH_2$ (Cl), -$CH(I)CH_2$(I), -$CH(CH_3)CH_2(CH_3)$, -$CH_2C(CH_3)_3$, -$CH_2CH_2CH_3$, -CH_2Cl, -CH_2I, -CH_2F, H, Cl, I, F, -$CH(CH_3)CH(CH_3)_2$, -$CH(Cl)CH(Cl)_2$, -$CH(I)CH(I)_2$, -$CH(F)CH(F)_2$, -CH_2CHCH_2, -$C(Cl)_2CH(Cl)_2$, -$C(I)_2CH(I)_2$, -$C(Cl)_3$, $C(I)_3$, -CH_2COCH_3, -CH_2COCl, -$CH_2CO(I)$, -CH_2OCH_3, -$CH(I)(CH_3)$, -$C(Cl)_2(CH_3)$, -$CH_2CH(CH3)_2$, -$CH_2CH(Cl)_2$, -$CH_2CH(I)_2$, -$CH_2C(Cl)_3$, -$CH_2C(I)_3$, -$CH(Cl)_2$, -$CH(I)_2$, -$C(CH3)_2CH(CH3)_2$, -NH-$C(CH_3)_3$, -NH-$CH(CH_3)_2$, -NH-CH_2CH_3, -NH-CH_3, -SCH_3, -SCH_2CH_3, -$SCH(CH3)_2$, -$SC(CH_3)_3$, -$CH_2C_6H_5$ and -C_6H_5 or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0.

2. (cancelled)

3. (previously presented) The compound of claim 1 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

4.-13 (cancelled)

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14. (previously presented) A method to deliver a prodrug of epinephrine comprising: the steps of: providing epinephrine in a unit dosage form, formulated for sublingual or buccal administration, wherein the unit dosage form is a rapidly dissolving film, to a patient in need of treatment thereof, wherein the prodrugs of epinephrine has a Log P value in the range of about 0.5-6.0.

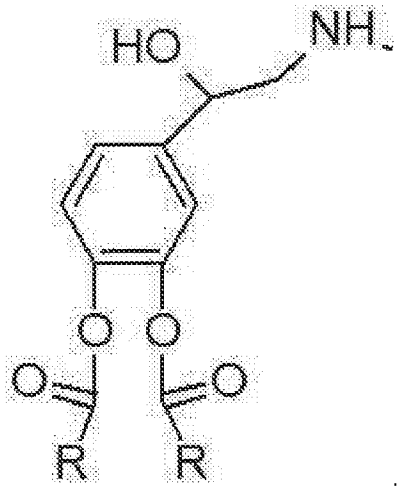
15. (cancelled)

16. (original) The method of claim 14 wherein the prodrugs of epinephrine has a Log P value in the range of about 1.0-5.0.

17. (cancelled)

18. (original) The method of claim 14 further comprising: providing said prodrug of epinephrine in a unit dosage form to a patient in need of anaphylactic treatment.

19. (previously presented) A compound of a Formula:



wherein R is selected from the group consisting of: CH_3, CH_2CH_3, and $CH(CH_3)_2$ wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration.

20. (previously presented) The compound of claim 19, wherein the compound is selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-

methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

21 (original) The compound of claim 19, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

22. (cancelled).

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AMENDMENTS TO THE SPECIFICATION

Page 1, just below the title, insert the following headings and paragraph:

CROSS REFERENCE TO RELATED APPLICATIONS:

This application is a § 371 National Stage Application of PCT/US17/60761 application filed 09-NOV 2017 and U.S. provisional patent application Serial No. 62/421,316 filed 13-NOV-2016, under 35 U.S.C. § 111(a) (hereby specifically incorporated herein by reference).

[0001] STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT:

[0002] None.

REFERENCE TO SEQUENCE LISTING, A TABLE FOR A COMPUTER PROGRAM LISTING, COMPACT DISC APPENDIX:

[0003] None.

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Pharmaceutical Formulation for Sublingual or Buccal Delivery of Epinephrine

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [■] The attached application, or
- [ ] United States application or PCT international application number _____

filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Dr. Hassan Almoazen Date (Optional): 4-30-2019

Signature: Hassan ALMOAZEN

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1 minute 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.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	Hassan Almoazen
Filer:	Susan Bennett Fentress
Attorney Docket Number:	24050.0001US

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
BASIC NATIONAL STAGE FEE	2631	1	150	150
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**150**

Electronic Acknowledgement Receipt

EFS ID:	35922700
Application Number:	16347625
International Application Number:	PCT/US2017/060761
Confirmation Number:	8118
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	Hassan Almoazen
Customer Number:	76447
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001US
Receipt Date:	06-MAY-2019
Filing Date:	
Time Stamp:	12:03:23
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$150
RAM confirmation Number	050619INTEFSW12042100
Deposit Account	601480
Authorized User	Susan Fentress

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	371transmital.pdf	756241 378a54a332d8325178956d45342ef31f45c10f7f	no	3
Warnings:					
Information:					
2	Application Data Sheet	ads.pdf	1509151 74e2db340be00bfaa695b8abfcfbc055c4ba42f4	no	7
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Information Disclosure Statement (IDS) Form (SB08)	ids.pdf	605218 3ad8ec3a1617171147c245b5feff665ea1f82ef0	no	4
Warnings:					
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4	Non Patent Literature	ArunArya.pdf	237418 b1377e130c98a6a1ccb6de03525bb73393716806	no	8
Warnings:					
Information:					
5	Non Patent Literature	PCTUS17607report2.pdf	2327476 6b0c5f15be97f2ec4bf30e0033bad26c87f8a6b6	no	43
Warnings:					
Information:					
6	Non Patent Literature	PCTUS1760761report.pdf	647745 19e643e1e599ef19eb27395fd95c368a6af66adb	no	10

Warnings:					
Information:					
7	Non Patent Literature	pubchem492.pdf	160033 929d07c99b648c33109993bff6f45a539826bb8d	no	14
Warnings:					
Information:					
8	Non Patent Literature	Qalref.pdf	240793 c9399c684b4cd5f59cf14a90ba70b914b950aef2	no	6
Warnings:					
Information:					
9	Non Patent Literature	rawas-qalaji.pdf	198659 be585a42498a00464ee82f1d70ba7d8e6d0705b7	no	6
Warnings:					
Information:					
10	Non Patent Literature	SINGH.pdf	145005 baa03ce8b2d9ea285e99da8aae8fff7ad9aa7cc3	no	6
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Information:					
11	Non Patent Literature	pubchem.pdf	160033 13214c6ca958d804a7d7a2315561db4962d23f0a	no	14
Warnings:					
Information:					
12	Petition to make special under Patent Prosecution Hwy	pph.pdf	296855 2efd80599c5d7b9f91bd9f2061d87b5716c03646	no	2
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13	Petition to make special under Patent Prosecution Hwy	chapter2.pdf	2329430 383d102e1691fb5c0c428545483b8267e8d36108	no	43
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14	Non Patent Literature	hussain.pdf	648028 e727f9aff3d92183e53af787da0970e3102d3cdb	no	3
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15	Claims	preliminaryamendmentclaims.pdf	214976 008b2c91e4c8af1ad5e67717d995398bb229f205	no	3
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16	Specification	preliminaryamendmentspec.pdf	57232 5bf2a4531eb89a5c148c18a5c0dcdcf6e67b7107	no	1
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17	Preliminary Amendment	preliminaryamendmentupdated.pdf	142021 219fe3882275af09d1f9dec5e1564457b9471753	no	2
Warnings:					
Information:					
18	Oath or Declaration filed	decupdated.pdf	146864 bca53beee404cddc753bb9e03e28b7608efbe27e	no	1
Warnings:					
Information:					
19	Fee Worksheet (SB06)	fee-info.pdf	29822 be3569098a21bf90a860007816f0b93682b783a2	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	10853000	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CONFIRMATION NO.:	Unassigned
APPLICATION NO.:	Unassigned (371 application of PCT/US17/60761)
FILED:	Concurrently Herewith
ART UNIT:	Unassigned
TITLE:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

PRELIMINARY AMENDMENT

Dear Sir:

Prior to the initial examination on the merits, please amend the above-identified applications as follows:

Amendments to the Specification: begin on page 2 of this paper.

Amendments to the Abstract: none.

Amendments to the Claims: begin on page 3 of this paper.

Amendments to the Drawings: None.

Remarks/Arguments: begin on page 6 of this pager.

Remarks:

This application is a § 371 National Stage Application of PCT/US17/60761 application filed 11-09-2017 wherein claims 1. 3-14,16,18-22 were found in the International Preliminary Report on Patentability (as amended by article 34) to be novel, non-obvious and have technical merit.

Applicant respectfully submits that the pending claims are in condition for allowance based on the patent prosecution highway request filed herewith. The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. 60-1480.

Respectfully submitted,

/Susan B Fentress/

Susan B. Fentress, Agent of Record
Reg. No. 31327
20 S Dudley, No 803
Memphis, Tennessee 38103
Telephone No. (901) 525-1455
Dated: May 6, 2019

PTO-1390 (01-18)
Approved for use through 8/31/2019. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

Attorney Docket No.	U.S. Application No. (if known, see 37 CFR 1.5)
24050.0001US	62/421,316

International Application No.	International Filing Date	Priority Date Claimed
PCT/US17/60761	11-09-2017	11-13-2016

Title of Invention
PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

First Named Inventor
Hassan Almoazen

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). NOTE: The express request under 35 U.S.C. 371(f) will not be effective unless the requirements under 35 U.S.C. 371(c)(1), (2), and (4) for payment of the basic national fee, copy of the International Application and English translation thereof (if required), and the oath or declaration of the inventor(s) have been received.

2. ☐ A copy of the International Application (35 U.S.C. 371(c)(2)) is attached hereto (not required if the International Application was previously communicated by the International Bureau or was filed in the United States Receiving Office (RO/US)).

3. An English language translation of the International Application (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).

4. An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))
   a. ☒ is attached.
   b. ☐ was previously filed in the international phase under PCT Rule 4.17(iv).

Items 5 to 8 below concern amendments made in the international phase.

PCT Article 19 and 34 amendments

5. ☐ Amendments to the claims under PCT Article 19 are attached (not required if communicated by the International Bureau) (35 U.S.C. 371(c)(3)).

6. ☐ English translation of the PCT Article 19 amendment is attached (35 U.S.C. 371(c)(3)).

7. ☐ English translation of annexes (Article 19 and/or 34 amendments only) of the International Preliminary Examination Report is attached (35 U.S.C. 371(c)(5)).

Cancellation of amendments made in the international phase

8a. ☐ Do not enter the amendment made in the international phase under PCT Article 19.

8b. ☐ Do not enter the amendment made in the international phase under PCT Article 34.

NOTE: A proper amendment made in English under Article 19 or 34 will be entered in the U.S. national phase application absent a clear instruction from applicant not to enter the amendment(s).

The following items 9 to 17 concern a document(s) or information included.

9. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

10. ☒ A preliminary amendment.

11. ☒ An Application Data Sheet under 37 CFR 1.76.

12. ☐ A substitute specification. NOTE: A substitute specification cannot include claims. See 37 CFR 1.125(b).

13. ☐ A power of attorney and/or change of address letter.

14. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.3 and 37 CFR 1.821-1.825 (not required if sequence listing in text format was indicated on the PCT Request as part of the International Application and the sequence listing was published as part of the international application).

15. ☐ Assignment papers *(cover sheet and document(s))*. Name of Assignee: _____

16. ☐ 37 CFR 3.73(c) Statement *(when there is an Assignee)*.

This collection of information is required by 37 CFR 1.414 and 1.491-1.492. 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 15 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 247

U.S. APPLN. No. (if known – see 37 CFR 1.5)	INTERNATIONAL APPLICATION No.	ATTORNEY DOCKET No.
	PCT/US17/60761	24050.0001US

17. [x] Other items or information:

PPH request

The following fees have been submitted.	CALCULATIONS
18. [ ] Basic national fee (37 CFR 1.492(a)) $300	$ 150.00
19. [x] Examination fee (37 CFR 1.492(c)) • If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... $0 • All other situations $760	$ 0
20. [x] Search fee (37 CFR 1.492(b)) • If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... $0 • Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority ..... $140 • International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB ..... $520 • All other situations $680	0 $
TOTAL OF 18, 19, and 20 =	$ 150.00

[ ] Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)).

Fee for each additional 50 sheets of paper or fraction thereof $400

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round up to a whole number)	RATE
- 100 =	/ 50 =		x $400

0

$

Surcharge for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h)) $140	$ 0

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	8 - 20 =		x $100	$ 0
Independent claims	3 - 3 =		x $460	$ 0
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $820	$

Fee for submission of Sequence Listing text file of 300 MB to 800 MB (37 CFR 1.21(o)(1)) $1,000	$ 0
Fee for submission of Sequence Listing text file of more than 800 MB (37 CFR 1.21(o)(2)) $10,000	$ 0
Processing fee for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i)) ..... $140 +	$ 0
TOTAL OF ABOVE CALCULATIONS =	$ 150.00
[x] **Applicant asserts small entity status.** See 37 CFR 1.27. Fees above are reduced by ½.	
[ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Fees above are reduced by ¾. Applicant must attach form PTO/SB/15A or B or equivalent.	
TOTAL NATIONAL FEE =	$ 150.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) ..... $50.00 per property +	$
TOTAL FEES ENCLOSED =	$ 150.00

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a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees.

c. ☒ The Director is hereby authorized to charge additional fees which may be required, or credit any overpayment, to Deposit Account No. 501480 as follows:

i. ☒ any required fee.

ii. ☐ any required fee except for excess claims fees required under 37 CFR 1.492(d) and (e) and multiple dependent claim fee required under 37 CFR 1.492(f).

d. ☒ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

ADVISORY: If filing by EFS-Web, do **NOT** attach the PTO-2038 form as a PDF along with your EFS-Web submission. Please be advised that this is not recommended and by doing so your credit card information may be displayed via PAIR. To protect your information, it is recommended to pay fees online by using the electronic payment method.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the international application to pending status.

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 1: 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.

NOTE 2: A U.S. national stage application may not claim priority to the international application of which it is the national phase. The filing date of a U.S. national stage application is the international filing date. See 35 U.S.C. 363.

Correspondence Address

☒ The address associated with Customer Number: 76447 OR ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone			
Email					

Signature	/susan fentress/	Date	May 6, 2019
Name (Print/Type)	Susan Fentress	Registration No. (Attorney/Agent)	31327

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001US
	Application Number	
Title of Invention	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE	

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
Dr.	Hassan		Almoazen	

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

City	Bartlett	State/Province	TN	Country of Residence	US

Mailing Address of Inventor:

Address 1	3133 Hill Lake Drive		
Address 2			
City	Bartlett	State/Province	TN
Postal Code	38135	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	76447		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE		
Attorney Docket Number	24050.0001US	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	9	Suggested Figure for Publication (if any)	2

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001US
	Application Number	
Title of Invention	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE	

Filing By Reference:

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

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

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

Publication Information:

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

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

Representative Information:

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

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	76447		

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	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	a 371 of international	PCTUS1760761	2017-11-09

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001US
	Application Number	
Title of Invention	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE	

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS1760761	Claims benefit of provisional	62421316	2016-11-13
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			

Foreign Priority Information:

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

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.			

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

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001US
	Application Number	
Title of Invention	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE	

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001US
	Application Number	
Title of Invention	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE	

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

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	Iono Pharma, LLC

Mailing Address Information For Applicant:

Address 1	3133 Hill Lake Drive		
Address 2			
City	Bartlett	**State/Province**	TN
Country		Postal Code	38135
Phone Number		Fax Number	
Email Address			

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

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001US
	Application Number	
Title of Invention	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE	

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.

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

Organization Name	Iono Pharma, LLC

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	3133 Hill Lake Drive		
Address 2			
City	Bartlett	**State/Province**	TN
Country i		Postal Code	38135
Phone Number		Fax Number	
Email Address			

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

Signature:

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

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

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

Signature	/susan b fentress/			Date (YYYY-MM-DD)	2019-05-06
First Name	susan	Last Name	fentress	Registration Number	31327

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

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001US
	Application Number	
Title of Invention	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE	

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	
First Named Inventor	Dr. Hassan Almoazen
Art Unit	
Examiner Name	
Attorney Docket Number	24050.0001US

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	3809714	A	1974-05-07	Hussain et al.	Entire Document
	2	3825583	A	1974-07-23	Hussain et al.	Entire Document
	3	4136145	A	1979-01-23	Fuchs et al.	Entire Document
	4	4145441	A	1979-03-20	Bodor	Entire Document
	5	4320144	A	1982-03-16	Resnick	Entire Document

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20030180357	A1	2003-09-25	Martino et al.	Entire Document

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Dr. Hassan Almoazen
	Art Unit	
	Examiner Name	
	Attorney Docket Number	24050.0001US

	2	20070202163	A1	2007-08-30	Rawas-Qalaji et al.	Entire Document

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	ARYA, A. et. al., "Fast dissolving oral films: An innovative drug delivery system and dosage form," Int. J. ChemTech Res., vol. 2, no. 1, pp. 576–583, 2010.	☐
	2	HUSSAIN, A, Journal of Pharmaceutical Sciences, Vol. 65, No. 10, October 1976, p: 1510-1512.	☐
	3	International Preliminary Report on Patentability PCT/US2017/060761 02.11.2018	☐
	4	International Search Report PCT/US2017/060761 25.01.2018	☐
	5	PUBCHEM-CID-70464361	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Dr. Hassan Almoazen
	Art Unit	
	Examiner Name	
	Attorney Docket Number	24050.0001US

	6	PUBCHEM-CID-969492	☐
	7	RAWAS-QALAJI, et al., Adrenaline (epinephrine) microcrystal sublingual tablet formulation: enhanced absorption in a preclinical model, J of Pharmacy and Pharmacology, 67.pp 20-25 (2014).	☐
	8	RAWAS-QALAJI, M. et. al, Sublingual epinephrine tablets versus intramuscular injection of epinephrine:Dose equivalence for potential treatment of anaphylaxis. J of Allergy Clin Immunol, v 117 no 2, 398 (2006)	☐
	9	SINGH, S. et. al. "Formulation and Evaluation of Rapidly Disintegrating Film of Levocetrizine Hydrochloride," Pharmacia, vol. 2, no. 2, pp. 208--220, 2010.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Dr. Hassan Almoazen
	Art Unit	
	Examiner Name	
	Attorney Docket Number	24050.0001US

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/susan b fentress/	Date (YYYY-MM-DD)	2019-05-06
Name/Print	Susan B Fentress	Registration Number	31327

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference **24050.0001PCT**	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT/US2017/060761**	International filing date *(day/month/year)* **09 November 2017 (09.11.2017)**	Priority date *(day/month/year)* **13 November 2016 (13.11.2016)**
International Patent Classification (IPC) or both national classification and IPC IPC: A61K 31/137 CPC: A61K 9/0056, A61J 7/0053, A61J 1/035, A61K 9/006		
Applicant **Inon Phama, LLC**		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 39 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions).
      ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4*bis*, 70.2(e), 70.16 and 91.2).
      ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)).
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3*ter* of Annex C of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☑ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☑ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☑ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20 April 2018 (20.04.2018)	**29 October 2018 (29.10.2018)**
Name and mailing address of the IPEA/US **Commissioner for Patents** **Mail Stop PCT, Attn: IPEA/US** **P.O. Box 1450** **Alexandria, VA 22313-1450** Facsimile No. **(571)273-8300**	Authorized officer **SAJJADI, Fereydoun G** Telephone No. **572-272-3311**

Form PCT/IPEA/409 (cover sheet) (January 2015)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2017/060761

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:
   - [x] the international application in the language in which it was filed.
   - [ ] a translation of the international application into _____ which is the language of a translation furnished for the purposes of:
     - [ ] international search (Rules 12.3(a) and 23.1(b))
     - [ ] publication of the international application (Rule 12.4(a))
     - [ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:
   - [ ] the international application as originally filed/furnished, or
   - [x] the description:
     pages **none** as originally filed/furnished.
     pages* **none** received by this Authority on **(..)**
     pages* **1-17** received by this Authority on **20 April 2018 (20.04.2018)**
   - [x] the claims:
     Nos. _____ as originally filed/furnished.
     Nos.* _____ as amended (together with any statement) under Article 19
     Nos.* **1-22** received by this Authority on **20 April 2018 (20.04.2018)**
   - [x] the drawings:
     pages **none** as originally filed/furnished.
     pages* **none** received by this Authority on **(..)**
     pages* **1/9-9/9** received by this Authority on **20 April 2018 (20.04.2018)**
   - [ ] a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages _____
   - [ ] the claims, Nos. _____
   - [ ] the drawings, sheets/figs _____
   - [ ] the sequence listing *(specify)*: _____
4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-*bis*)):
   - [ ] the description, pages _____
   - [ ] the claims, Nos. _____
   - [ ] the drawings, sheets/figs _____
   - [ ] the sequence listing *(specify)*: _____
5. [ ] This report has been established:
   - [ ] taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-*bis*) and 70.2(e)).
   - [ ] without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4*bis* and 70.2(e)).
6. With regard to top-up searches (Rules 66.1*ter* and 70.2(f)):
   - [x] A top-up search was carried out by this Authority on **29 October 2018 (29.10.2018)**
     - [ ] Additional relevant documents have been discovered during the top-up search.
   - [ ] No top-up search was carried out by this Authority because it would serve no useful purpose.
7. [ ] Supplementary international search report(s) from Authority(ies) _____ has/ have been received and taken into account in establishing this report (Rule 45*bis*.8(b) and (c)).

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Form PCT/IPEA/409 (Box No. I) (January 2015)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2017/060761

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1, 3-14, 16, 18-22	YES
	Claims		NO
Inventive step (IS)	Claims	1, 3-14, 16, 18-22	YES
	Claims		NO
Industrial applicability (IA)	Claims	1, 3-14, 16, 18-22	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Claims 1, 3-14, 16, 18-22 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the 2-methylamino-1-hydroxyethyl side chain nor their.use to treat said alilments.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2017/060761

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 1 compound Formula has a structure that is unclear with respect to the primary nitrogen atom substituents. The group is represented as NH, but there appears to be a partial character at the base of the H on NH. This could represent a subscript number or an incomplete bond. The instant specification indicates that N has a methyl substituent in several Key examples (see Fig 1-2) so that the nitrogen atom has an H and a methyl substituent and therefore the structure was interpreted in that way for the purposes of the search and the opinion.

For the purposes of the search and the opinion, the group CH2CHCH2 was interpreted to mean -CH2CH=CH2 , the substituent group CHCH2 was interpreted to mean CH=CH2, the substituent group CHCHCH2was interpreted to mean CH=CHCH2,

Attorney Docket Number
24050.0001PCT

REPLACEMENT SHEET

TITLE OF THE INVENTION: PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF A PRO-DRUG OF EPINEPHRINE

Field of the Invention

[0001] The present invention relates to pharmaceutical compositions for the treatment of anaphylaxis formulated for rapid sublingual or buccal delivery, *i.e.*, compounds that dissolves in the oral cavity. In one embodiment, the delivery vehicle is a rapidly dissolving film. The films contain a novel epinephrine pro-drug formulated for the rapid delivery of the drug to a patient in need of treatment, such as for example, a patient in need of treatment for anaphylaxis.

Description of Related Art Including Information

[0002] Epinephrine is considered the primary choice for the treatment of anaphylaxis which is a life threatening allergic reaction that might lead to death if untreated especially in children. A study reported that one in every 10,000 children has an anaphylactic attack per year. Epinephrine is the drug of choice for the treatment of anaphylactic shock in children and adults. It is highly soluble in water, highly hydrophilic (log P -0.68) and can be oxidized readily. Based on the current physicochemical properties of epinephrine, the only delivery available in the market is intramuscular injection. The administration of proper therapeutic agents, such as, epinephrine must be prompt. This is usually performed through the usage of auto-injectors such as EPIPEN (MYLAN) or TWINJECT (SHIONOGI PHARMA, INC.) that deliver the required dose in the mid-outer thigh either subcutaneously or intramuscularly. However, many disadvantages are reported with the usage of these injectors such as high cost, inaccurate administration, short half-life, patient's fear of needles, accidental injections, and unavailability of a sufficient number of fixed prefilled doses.

[0003] These shortcomings affect greatly the patient compliance and adherence to these injectors. In addition, it is very challenging to adjust the dose to different children ages as there are only two premeasured fixed epinephrine doses (0.15 and 0.3 mg). Recent study showed that only 17% of pediatric patients who have experienced anaphylactic symptoms have used prescribed auto injectors.

Other available delivery systems such as syringes or inhalers are also underused due to their lack of rapid and accurate dosing. Therefore, there is growing interest in the development of an alternative non-invasive delivery system that can easily provide accurate doses of epinephrine.

[0004] Anwar A. Hussain and James E. Truelove were granted patents related to the synthesis of novel esters of [(methylamino)methyl] benzyl alcohol which is epinephrine. The purpose of the Hussain's *et. al.* invention was to develop a prodrug of epinephrine HCl with superior lipid solubility to enhance penetration through the cornea of the eye to treat glaucoma. Hussain *et. al.* synthesized four different prodrugs for this purpose (see structures 7A, 7B, 7C, 7D). These four molecules were tested in human, rabbit and horse plasmas and found that 3, 4 – dipivalyl-α-[(methylamino) methyl] benzyl alcohol hydrochloride (structure 7D) shows the best penetration profile into the eye. Hussain's et. al. didn't evaluate the log P of these molecules nor did they evaluate the sublingual or buccal permeability or absorption. Their main focus was to develop a prodrug specifically for the eye. Since the initial publishing of Anwar's patents in 1974 and 1975, no one has followed up or even published any new data on structures 7A, 7B, and 7C. Dipivalyl-α-[(methylamino)] benzyl alcohol hydrochloride (7D) was further developed into a drug delivery system for glaucoma (Dipivefrin or Propine). Hussain and Truelove selected this prodrug for further development because of several physicochemical and biological qualities. The first quality was estimating the delay before onset of seizure for this prodrug was about 8-10 minutes, the second quality was the rate of hydrolysis expressed as $t_{1/2}$ in human plasma was about 1,800 seconds and the third quality was the $t_{1/2}$ hydrolysis and oxidation *in vitro* was 700 and 300 days respectively. In a separate publication (Journal of Pharmaceutical Sciences, Vol. 65, No. 10, October 1976, p: 1510-1512), Hussain *et. al.* shared the graphs for the *in vitro* hydrolysis of this particular prodrug using rabbit eye homogenate and compared the hydrolysis among three different plasmas (human, rabbit, rabbit eye homogenate).

[0005] Films that incorporate a pharmaceutically active ingredient are disclosed in U.S. Pat. No. 4,136,145 to Fuchs, *et al.* ("Fuchs"). These films can be formed into a sheet, dried and then cut into individual doses. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body,

including the mouth, rectal, vaginal, nasal and ear areas. A drug delivery vehicle must provide a high level of uniformity with respect to the dosage delivered.

BRIEF SUMMARY OF THE INVENTION

[0006] This invention relates to pharmaceutical compositions made by modifying the physicochemical properties of epinephrine in order to enhance its permeability through biological membranes (sublingual and buccal membranes). Several prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring, by chemically reacting the two groups with several acid moieties to form an ester bond with different alkyl chains. The addition of an alkyl group will enhance the lipophilicity of epinephrine (increase log P) and will consequently increase its permeability through the biological membranes (sublingual and buccal tissues in the oral cavity). The 3 and 4 positions represent meta and para locations with respect to the carbon in position 1 on the phenolic ring of epinephrine. Once the prodrug penetrates biological membranes (sublingual and buccal), the biological enzyme carboxyesterase will degrade the ester bond and release epinephrine for therapeutic activity. A prodrug is a biologically inactive compound that can be metabolized in the body to produce a drug. On characteristic of the selected prodrug compounds is fast hydrolysis in plasma.

[0007] In another embodiment, the subject matter includes a method to deliver epinephrine involving the steps of: providing epinephrine in a unit dosage form formulated for sublingual or buccal administration, wherein the unit dosage form is a rapidly dissolving film and the unit dosage form provides the pharmaceutical pro-drug of epinephrine. More specifically, this method involves providing pharmaceutical pro-drug compositions epinephrine in a unit dosage form to patients in need of anaphylactic treatment.

[0008] The subject matter includes a pharmaceutical formulation made of: a compound as depicted in a formula A and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula B and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula C and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient,

wherein R_4 is selected for the group consisting of: Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula D and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula 4E and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula 4F and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula G and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: H, I, Cl, $CH_2CH_2CH_3$ & $CH_2CH_2CH_2CH_3$, CH_2Cl, CH_2I and CH_2F A pharmaceutical formulation made of: a compound as depicted in a formula H and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula 6I and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: Cl, I and CH_3. The compound is formulated in a unit dosage form as a rapidly dissolving film. The invention further provides use of the pharmaceutical formulation in a patient in need of anaphylactic treatment.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWING(S):

[00010] The invention can be best understood by those having ordinary skill in the art by reference to the following detailed description when considered in conjunction with the accompanying drawings in which:

[00011] **FIG. 1** shows the generic chemical structure of a biologically inactive compound of this invention.

[00012] **FIGS. 2A-D** show exemplary compounds of the present invention, formula A shown as **FIG. 2A**, a species of formula A as **FIG. 2B**, formula B shown as **FIG. 2C** and a species of formula B as shown as **FIG. 2D**.

[00013] **FIGS. 3 A-D** show exemplary compounds of the present invention, formula C as **FIG. 3A**, a species of formula C as **FIG. 3B**, formula D shown as **FIG. 3C** and a species of formula D as shown as **FIG. 3D**.

REPLACEMENT SHEET

[00014] **FIGS. 4 A-D** show exemplary compounds of the present invention, formula E as **FIG. 4A**, a species of formula E as **FIG. 4B**, formula F shown as **FIG. 4C** and a species of formula F as shown as **FIG. 4D**.

[00015] **FIGS. 5 A-D** show exemplary compounds of the present invention, formula G shown as **FIG. 5A**, a species of formula G as shown as **FIG.5B**, a species of formula G as shown as **FIG. 5C and** a species of formula G as shown as **FIG. 5D**.

[00016] **FIGS. 6 A-D** show exemplary compounds of the present invention formula H shown as **FIG. 6A**, a species of formula H as **FIG. 6B**, formula I shown as **FIG. 6C** and a species of formula I as shown as **FIG. 6D**

[00017] **FIGS. 7 A-D** show Anwar A. Hussain and James E. Truelove compounds.

[00018] **FIG. 8** shows a stress-strain profile of the optimized epinephrine fast dissolving film.

[00019] **FIG. 9** shows a release profile of the epinephrine from the optimized fast dissolving film in 500 ml Simulated Saliva at 37 °C.

DETAILED DESCRIPTION OF THE INVENTION:

[00020] The present invention may be understood more readily by reference to the following detailed description of the invention. It is to be understood that this invention is not limited to the specific devices, methods, conditions or parameters described herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed invention. Also, as used in the specification including the appended claims, the singular forms "a," "an," and "the" include the plural, and reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise. Ranges may be expressed herein as from "about" or "approximately" one particular value and/or to "about" or "approximately" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment.

[00021] These and other aspects, features and advantages of the invention will be understood with reference to the detailed description herein, and will be realized

by means of the various elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description of the invention are exemplary and explanatory of preferred embodiments of the inventions, and are not restrictive of the invention as claimed. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Reference will now be made in detail to the presently preferred embodiments of the invention, examples of which are illustrated in the accompanying drawings. Throughout the following detailed description, the same reference numerals refer to the same elements in all figures.

[00022] The present invention provides a novel biologically inactive compound that can be metabolized in the body to produce a drug that has the biological activity of epinephrine. Epinephrine acts on nearly all body tissues. Its actions vary by tissue type and tissue expression of adrenergic receptors. For example, high levels of epinephrine cause smooth muscle relaxation in the airways but cause contraction of the smooth muscle that lines most arterioles. The present subject matter relates to modifying the physicochemical properties of epinephrine in order to enhance its permeability through biological membranes (sublingual and buccal membranes. FIG. 1 shows the generic chemical structure of a biologically inactive compound of this invention, while Table 1 shows exemplary prodrugs of epinephrine made by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring along with Log P values or a pharmaceutically acceptable salt thereof. The prodrugs of epinephrine preferably have a Log P value in the range of about 0.5-6.0. and more preferably between 1.0-5.0. This range was listed as a table of marketed sublingual tablets and films in Ashraf et. al "Considerations in developing sublingual tablets-An overview", Pharmaceutical Technology, 2014, 38(11). Log P is the logarithmic value of the ratio of two concentrations of a compound in a mixture of two immiscible liquids such as water and octanol at equilibrium. Log P values can be calculated mathematically by the use of PERCEPTA PLATFORM software (ACD Labs, Toronto, Ontario, Canada).

TABLE 1

R	Log P	R	Log P
R= $CHCH_2$	-0.20	R= CH_2COCH_3	-1.44
R= $CHCHCH_3$	+0.84	R= CH_2COCl	-0.21
R= $CHCH_2Cl$	+0.05	R= CH_2COI	+1.10
R= $CHCH_2I$	+1.36	R= CH_2OCH_3	-1.29
R= $CHClCH_2Cl$	+0.78	R= $CHICH_3$	+1.82
R= $CHICH_2I$	+4.0	R= $CClClCH_3$	+1.36
R= $CHCH_3CH_2CH_3$	+1.85	R= $CH_2CHCH_3CH_3$	+1.85
R= $CH_2CCH_3CH_3CH_3$	+2.55	R= $CH_2CHClCl$	+1.06
R= $CH_2CH_2CH_3$	+0.8	R= CH_2CHII	+4.09
R= CH_2Cl	-0.51	R= $CH_2CClClCl$	+2.97
R= CH_2I	+1.12	R= CH_2CIII	+7.68
R= CH_2F	-0.85	R= $CHClCl$	+0.66
R= $CIII$	+8.13	R= $CHII$	+4.03
R= Cl	+1.24	R= $CCH_3CH_3CHCH_3CH_3$	+3.24
R= I	+2.55	R= $NHCCH_3CH_3CH_3$	+1.63
R= F	+0.72	R= $NHCHCH_3CH_3$	+1.28
R= $CHCH_3CHCH_3CH_3$	+2.54	R= $NHCH_2CH_3$	+0.93
R= $CHClCHClCl$	+2.08	R= $NHCH_3$	+0.40
R= $CHICHII$	+7.09	R= SCH_3	+1.92
R= $CHFCHFF$	+0.80	R=SCH_2CH_3	+2.45
R= CH_2CHCH_2	+0.07	R=$SCHCH_3CH_3$	+2.80
R= $CClClCHClCl$	+4.18	R= $SCCH_3CH_3CH_3$	+3.15
R= $ClICHII$	+11.29	R= $CH_2C_6H_5$	+2.52
R= $CClClCl$	+2.90	R= C_6H_5	+3.10

[00023] A pro-drug is a derivative of epinephrine selected for fast permeability through sub-lingual and buccal membranes (*ie* a compound that dissolves in the oral cavity) and fast hydrolysis (half-life $t_{1/2}$ range from 1-6 minutes) by plasma enzymes to form epinephrine when delivered. These characteristics are physical properties of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film. Now referring to **FIG. 2**, derivatives of epinephrine are shown. **FIG. 2A**, showing structure **A** represents di-ester derivatives of epinephrine where the R_1 can be a short alkyl chain of CH_3, CH_2CH_3, $CH_2CH_2CH_3$, or $CH_2CH_2CH_2CH_3$, Cl or I. A representative molecule of this group compounds is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3-methylbutanoate) having a CLogP: 2.0114 shown as **FIG. 2B**. **FIG. 2C**, showing structure **B** represents derivatives of

epinephrine where R_2 = CH_3, Cl or I. A representative molecule of this group of compounds is 4-(1-hydroxy-2-(methylamino) ethyl)-1,2-phenylene bis(3,3-dimethylbutanoate) having a CLogP: 2.8094 shown as **FIG. 2D**. Adding H, CH_3, Cl or I change the Log P of the prodrug and adds a non-toxic moiety to the molecule. The rate of hydrolysis of each ester can increase or decrease depending on how the atom in position R_4 influences the ester group

[00024] Now referring to **FIG. 3**, derivatives of epinephrine are shown. **FIG. 3A**, showing structure **C** represents a derivative of epinephrine where R_3 = Cl or I. A representative molecule of the group is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dichloroacetate) having a CLogP: 1.4494 shown as **FIG. 3B**. **FIG. 3C**, showing structure **D** represents a derivative of epinephrine where R_4 = Cl or I. A representative molecule of the groups is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,2-trichloroacetae) having a CLogP: 2.8554 shown as **FIG. 3D**. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

[00025] Now referring to **FIG. 4** derivatives of epinephrine are shown. **FIG. 4A**, showing structure **E** represents a derivative of epinephrine where R1 = CH_3, Cl or I. A representative molecule is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-dimethylbutanoate) having a CLogP: 2.6294 shown as **FIG. 4B**. **FIG. 4C**, showing structure **F** represents a derivative of epinephrine where R_2 = CH_3, Cl or I. A representative molecule is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,3-trimethylbutanoate) having a CLogP: 3.4274 shown as **FIG. 4D**. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

[00026] Now referring to **FIG. 5**, derivatives of epinephrine are shown. **FIG. 5A**, showing structure **G** represents a derivative epinephrine where R_1 = H, I, Cl , $CH_2CH_2CH_3$ & $CH_2CH_2CH_2CH_3$, CH_2Cl, CH_2I or CH_2F. Representative molecules are: **5G** 4- (1-hydroxy-2-(methylamino) ethyl) 1,2-phenylene dicarboniodidate having a Clog: 1.084 (**FIG. 5B**);. **5G'** 4-(1-hydroxy-2-(methylamino-ethyl)-1,2-phenylene bis (2-iodoacetate) having a CLogP: 0.3834 (**FIG. 5C**) and Structure **5G"** 4-(1-hydroxy-2-methylamino)ethyl)-1,2-phenylene dibutyrate) having a CLogP: 1.2134 (**FIG. 5D**).

[00027] Now referring to **FIG. 6**, a derivative epinephrine is shown. **FIG. 6A**, showing structure **H** represents a derivative of epinephrine where R_2 = H, CH_3, Cl or I. A representative example is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene (2*E*,2'*E*)-bis(but-2-enoate) having a CLogP: 1.2054 shown as **FIG. 6B**. **FIG. 6C**, showing [[S]structure **I** represents a derivative of epinephrine where R_3 = Cl, I or CH_3. A representative example is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylbutanoate) having a CLogP: 1.8314 shown as **FIG. 6D**

[00028] Now referring to **FIG. 7**, the compounds of the invention as shown in US patent 3,809,714 and US patent 3,825,583 hereby incorporated by reference. Representative molecules include: **7A** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene diacetate having a DLogP: -0.9026. **7B** 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate) having a CLogP: 0.773300. **7C** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate having a CLogP: 0.1554. **7D** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate) having a CLogP: 1.5714. If these molecules show fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme (half-life 1-6 minutes) a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film. The subject matter includes: uses of a pharmaceutical formulation in a patient in need of anaphylactic treatment, wherein the pharmaceutical formulation is made of a compound selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient. A pharmaceutical formulation made of a compound selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

TABLE 2

R	Log P
Structure 7A R= CH_3	-0.97
Structure 7C R= CH_2CH_3	+0.09
Structure 7B R= $CHCH_3CH_3$	+0.79
Structure 7D R= $CCH_3CH_3CH_3$	+1.49

[00029] The present invention further provides a pharmaceutical composition made of at least one compound or mixture of compounds of the invention in a pharmaceutically acceptable carrier thereof. The invention features a pharmaceutical composition in unit dosage form formulated for sublingual or buccal administration. The delivery systems include: fast dissolving films, oral dissolving tablets, inhalation, and nasal delivery. In one embodiment, the unit dosage form of the present invention is a film for the delivery of epinephrine hydrochloride, as an anaphylactic treatment in a patient, such as for a pediatric or geriatric patient. A typical rapidly dissolving film is made of a drug, a water-soluble polymer, a plasticizer, a saliva stimulating agent, a surfactant and other fillers such as sweetening agents and flavors in case of bitter taste drugs. *See e.g.* A. Arya, A. Chandra, V. Sharma, and K. Pathak, "Fast dissolving oral films: An innovative drug delivery system and dosage form," *Int. J. ChemTech Res.*, vol. 2, no. 1, pp. 576–583, 2010.D. P. Lettre, "Formulation and Evaluation of Rapidly Disintegrating Film of Levocetrizine Hydrochloride," *Pharmacia*, vol. 2, no. 2, pp. 208–220, 2010.

[00030] For the present invention, the drug is epinephrine, a prodrug of epinephrine or a salt thereof. The typical dose of epinephrine for anaphylactic treatment is 0.3 to 0.5 mg in adults and 0.01 mg/kg up to a maximum of 0.3 mg in children administered through intramuscular route. In this study, 13mg/9 cm^2 of epinephrine (5.9 % w/w) are used as the dose size. This quantity is calculated for 6-7-year-old child according to Clark's rule Pediatric dose = Adult dose x (child's weight/150).

[000031] A typical dose of 40 mg was based on a study in rabbits that showed a dose bioequivalence between a 40mg epinephrine tablet administered sublingually

and 0.3 mg epinephrine administered intramuscularly using Epi pen, Injectors, Rawas-Qalaji et. al. Biopharm Drug Dispos. 27: 427-435 (2006). Furthermore, the time to reach maximum epinephrine concentration after a 0.3 mg EPIPEN (Mylan Specialty L.P.) injection in children is reported at 8±2 minutes. In another study, maximum plasma epinephrine concentration is reached within 34±14 minutes using 0.01 mg/kg dose injection of epinephrine subcutaneously in the deltoid region.

[00032] The polymer and the optimal amount of polymer are selected to obtain a non-sticky and functional film. A film-forming polymer should have good wetting property, high spread ability, good feeling in the mouth and should be safe and non-irritant. Many studies have showed that polymer content of at least 10 -15 % is needed in order to formulate proper film of proper thickness after drying in order to peel the film off from the release line. In one exemplary embodiment, the polymer is a water soluble modified hydroxypropyl starch that is specifically manufactured for aqueous film coating in immediate release solid oral dosage forms.

[00033] A plasticizer is used to form the rapidly dissolving film. The plasticizer enhances the flow of the polymer and improve the tensile strength and elongation of the fill. Several plasticizers are commonly used in rapidly dissolving film preparation such as glycerol, di-butylphthalate, and polyethylene glycols and they are usually used up to 20 % concentration of dry polymer weight.

[00034] The function of the surfactant is to facilitate the solubilization or wetting of the film and subsequently causing the film to disintegrate quickly, releasing the drug to be absorbed through the buccal cavity. Surfactants can include Tween 80, which is a complex mixture of polyoxyethylene ethers used as emulsifiers or dispersing agents in pharmaceuticals.

[00035] A saliva stimulating agent used to facilitate the delivery of the drug using a rapidly dissolving film to the patient. Other fillers, such as sweetening agents and flavors in case of bitter taste drugs and colors are added to the rapidly dissolving film to facilitate the delivery of the drug using a rapidly dissolving film to the patient. Typically, acids such as citric acid, malic acid, lactic acid and ascorbic acid are used as chemical stimulants of saliva secretion. However, citric acid is the most preferred among them. Xylitol and Tutti Frutti flavor are used for taste masking. Xylitol is an effective sweetening agent which has equal sweetness to sucrose.

[00037] Examples:Four formulations are prepared in this example. Epinephrine is soluble in Lycoat 720 (modified hydroxypropyl starch) water mixture. This hydrophilic polymer solubilizes epinephrine HCl, form a high viscosity gel that spreads well as we cast the film and lead to a non-sticky dry film after water evaporation. This polymer doesn't have any oxyethylene groups that can promote the oxidation of epinephrine nor it has glucose units that promotes water adsorption. The other ingredients added such as tween, glycerin decreased the rigidity of the film and improved elasticity. sodium metabisulfite was added to prevent and long-term oxidation of epinephrine HCl in the film. The citric acid brings the pH of the gel to the maximum stability range for epinephrine. The percentages of the polymer are shown in (Table 3). The polymer percentages are (20, 25, 27 and 30 %) of the total formulation weights. The polymer used in this example is LYCOAT (Ferromet). LYCOAT is a water soluble modified hydroxypropyl starch that is specifically manufactured for aqueous film coating in immediate release solid oral dosage forms.

[00038] **Table 3: List of the compositions of the four FDFs formulations.**

Ingredient (% w/w)	Use	F1	F2	F3	F4
Epinephrine HCl	Drug	5.9	5.9	5.9	5.9
Sodium Metabisulfite	Antioxidant	5.9	5.9	5.9	5.9
Lycoat 720 (hydroxypropyl starch)	Film-forming polymer	20	25	27	30
Glycerin	Plasticizer	3	3	3	3
Tween 80	Surfactant	2	2	2	2
Citric Acid Monohydrate	Buffer; increases absorption in oral cavity	0.5	0.5	0.5	0.5
Sodium Citrate Monobasic	Buffer	0.5	0.5	0.5	0.5

Xylitol	Sweetener	10	10	10	10
Tutti Frutti	Flavor	6	6	6	6
Water		46.2	41.2	39.2	36.2

[00039] Glycerin is used as a plasticizer to provide the proper elasticity for the film (Table 1). A plasticizer imparts a certain level of flexibility to the film by decreasing its brittleness. Films in this example are prepared using 3% glycerol which is equivalent to 10-15 % of the amount of polymer used.

[00040] Tween 80 is used as a surfactant (Table 2). Citric acid is used to adjust the pH and can be used in rapidly dissolving film as a saliva simulating agent to increase the secretion rate of saliva which will further improve the disintegration time of the film. Finally, the addition of an antioxidant is very important for the stability of epinephrine. Prompt oxidation of epinephrine in aqueous solutions results in a colored inactive product which has been reported. Therefore, different types of antioxidants are used in the commercial injectors such as sodium metabisulfite, EDTA and ascorbic acid achieving shelf life of two years. In this exemplary embodiment, the addition of sodium metabisuflite stabilizes the film.

[00041] However, films formed by formulations 1, 2 and 3 are too sticky after drying rendering them unusable. Formulation 4, having 30 % polymer content, formed a smooth, transparent, flexible and uniform film and therefore it is selected for further testing. The difference in stickiness is clearly related to the variation of the polymer content. This comes in agreement with a previous study that showed that using 22.5% of LYCOAT polymer formed a thin and flexible but sticky film at that concentration concluding that a higher percentage of polymer is needed.

[00042] Physical properties of the film prepared by formulation 4 are evaluated such as elastic modulus, thickness, content uniformity and dissolution time. Assessing these parameters is essential to determine the efficiency and usability of the film by patients. Elastic modulus is first studied as it represents a clear measure of the stiffness level of the film. It is calculated as the ratio of the applied stress over strain on a specific section.

[00043] Elastic's modulus= (Force at corresponding strain/cross section area) ×1/ (corresponding strain).

[00044] Now referring to **FIG. 8**, the profile of the film is illustrated showing a small increase in the applied strain to the film causes a quick increase in stress reaching a value of 0.1 MPa at 20 % strain level. As the strain increases further above 20 %, the increase magnitude in stress decreases gradually until it reaches a semi-plateau at value 0.16 MPa where % stress is 80 %. The value of elastic modulus is determined at 1.325 MPa which is an indication of very good flexibility of the film (Table 3).

[00045] **Table 4: List of physical properties of the optimized film**

Test	Results
Elastic Modulus	1.325±0.2 MPa
Thickness	0.29±0.01 mm
Content Uniformity	93% ± 10%

[00046] The thickness of the film at different locations is measured at 0.29 mm with very small margin of variability which is an indication of the high uniformity of the film (Table 4). A maximum thickness variation of 5 % is permitted in the preparation of the rapidly dissolving film. A uniform thickness across the film as it directly correlates with the accuracy of the dose in the film. Drug content in film is measured at 93 % ±10 indicating high level of consistency of epinephrine dose within the film (Table 2), as a limit of 85 -115 % of content uniformity is acceptable according to USP.

[00047] Now referring to **FIG. 9**, the dissolution profile of epinephrine from the film in terms of rate and extent in simulated saliva is determined on six samples of the optimized film. More than 90 % of epinephrine is released from the film within 7.2 minutes.

[00048] Taste and disintegration time of the optimized film are evaluated on 6 volunteers (Table 3). The disintegration time is the time when the film starts to break

or disintegrates. Volunteers reported 10 -30 seconds disintegration time (Table 3). This complies with the regulations set by United State Pharmecopeia (USP) for disintegration time of oral films (not exceeding 30 seconds). Bitterness of epinephrine is masked efficiently according to volunteer's comments (Table 5). Four volunteers sensed no bitterness of the film while the other two volunteers reported slight to very slight sensation of bitterness. Moreover, no tongue constriction is reported by any of the volunteers. This data presents clear proof of the efficiency of rapidly dissolving film in taste masking the bitterness of epinephrine and an indication of strong potential for using a rapidly dissolving film as a replacement therapy of epinephrine injections for children.

[00049] **Table 5**: *In vivo* taste and disintegration time evaluation of the optimized epinephrine FDF.

Volunteer	Bitterness	Tongue Constriction	Disintegration Time
1	None	None	~10 seconds
2	None	None	~10 seconds
3	Slight	None	~20 seconds
4	None	None	~30 seconds
5	Very slight	None	~20 seconds
6	None	None	~30 seconds

[00050] Materials--Epinpherine hydrochloride, sodium metabisulfite, citric acid monohydrate and sodium citrate monobasic are purchased from Sigma Aldrich (St. Louis, MO). Lycoat® RS720 is obtained from Roquette (Lestrem, France). Glycerin and tween 80 are purchased from Fisher Chemicals (Pittsburg, PA). Xylitol is purchased from Gallipot (St. Paul, MN). Tutti Frutti is obtained from LorAnn Oils (Lansing, MI). Film Preparation--Several rapidly dissolving films are prepared by a solvent casting technique to choose the optimum film formulation. The formulation

compositions of the rapidly dissolving film are mentioned in Table 3. LYCOAT and Xylitol are dissolved in warm water. The solution is then placed in a sonicator for two hours and then the solution is left overnight to ensure the removal of all entrapped air bubbles. Other excipients and Epinephrine HCl are added to the solution on the next day at room temperature. The mixture is then placed again in a sonicator for 40 minutes. The mixture is then spread onto a checkered paper covered by plastic sheet using a stainless-steel bar applicator. The film is left to dry overnight and is cut into 9 mm^2 small film strips.

[00053] Physical properties-The thickness and elastic modulus of the optimized film is evaluated using Dynamic Mechanical Analyzer (Q800 DMA, TA instruments, New Castle, DE). This is important to evaluate tensile properties of the films. Three strips of the optimized films are tested at 25 °C according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02). Each film is positioned between the grips of the instrument. The preload force is set at 0.01 N and the final force at 15N. The initial grip separation is set to 60 mm and crosshead speed is set to 500 mm/min. The test is terminated when the film breaks. Elastic modulus is determined as the slope of the straight-line part of the stress-strain curve and it is expressed in force per unit area (MPa).

[00054] Drug content uniformity: Specific areas are cut from six different films and weighted to calculate the estimated amount of drug in each area. Films are then dissolved in 100 ml of citric acid buffer. The media are stirred and then filtered using 0.45 um filters (Millipore Corporation, Millipore, Vimodron, Italy) and epinephrine content is assessed using UVmini-1240 UV-Vis Spectrophotometer (Shimadzu, Japan) at wavelength 280 nm. Epinephrine content is determined by calculating the percentage of the measured epinephrine to the estimated amount in each film.

[00055] *In vitro* dissolution test: For the dissolution test, rapidly dissolving film are evaluated using USP dissolution apparatus II, paddle (Distek Evolution 6100, North Brunswick, NJ). Six strips are placed in different 1 L vessels containing 500 ml Simulated Saliva. The temperature of the dissolution media is set to 37 C and rpm is set to 50 rpm. Samples are taken at different time points throughout the time of the experiment (15 mins), and the amount of epinephrine released in the media is determined by UVmini-1240 UV-Vis Spectrophotometer (Shimadzu, Japan) at 280 nm.

[00056] Human taste panel--To evaluate the palatability of optimized epinephrine film, a taste evaluation study is performed on six healthy volunteers. The study is carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), and all volunteers are informed in advance of the related details and the goal of the study and their consents are obtained. Volunteers are asked to place the film on the interior surface of their buccal cavity until the film is fully disintegrated. Volunteers then rinsed their mouths with drinking water. Volunteers have to report their findings of the presence of bitterness or not, any tongue restriction and how long it took for full disintegration of the film.

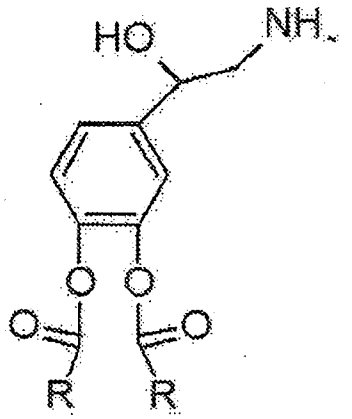
[00057] Equivalent elements can be substituted for the ones set forth above such that they perform in substantially the same manner in substantially the same way for achieving substantially the same result. It is believed that the system and method of the present invention and many of its attendant advantages will be understood by the foregoing description. It is also believed that it will be apparent that various changes may be made in the form, construction and arrangement of the components thereof without departing from the scope and spirit of the invention or without sacrificing all of its material advantages. The form herein before described being merely exemplary and explanatory embodiment thereof. It is the intention of the following claims to encompass and include such changes.

Attorney Docket Number
24050.0001PCT

REPLACEMENT SHEET

CLAIMS

1. A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:



wherein R is selected from the group consisting of: $-CHCH_2$, $-CHCHCH_3$, $-CH_2-CH_2-Cl$, $-CHCH_2I$, $-CH(Cl)CH_2(Cl)$, $-CH(I)CH_2(I)$, $-CH(CH_3)CH_2(CH_3)$, $-CH_2C(CH_3)_3$, $-CH_2CH_2CH_3$, $-CH_2Cl$, $-CH_2I$, $-CH_2F$, H, Cl, I, F, $-CH(CH_3)CH(CH_3)_2$, $-CH(Cl)CH(Cl)_2$, $-CH(I)CH(I)_2$, $-CH(F)CH(F)_2$, $-CH_2CHCH_2$, $-C(Cl)_2CH(Cl)_2$, $-C(I)_2CH(I)_2$, $-C(Cl)_3$, $C(I)_3$, $-CH_2COCH_3$, $-CH_2COCl$, $-CH_2CO(I)$, $-CH_2OCH_3$, $-CH(I)(CH_3)$, $-C(Cl)_2(CH_3)$, $-CH_2CH(CH3)_2$, $-CH_2CH(Cl)_2$, $-CH_2CH(I)_2$, $-CH_2C(Cl)_3$, $-CH_2C(I)_3$, $-CH(Cl)_2$, $-CH(I)_2$, $-C(CH3)_2CH(CH3)_2$, $-NH-C(CH_3)_3$, $-NH-CH(CH_3)_2$, $-NH-CH_2CH_3$, $-NH-CH_3$, $-SCH_3$, $-SCH_2CH_3$, $-SCH(CH3)_2$, $-SC(CH_3)_3$, $-CH_2C_6H_5$ and $-C_6H_5$ or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0.

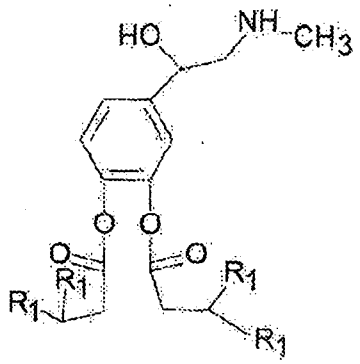
2.

3. The compound of claim 1 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

4. Use of the pharmaceutical composition of claims 1 or 3 in a patient in need of anaphylactic treatment.

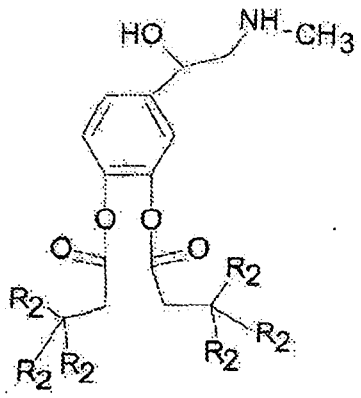
REPLACEMENT SHEET

5. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, Cl and I.

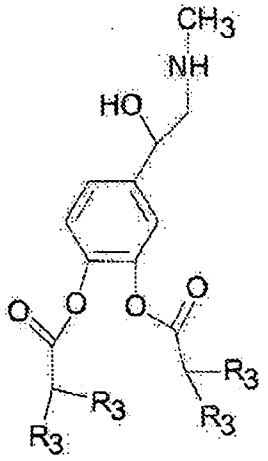
6. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: CH_3, Cl and I.

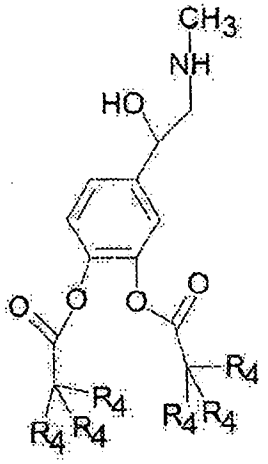
REPLACEMENT SHEET

7. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: Cl and I.

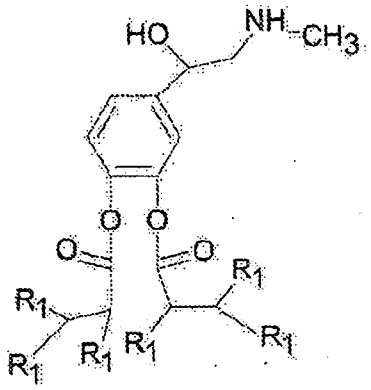
8. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_4 is selected for the group consisting of: Cl and I.

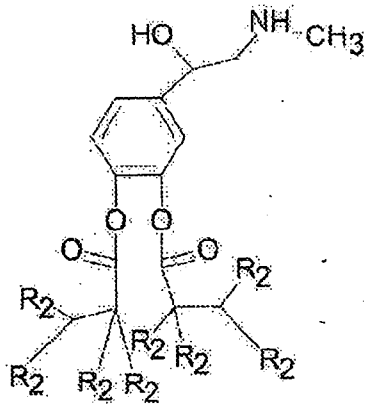
REPLACEMENT SHEET

9. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, Cl and I.

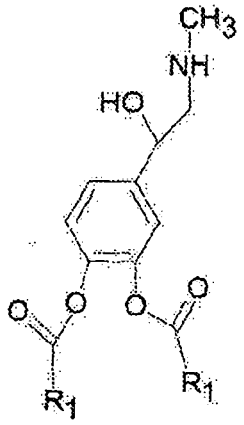
10. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: CH_3, Cl and I.

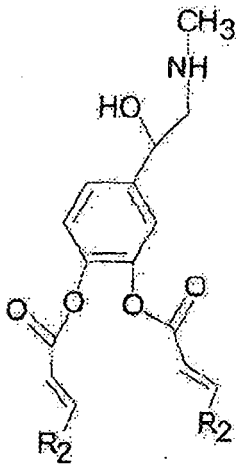
REPLACEMENT SHEET

11. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: H, I, Cl, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, CH_2Cl, CH_2I and CH_2F.

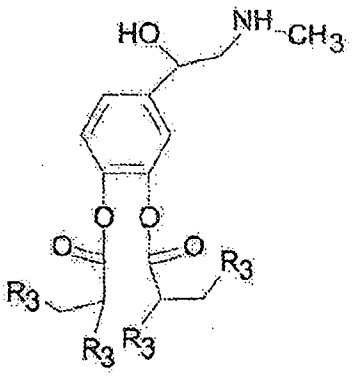
12. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3, Cl and I.

REPLACEMENT SHEET

13. A compound of a Formula:



and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: Cl, I and CH_3

14. A method to deliver a prodrug of epinephrine comprising: the steps of: providing epinephrine in a unit dosage form, formulated for sublingual or buccal administration, wherein the unit dosage form is a rapidly dissolving film, to a patient in need of treatment thereof, wherein the prodrugs of epinephrine has a Log P value in the range of about 0.5-6.0.

15.

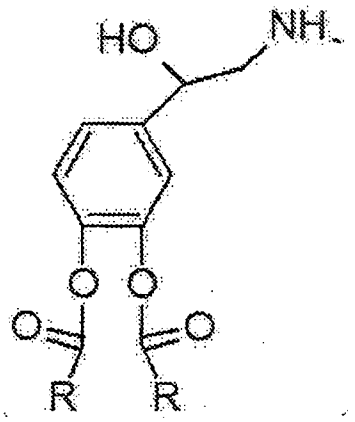
16. The method of claim 14 wherein the prodrugs of epinephrine has a Log P value in the range of about 1.0-5.0.

17.

18. The method of claim 14 further comprising: providing said prodrug of epinephrine in a unit dosage form to a patient in need of anaphylactic treatment.

REPLACEMENT SHEET

19. A compound of a Formula:



wherein R is selected from the group consisting of: CH_3, CH_2CH_3, and $CH(CH_3)_2$; wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration.

20. The compound of claim 19, wherein the compound is selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

21. The compound of claim 19, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

22. Use of the pharmaceutical formulation of claims 19 and 21 in a patient in need of anaphylactic treatment.

Replacement Sheet

1/9

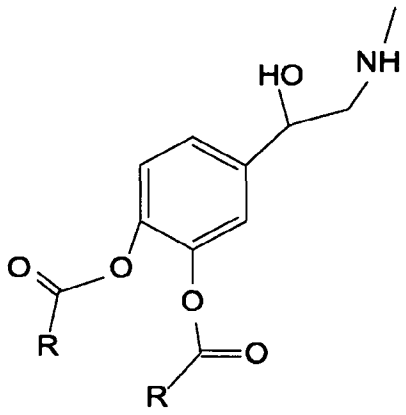
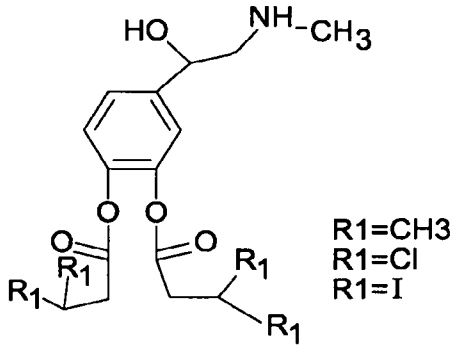


FIG. 1

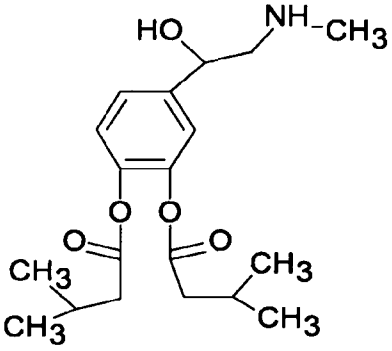
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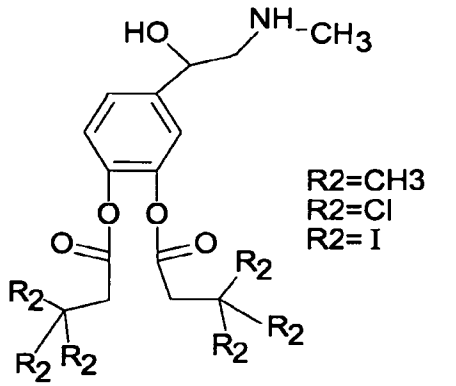
Formula A

FIG. 2A



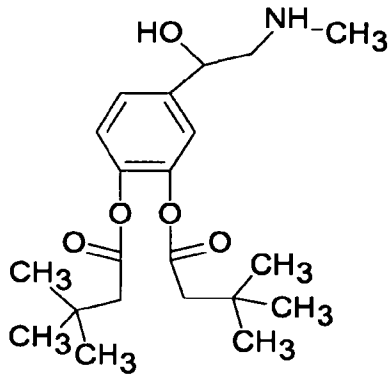
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3-methylbutanoate)
CLogP: 2.0114

FIG. 2B



Formula B

FIG. 2C

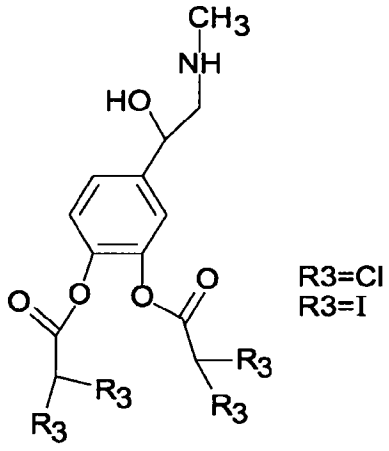


4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3,3-dimethylbutanoate)
CLogP: 2.8094

FIG. 2D

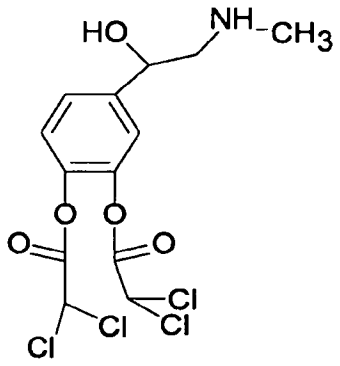
Replacement Sheet

3/9



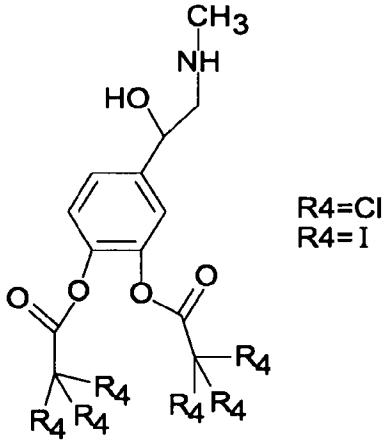
Formula C

FIG. 3A



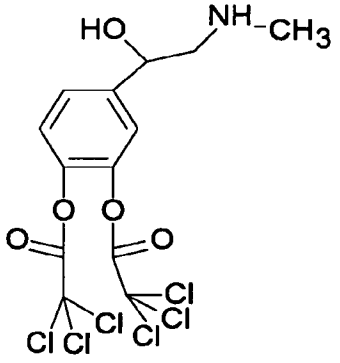
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dichloroacetate)
CLogP: 1.4494

FIG. 3B



Formula D

FIG. 3C

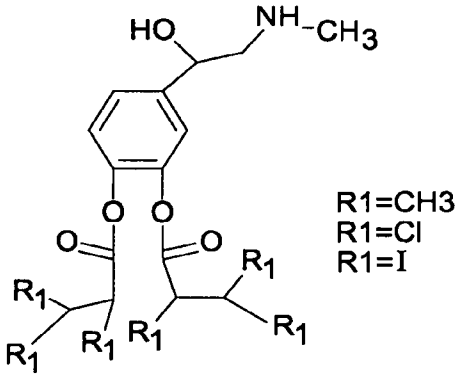


4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,2-trichloroacetate)
CLogP: 2.8554

FIG. 3D

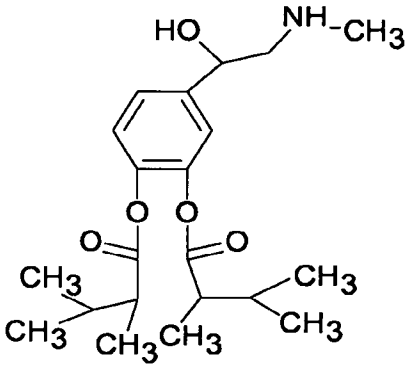
Replacement Sheet

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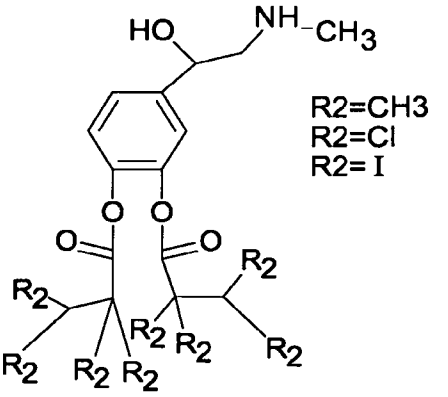
Formula E

FIG. 4A



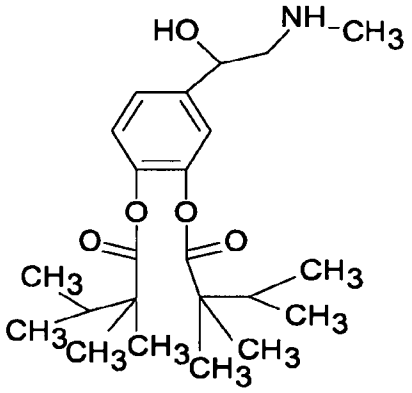
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-dimethylbutanoate)
CLogP: 2.6294

FIG. 4B



Formula F

FIG. 4C

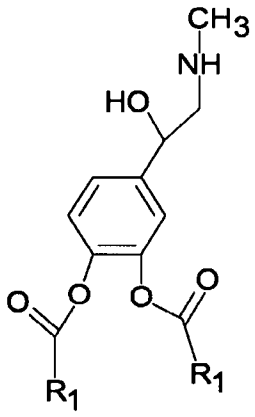


4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3,3-trimethylbutanoate)
CLogP: 3.4274

FIG. 4D

Replacement Sheet

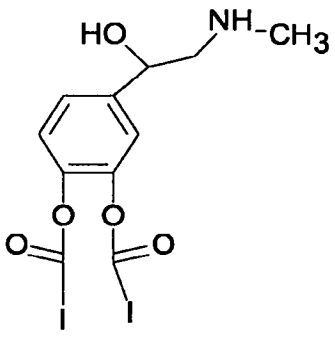
5/9



R1=H
R1= I
R1=Cl
R1=CH2CH2CH3
R1=CH2CH2CH2CH3
R1=CH2Cl
R1=CH2I
R1=CH2F

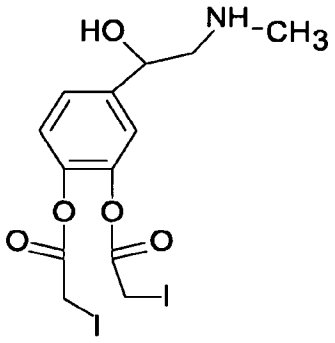
Formula G

FIG. 5A



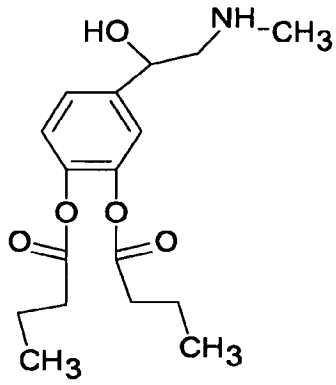
4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene dicarboniodidate
CLogP: 1.0854

FIG. 5B



4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene bis(2-iodoacetate)
CLogP: 0.3834

FIG. 5C

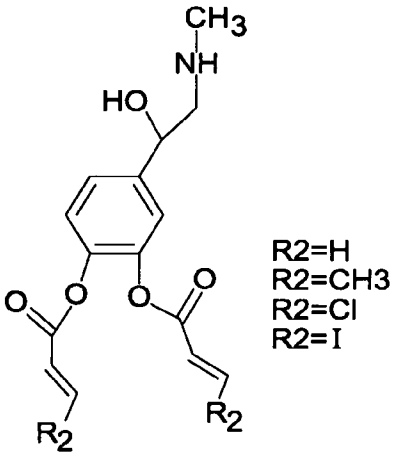


4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene dibutyrate
CLogP: 1.2134

FIG. 5D

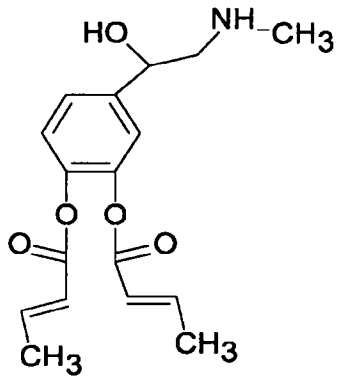
Replacement Sheet

6/9



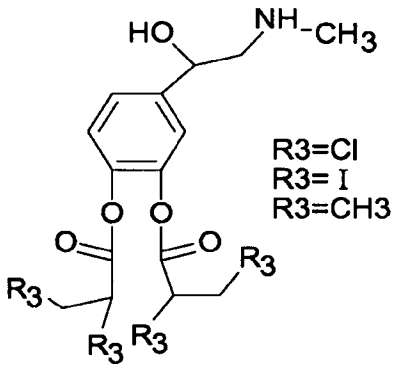
Formula H

FIG. 6A



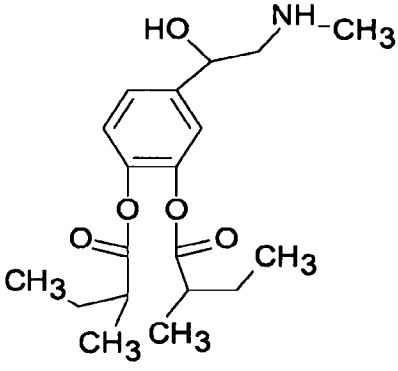
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene (2*E*,2'*E*)-bis(but-2-enoate)
CLogP: 1.2054

FIG. 6B



Formula I

FIG. 6C

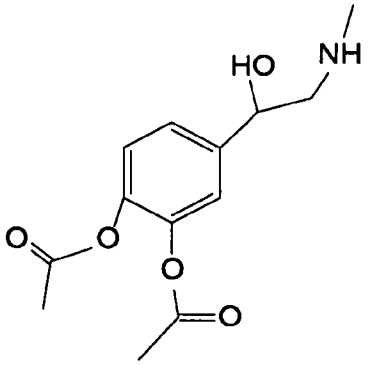


4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylbutanoate)
CLogP: 1.8314

FIG. 6D

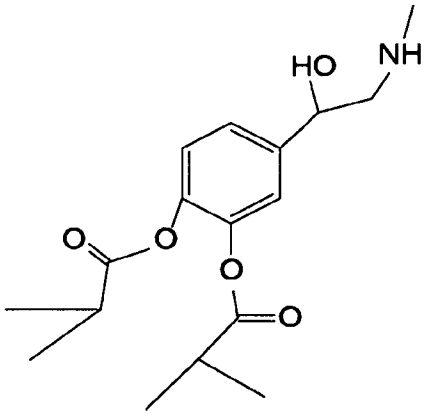
Replacement Sheet

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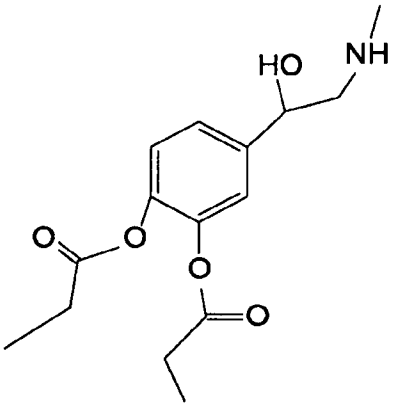
4-(1-hydroxy-2-(methylamino)ethyl)-1, 2-phenylene diacetate
CLogP: -0.9026

FIG. 7A



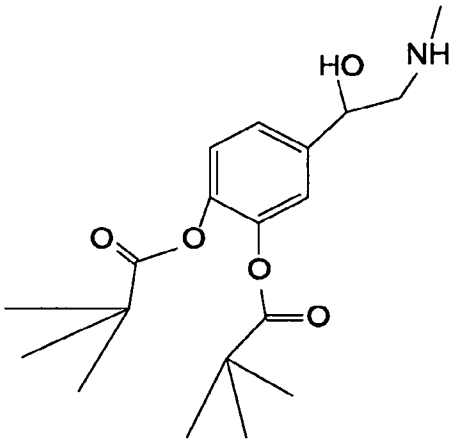
4-(1-hydroxy-2-(methylamino)ethyl)-1, 2-phenylene bis(2-methylpropanoate)
CLogP: 0.7733

FIG. 7B



4-(1-hydroxy-2-(methylamino)ethyl)-1, 2-phenylene dipropanoate
CLogP: 0.1554

FIG. 7C



4-(1-hydroxy-2-(methylamino)ethyl)-1, 2-phenylene bis(2,2-dimethylpropanoate)
CLogP: 1.5714

FIG. 7D

Replacement Sheet

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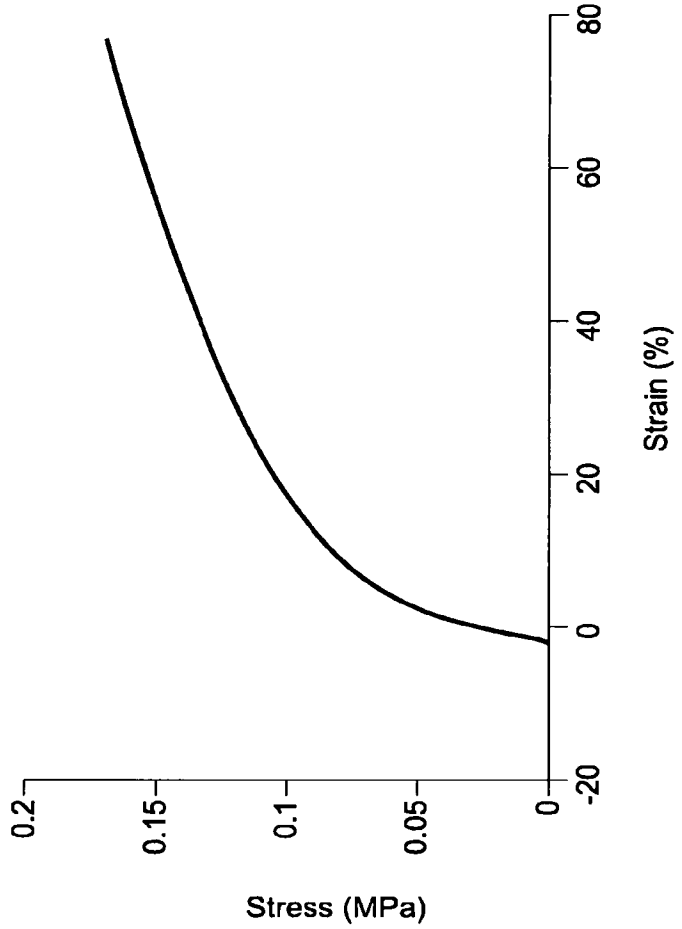


FIG. 8

AMENDED SHEET - IPEA/US

Replacement Sheet

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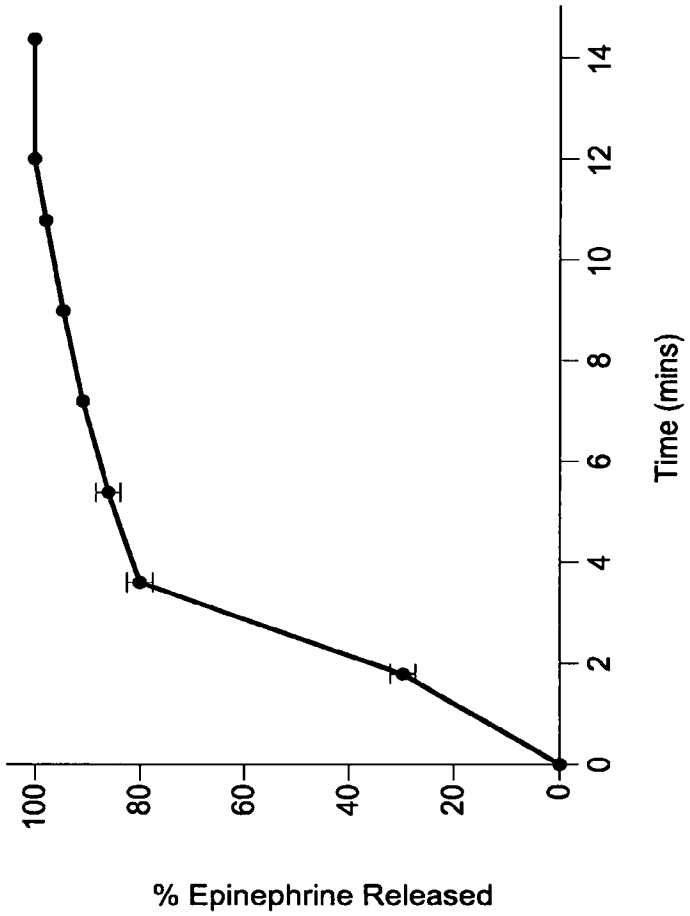


FIG. 9

APPL. NO.: PCT/US2017/060761

APPLICANT: Iono Phama, LLC

FILED: 09 NOV 2017

TITLE: PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

Article 34 Letter

Dear Sirs:

REPLACMENT FIGURES 2-6 are herewith submitted to correct confusion caused by the renumbering of the drawing per the PCT requirement. The original figures referred to structure numbers, while the replacement figures were numerically sequential, thus causing confusion regarding the structure number.

The specification has been updated to remove the confusion between structure reference and figure numbers that was inadvertently caused by the submission of renumbered figures. No new matter is added. The reference paragraphs are to the replacement specification as filed herewith.

Claim 1 has been amended to standardize the nomenclature according to the suggestion of the examiner and to incorporate the subject matter of claim 2 and 15.

Claims 2 canceled.

Claim 3 amended to depend on claim 1.

Claim 4 amended to depend on claims 1 and 3.

Claim 5 is amended to be an independent claim and to add the compound of formula A. Support **FIG. 2** and [0012] and [0023] and to limit the R group to: wherein R_1 is selected for the group consisting of: CH_3, Cl and I.

Claim 6 is amended to be an independent claim and to add the compound of formula B. Support **FIG. 2** and [0012] and [0023] and the r group CH_3

Claim 7 is amended to be an independent claim and to add the compound of formula C. Support FIG. 3 and [0013] and [0024].

Claim 8 is amended to be an independent claim and to add the compound of formula D. Support FIG. 3 and [0013] and [0024].

Claim 9 is amended to be an independent claim and to add the compound of formula E. Support FIG. 4 and [0014] and [0025]and the r group CH_3

Claim 10 is amended to be an independent claim and to add the compound of formula F. Support FIG. 4 and [0014] and [0025] and the r group CH_3

Claim 11 is amended to be an independent claim and to add the compound of formula G. Support FIG. 5 and [0015] and [0025].

Claim 12 is amended to be an independent claim and to add the compound of formula H. Support FIG. 6 and [0016] and [0026].

Claim 13 is amended to be an independent claim and to add the compound of formula I. Support FIG. 6 and [0016] and [0027].

Claim 14 epinephrine was deleted and the Log P value in the range of about 0.5-6.0 for the prodrug from claim 15 was added.

Claim 15 cancelled.

Claim 16 original.

Claim 17 cancelled.

Claim 18 original.

Claim 19 reformat ~~$CHCH_3CH_3$~~ to $CH(CH_3)_2$ and delete structure: ~~$CCH_3CH_3CH_3$~~,

Claim 20 structure ~~4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate).~~

Claim 21 original.

Claim 22 amended to depend on claim 19

Comments:

It is noted that claim 1 is anticipated by a compound at col 5, designated as compound 7. Bodor teaches compound 7 has the R group -C(CH3)3. However, the R group claimed is: -CH2C(CH3)3, which is not the same compound. The applicant has selected the claimed R group based on log P values (as claimed) and not on any other physical chemical factors. Thus, the disclosure in Bodor does not disclose or suggest the claimed compounds to one skilled in the art. The same argument applies to the obviousness of claims 5, 11 and 13.

Regarding claims 1-4, it is beyond the knowledge of someone skillful in the art to combine the teachings of Rawas-Qalaji and Bodor to come up with the concept of modifying Bodor's compounds in structure I (a general formula for epinephrine prodrug derivatives), which he teaches for the treatment of hemorrhoids as a topical rectal application and then apply Rawas-Qalaji teachings to modify the application in order to treat anaphylactic shock by sublingual or buccal absorption. Bodor's compounds structure II and III are not epinephrine derivatives and are not effective to treat anaphylactic shock. It is beyond the knowledge of someone skillful in the art to combine the teachings of Rawas-Qalaji with Bodor to obtain the claimed invention. There is no scientific rationale to use Bodor's compounds for anaphylaxis as he teaches for the treatment of hemorrhoids (topical rectal application). On the other hand, Rawas-Qalaji teach about treating anaphylaxis by sublingual or buccal absorption of epinephrine. Bodor doesn't teach that any compounds included in structures I, II and III are effective for treating anaphylaxis. To the contrary, Bodor teaches that his compounds are active locally in the rectal area. Usually, Hemorrhoids are treated locally and not by oral or sublingual route (this is a medical fact). It is novel for someone to propose that Bodor's compounds can be used to

treat anaphylaxis and it is beyond the knowledge of someone skillful in the art. In the present invention epinephrine prodrugs are absorbed by sublingual tissues then cleaved in plasma in order to release epinephrine.

Claim 1 has been amendment: "A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration".

Regarding claim 5, Bodor teaches compound 17 which has R group -CHCHCH2CHCH2; however, this compound is not set out in any of the pending claims. Bodor's compound 17 has two side chains of six carbons each with two double bonds while the compound in 2A [0023] has two side chains of 4 carbons each with no double bonds. We disagree with the comment "but the compound of Bodor doesn't have the propyl substituent branching off the third carbon of the hexadienoyl moiety."

Regarding claim 11, in compound 5G [00026] we have listed R1 as -CH2CH2CH3 or -CH2CH2CH2CH3. Bodor teaches away from R1 as -CH2CH2CH3 or -CH2CH2CH2CH3. In fact, compound 17 in Bodor patent has R listed as CHCHCH2CHCH2. This R group is not listed in any of claims. The fifth substituent listed for compound 5G is -CH2CH2CH2CH3. In compound 17, Bodor teaches away from R1 as -CH2CH2CH2CH3. In fact, compound 17 in Bodor patent has R group listed as CHCHCH2CHCH2 with two double bonds. This R group is not listed in any of our claims and doesn't bear any similarity to compound 5G with R1 -CH2CH2CH2CH3. It is noted that: "but the compound of Bodor doesn't teach any of the substituents exactly" which is a true comment. Our argument, why would someone skilled in the art look at Bodor's compound 17 and reduce the number of side chains to 4 and saturate two double bonds?

Regarding claim 13, compound 6l para [0027] when the R is CH3 in formula I we get a side chain -CH1(CH3)CH2(CH3) and not -CH2(CH3)CH2(CH3) and not as recited in the opinion on patentability R3 -CH2CH2CH2CH3. In compound 17, Bodor teaches away from the claimed subgroup. In compound 17 Bodor teaches R as -CHCHCH2CHCH2 with two double bonds. There are no double bonds in compound 6l. When the R3 group in compound 6l is CH3, the ester side chain will become CH2(CH3)CH2(CH3) and not as shown by the reviewer R3 -CH2CH2CH2CH3. Claim 13 does not claim CH2(CH3)CH2(CH3) as an R group.

In compound 17, Bodor teaches away from this subgroup. In compound 17, Bodor teaches for -CHCHCH2CHCH2 with two double bonds and no side branching. Since there are no double bonds in compound 6l, and considering the reviewer's comment "but the compound of Bodor doesn't teach the branching of R3 group or any of the R3 substituent directly", we find the comparison between Bodor compound 17 and compound 6l not clearly justified

Regarding claims 14 and 18 since Rawas-Qalaji teaches away from the use of any prodrugs in fast dissolving tablets or films, we have amended the claim to include the Log P value in the range of about 0.5-6.0 of a prodrug in the claim and omit epinephrine. The problem with epinephrine is that it has a very low log P (highly hydrophilic) and cannot be absorbed by the GI tract. In addition, within the GI tract, it can be oxidized in the intestinal lumen and can lose its efficacy. Bodor teaches about using epinephrine prodrugs rectally to treat hemorrhoids and to overcome the stability problem. Bodor does not teach about the **systemic absorption** of epinephrine prodrugs. On the other hand, Rawas-Qalaji teaches about the use of epinephrine in fast dissolving tablets but does not teach about using Log P to evaluate epinephrine or the design of new prodrugs to improve systemic

absorption. Neither Rawas-Qalaji and Bodor do not teach about enhancing the membrane permeability by increasing lipophilicity of the prodrug molecules. It is highly unlikely for someone skillful in the art to combine the teachings of Rawas-Qalaji and Bodor with log P and propose that increasing log P between 0.5-6 can increase sublingual permeability. Consequently, the presently formatted claims are not disclosed or suggested in the prior art.

Claims 19-22 structure 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate was deleted. The remaining compounds are not disclosed or suggested in the cited art.

Applicant respectfully suggest that the pending claims are novel, non-obvious and have technical applicability.

Respectfully Submitted
/Susan B Fentress/
Susan B. Fentress, Agent of record 31327
20 Dudley Suite 803
Memphis, TN 38103 USA
Telephone No. 901-371-6664
Email: sfentress@veritaygroup.com
Dated: April 20, 2018

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 24050.0001PCT	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 17/60761	International filing date *(day/month/year)* 09 November 2017 (09.11.2017)	(Earliest) Priority Date *(day/month/year)* 13 November 2016 (13.11.2016)
Applicant IONO PHARMA, LLC		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 12 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. 2

   ☒ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/60761

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/137 (2017.01)
CPC - A61K 9/0056, A61J 7/0053, A61J 1/035, A61K 9/006

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y -- A	US 4,145,441 A (BODOR) 20 March 1979 (20.03.1979), entire document, especially: col 5, preferred compound (1) 3,4-dipivalyloxy-a-[(methylamino)methyl]benzyl alcohol; col 5, preferred compound (7) 3-(trimethylaceloxy)-a-[(methylamino)methyl]benzyl alcohol; col 5, preferred compound (17) 3,4-di-2,5-hexadienoyloxy-a-[(methylamino)methyl]-benzyl alcohol; col 1, ln 7-10; col 1, ln 12-21; col 1, ln 34-44; col 4, ln 59-68; col 10, ln 15-17, Claim 40.	1,5,11,13 --- 2-4,15-16, 18-22 --- 6-10,12
X -- Y	US 2007/0202163 A1 (RAWAS-QALAJI et al.) 30 August 2007 (30.08.2007), entire document, especially: para [0004]; para [0007]; para [0130]; para [0131]; para [0139].	14,17 --- 2-4, 15-16,18,20-22
Y	US 2003/0180357 A1 (MARTINO et al.) 25 September 2003 (25.09.2003), entire document, especially: para [0011]; para [0025].	19-22
A	US 4,320,144 A (RESNICK) 16 March 1982 (16.03.1982), entire document, especially: col 3, ln 13-47, l,5-bis[(3-dichloropropanoyloxyphenyl)oxy] pentane.	6-10,12
A	PubChem-CID-70464361, Create Date: 01 December 2012 (01.12.2012), pg 3, Fig.	1-22
A	PubChem-CID-969492, Create Date: 09 July 2005 (09.07.2005), pg 3, Fig.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 January 2018	25 JAN 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: SUSAN B. FENTRESS
VERITAY GROUP, IP
20 DUDLEY SUITE 803
MEMPHIS, TN 38103

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	25 JAN 2018
Applicant's or agent's file reference 24050.0001PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 17/60761	09 November 2017 (09.11.2017)	13 November 2016 (13.11.2016)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/137 (2017.01)
CPC - A61K 9/0056, A61J 7/0053, A61J 1/035, A61K 9/006

Applicant IONO PHARMA, LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	08 January 2018	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 17/60761

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2-22	YES
	Claims	1	NO
Inventive step (IS)	Claims	6-10,12	YES
	Claims	1-5,11,13-22	NO
Industrial applicability (IA)	Claims	1-22	YES
	Claims	None	NO

2. Citations and explanations:

Claim 1 lacks novelty under PCT Article 33(2) as being anticipated by US 4,145,441 A to Bodor (hereinafter 'BODOR').

Regarding claim 1, Bodor teaches a compound of a Formula as indicated in the instant claim, wherein R is the ninth substituent group listed: CH2CCH3CH3CH3 (col 5, preferred compound (7) 3-(trimethylaceloxy)-a-[(methylamino)methyl]benzyl alcohol).

Claims 5, 11 and 13 lack an inventive step under PCT Article 33(3) as being obvious over Bodor.

Regarding claim 5, Bodor teaches the compound of claim I. Bodor further teaches the compound comprising: a compound as depicted in a formula 2A and a pharmaceutically acceptable carrier (col 10, ln 15-17, Claim 40, compound is topically co-administered with a nontoxic pharmaceutically acceptable rectal carrier) wherein R1 is CH2CH2CH3 (col 5, preferred compound (17) 3,4-di-2,5-hexadienoyloxy-a-[(methylamino)methyl]-benzyl alcohol), but the compound of Bodor does not have the propyl substituent branching off the third carbon of the hexadienoyl moiety. However, it would have been obvious to a person having ordinary skill in the art to prepare the compound with the propyl substituent branching off the third carbon of the hexadienoyl moiety by routine experimentation in order to identify the compound with the preferred physico-chemical properties for commercialization.

Regarding claim 11, Bodor teaches the compound of claim I. Bodor further teaches the compound comprising: a compound as depicted in a formula 5G and a pharmaceutically acceptable carrier (col 10, ln 15-17, Claim 40, compound is topically co-administered with a nontoxic pharmaceutically acceptable rectal carrier) wherein R1 is CH2CH2CH2CH2CH3 (col 5, preferred compound (17) 3,4-di-2,5-hexadienoyloxy-a-[(methylamino)methyl]-benzyl alcohol), which is similar to the fifth substituent listed for R1 in the instant claim, but the compound of Bodor does not teach any of the substituents exactly. However, it would have been obvious to a person having ordinary skill in the art to prepare the compound with the CH2CH2CH2CH3 substituent by routine experimentation in order to identify the compound with the preferred physico-chemical properties for commercialization.

Regarding claim 13, Bodor teaches the compound of claim I. Bodor further teaches the compound comprising: a compound as depicted in a formula 6I and a pharmaceutically acceptable carrier (col 10, ln 15-17, Claim 40, compound is topically co-administered with a nontoxic pharmaceutically acceptable rectal carrier) wherein R3 is CH2CH2CH2CH3 (col 5, preferred compound (17) 3,4-di-2,5-hexadienoyloxy-a-[(methylamino)methyl]-benzyl alcohol), which is similar to the third substituent listed for R3 in the instant claim, but the compound of Bodor does not teach the branching R3 group or any of the R3 substituents exactly. However, it would have been obvious to a person having ordinary skill in the art to prepare the compound with the CH3 substituent at both R3 positions by routine experimentation in order to identify the compound with the preferred physico-chemical properties for commercialization.

Claims 14 and 17 lack an inventive step under PCT Article 33(3) as being obvious over US 2007/0202163 A1 to Rawas-Qalaji (hereinafter 'RAWAS-QALAJI').

Regarding claim 14, Rawas-Qalaji teaches a method to deliver epinephrine (para [0131], Also provided herein are methods for the treatment of a patient in need of epinephrine therapy comprising the administration a fast disintegrating buccal or sublingual tablet described herein) comprising the steps of providing epinephrine in a unit dosage form (para [0130], the unit dosage weight is typically 150 milligrams, although other suitable sizes may also be used and are within the scope of the invention) formulated for sublingual or buccal administration (para [0131], Also provided herein are methods for the treatment of a patient in need of epinephrine therapy comprising the administration a fast disintegrating buccal or sublingual tablet described herein), but Rawas-Qalaji does not specifically teach wherein the compound is formulated as a rapidly dissolving film. However, it would have been obvious to a person having ordinary skill in the art to prepare the compound which is formulated as a rapidly dissolving film by routine experimentation in order to identify the formulation with the preferred physico-chemical properties for commercialization.

Regarding claim 17, Rawas-Qalaji teaches the method of claim 14 (see above discussion). Rawas-Qalaji further teaches the method further comprising: providing said epinephrine (para [0131], Also provided herein are methods for the treatment of a patient in need of epinephrine therapy comprising the administration a fast disintegrating buccal or sublingual tablet described herein) in a unit dosage form (para [0130], the unit dosage weight is typically 150 milligrams, although other suitable sizes may also be used and are within the scope of the invention) to a patient in need of anaphylactic treatment (para [0007], Epinephrine (EP) is the drug of choice for the treatment of anaphylaxis worldwide).

--Continued in first Supplemental Box--

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 1 compound Formula has a structure that is unclear with respect to the primary nitrogen atom substituents. The group is represented as NH, but there appears to be a partial character at the base of the H on NH. This could represent a subscript number or an incomplete bond. The instant specification indicates that N has a methyl substituent in several key examples (see Fig 1-2) so that the nitrogen atom has an H and a methyl substituent and therefore the structure was interpreted in that way for the purposes of the search and the opinion.

Chlorine atom is represented with capitol C and lowercase l as found on the periodic table of the elements. The presence of "CL" in claims is not proper, but is interpreted to mean "Cl". Therefore, CL was presumed to represent chlorine substituent.

Claim 1 definition for R substituent uses non-standard nomenclature for substructures and the specific formulas being indicated is unclear for the following species:

CHCH3CH2CH3, CH2CCH3CH3CH3, CHCH3CHCH3CH3, CHCLCHCLCL, CHICHII, CHFCHFF, CCLCLCHCLCL, CIICHII, CCLCLCL, CIII, CCLCLCH3, CH2CHCH3CH3, CH2CHCLCL, CH2CHII, CH2CCLCLCL, CH2CIII, CHCLCL, CHII, CCH3CH3CHCH3CH3, NHCCH3CH3CH3, NHCHCH3CH3, SCHCH3CH3, SCCH3CH3CH3

The meaning was not unclear for the following species:

H, CHCH2, CHCHCH3, CHCH2CL, CHCH2I, CHCLCH2CL, CHICH2I, CH2CH2CH3, CH2CL, CH2I, CH2F, CL, I, F, CH2CHCH3, CH2COCH3, CH2COCL CH2COI, CH2OCH3, CHICH3, NHCH2CH3, NHCH3, SCH3, SCH2CH3, CH2C6H5 and C6H5

For the purposes of the search and the opinion the group CH2CCH3CH3CH3 was interpreted to mean -CH2C(CH3)3 and the substituent group CCH3CH3CH3 was interpreted to mean C(CH3)3.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
--Box V.2--

Claims 2-4 lack an inventive step under PCT Article 33(3) as being obvious over Bodor in view of Rawas-Qalaji.

Regarding claim 2, Bodor teaches the compound of claim 1. Bodor further teaches topical administration (col 1, ln 7-10, The use of the Compounds of Formulas (I), (II) and (III) hereof as topical anti-inflammatory agents), but Bodor does not teach buccal or sublingual. However, Rawas-Qalaji teaches that sublingual administration is faster acting (para [0004], The sublingual route usually produces a faster onset of action than traditional orally administered tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolic processes) and Rawas-Qalaji further teaches buccal administration (para [0131], Also provided herein are methods for the treatment of a patient in need of epinephrine therapy comprising the administration a fast disintegrating buccal or sublingual tablet described herein) of a unit dosage (para [0130], the unit dosage weight is typically 150 milligrams, although other suitable sizes may also be used and are within the scope of the invention). It would have been obvious to a person having ordinary skill in the art to combine Rawas-Qalaji with Bodor because Bodor teaches a compound that is administered rectally specifically to increase stability of the compound upon delivery (col 1, ln 34-44, The compounds of the present invention are among other things characterized as stable at rectal pH) and Rawas-Qalaji teaches that sublingual administration avoids first pass metabolism (para [0004], The sublingual route usually produces a faster onset of action than traditional orally administered tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolic processes), which would enhance the bioavailability of drugs which are not stable in the digestive tract.

Regarding claim 3, Bodor in view of Rawas-Qalaji teaches the compound of claim 2. Rawas-Qalaji further teaches wherein the compound is formulated as a unit dosage form (para [0130], the unit dosage weight is typically 150 milligrams, although other suitable sizes may also be used and are within the scope of the invention) configured for sublingual or buccal administration (para [0131], Also provided herein are methods for the treatment of a patient in need of epinephrine therapy comprising the administration a fast disintegrating buccal or sublingual tablet described herein), and Bodor further teaches wherein the compound is formulated for topical administration (col 1, ln 7-10, The use of the Compounds of Formulas (I), (II) and (III) hereof as topical anti-inflammatory agents), but neither Rawas-Qalaji nor Bodor teaches wherein the compound is formulated as a rapidly dissolving film. However, it would have been obvious to a person having ordinary skill in the art to prepare the compound which is formulated as a rapidly dissolving film by routine experimentation in order to identify the formulation with the preferred physico-chemical properties for commercialization.

Regarding claim 4, Bodor in view of Rawas-Qalaji teaches the use of the pharmaceutical composition of claim 2. Rawas-Qalaji further teaches the use of the pharmaceutical composition in a patient in need of anaphylactic treatment (para [0139], In one embodiment, the present invention provides a method for the treatment of anaphylaxis in an adult comprising step of administering a dose of a buccal or sublingual fast disintegrating tablet comprising about 25 mg to about 75 mg epinephrine).

Claims 15-16 and 18 lack an inventive step under PCT Article 33(3) as being obvious over Rawas-Qalaji in view of Bodor.

Regarding claim 15, Rawas-Qalaji teaches the method of claim 14 (see above discussion). Rawas-Qalaji further teaches wherein the drug is epinephrine (para [0007], Epinephrine (EP) is the drug of choice for the treatment of anaphylaxis worldwide), but Rawas-Qalaji does not teach epinephrine prodrug thus Rawas-Qalaji does not teach wherein the prodrugs of epinephrine has a Log P value in the range of about 0.5-6.0. Bodor teaches epinephrine prodrug (col 4, ln 59-68, the pharmacologically active sympathomimetic amine form produced upon the metabolic release of the active drug to achieve its desired pharmacological and/or physiological effect), but Bodor does not specifically teach Log P values, thus Bodor does not teach wherein the prodrugs of epinephrine has a Log P value in the range of about 0.5-6.0. However, it would have been obvious to a person having ordinary skill in the art to test the value of Log P for epinephrine prodrug by routine experimentation in order to identify the compound with the preferred physico-chemical properties for commercialization. It would have been further obvious to combine Bodor with Rawas-Qalaji because Bodor teaches a compound that is administered rectally specifically to increase stability of the compound upon delivery (col 1, ln 34-44, The compounds of the present invention are among other things characterized as stable at rectal pH) and Rawas-Qalaji teaches that sublingual administration avoids first pass metabolism (para [0004], The sublingual route usually produces a faster onset of action than traditional orally administered tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolic processes), which would enhance the bioavailability of drugs which are not stable in the digestive tract.

Regarding claim 16, Rawas-Qalaji teaches the method of claim 14 (see above discussion). Rawas-Qalaji further teaches wherein the drug is epinephrine (para [0007], Epinephrine (EP) is the drug of choice for the treatment of anaphylaxis worldwide), but Rawas-Qalaji does not teach epinephrine prodrug thus Rawas-Qalaji does not teach wherein the prodrugs of epinephrine has a Log P value in the range of about 1.0-5.0. Bodor teaches epinephrine prodrug (col 4, ln 59-68, the pharmacologically active sympathomimetic amine form produced upon the metabolic release of the active drug to achieve its desired pharmacological and/or physiological effect), but Bodor does not specifically teach Log P values, thus Bodor does not teach wherein the prodrugs of epinephrine has a Log P value in the range of about 1.0-5.0. However, it would have been obvious to a person having ordinary skill in the art to test the value of Log P for epinephrine prodrug by routine experimentation in order to identify the compound with the preferred physico-chemical properties for commercialization. It would have been further obvious to combine Bodor with Rawas-Qalaji because Bodor teaches a compound that is administered rectally specifically to increase stability of the compound upon delivery (col 1, ln 34-44, The compounds of the present invention are among other things characterized as stable at rectal pH) and Rawas-Qalaji teaches that sublingual administration avoids first pass metabolism (para [0004], The sublingual route usually produces a faster onset of action than traditional orally administered tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolic processes), which would enhance the bioavailability of drugs which are not stable in the digestive tract.

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Supplemental Box

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Regarding claim 18, Rawas-Qalaji teaches the method of claim 14 (see above discussion). Rawas-Qalaji further teaches the method further comprising: providing said epinephrine drug (para [0131], Also provided herein are methods for the treatment of a patient in need of epinephrine therapy comprising the administration a fast disintegrating buccal or sublingual tablet described herein) in a unit dosage form (para [0130], the unit dosage weight is typically 150 milligrams, although other suitable sizes may also be used and are within the scope of the invention) to a patient in need of anaphylactic treatment (para [0007], Epinephrine (EP) is the drug of choice for the treatment of anaphylaxis worldwide), but Rawas-Qalaji does not teach prndrug of epinephrine. However, Bodor teaches epinephrine prodrug (col 4, ln 59-68, the pharmacologically active sympathomimetic amine form produced upon the metabolic release of the active drug to achieve its desired pharmacological and/or physiological effect). It would have been obvious to a person having ordinary skill in the art to combine Bodor with Rawas-Qalaji because Bodor teaches a compound that is administered rectally specifically to increase stability of the compound upon delivery (col 1, ln 34-44, The compounds of the present invention are among other things characterized as stable at rectal pH) and Rawas-Qalaji teaches that sublingual administration avoids first pass metabolism (para [0004], The sublingual route usually produces a faster onset of action than traditional orally administered tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolic processes), which would enhance the bioavailability of drugs which are not stable in the digestive tract.

Claim 19 lacks an inventive step under PCT Article 33(3) as being obvious over Bodor in view of US 2003/0180357 A1 to Martino et al. (hereinafter 'MARTINO').

Regarding claim 19, Bodor teaches a compound of a Formula as indicated in the instant claim, wherein R is the fifth substituent group listed: CCH3CH3CH3 (col 5, preferred compound (1) 3,4-dipivalyloxy-a-[(methylamino)methyl]benzyl alcohol), and wherein the compound is formulated in a dosage form for rectal administration (col 1, ln 12-21, the present invention is directed to certain selected sympathomimetic amine compounds which quite unexpectedly have been observed to exhibit anti-hemorrhoidal activity when rectally administered to a warm-blooded animal), but Bodor does not teach wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration. However, Martino teaches the same compound of a Formula as indicated in the instant claim, wherein R is the fifth substituent group listed: CCH3CH3CH3 (para [0025], Alternatively or in addition, such an ophthalmic drug can illustratively be an antiglaucoma or intraocular pressure lowering agent, such as (a) an .-adrenergic agonist or sympathomimetic, e.g., adrenolone, apraclonidine, brimonidine or dipivefrin; see also separately attached supporting document entitled PubChem-CID-969492 for the structure of dipivefrin), and Martino further teaches wherein the compound is formulated for sublingual or buccal administration (para [0011], placement of the tablet in the sublingual or buccal spaces is preferred), but neither Bodor nor Martino specifically teaches wherein the compound is formulated in a unit dosage form. However, it would have been obvious to a person having ordinary skill in the art to prepare the compound as formulated in a unit dosage form in order to identify the dosage form with the preferred therapeutic activity profile. It would have been further obvious to combine Martino with Bodor because Bodor teaches a compound that is administered rectally specifically to increase stability of the compound upon delivery (col 1, ln 34-44, The compounds of the present invention are among other things characterized as stable at rectal pH) and Martino teaches a formulation that dissolves in the oral mucosa (para [0011], The term .intraoral. herein refers to administration by placement of the tablet in the mouth of the subject, where the tablet disintegrates and/or dissolves, so that absorption of the drug typically occurs at least in part via the oral mucosa.) rather than the digestive tract (para [0011], The term .peroral. herein refers to administration via the mouth involving swallowing of the tablet without substantial prior disintegration of the tablet in the mouth, so that absorption of the drug typically occurs in the gastrointestinal tract), which would enhance the bioavailability of drugs which are not stable in the digestive tract.

Claims 20-22 lack an inventive step under PCT Article 33(3) as being obvious over Bodor in view of Martino, in further view of Rawas-Qalaji.

Regarding claim 20, Bodor in view of Martino teaches the compound of claim I9. Bodor further teaches wherein the compound is the fourth compound listed in the instant claim: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethy1propanoate) (col 5, preferred compound (7) 3-(trimethylaceloxy)-a-[(methylamino)methyl]benzyl alcohol), and a pharmaceutically acceptable carrier (col 10, ln 15-17, Claim 40, compound is topically co-administered with a nontoxic pharmaceutically acceptable rectal carrier). Rawas-Qalaji teaches a unit dosage form (para [0130], the unit dosage weight is typically 150 milligrams, although other suitable sizes may also be used and are within the scope of the invention), but none of Martino, Bodor or Rawas-Qalaji teaches wherein the compound is formulated as a rapidly dissolving film. However, it would have been obvious to a person having ordinary skill in the art to prepare the compound which is formulated as a rapidly dissolving film by routine experimentation in order to identify the formulation with the preferred physico-chemical properties for commercialization. It would have been further obvious to combine Rawas-Qalaji with Bodor because Bodor teaches a compound that is administered rectally specifically to increase stability of the compound upon delivery (col 1, ln 34-44, The compounds of the present invention are among other things characterized as stable at rectal pH) and Rawas-Qalaji teaches that sublingual administration avoids first pass metabolism (para [0004], The sublingual route usually produces a faster onset of action than traditional orally administered tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolic processes), which would enhance the bioavailability of drugs which are not stable in the digestive tract.

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Regarding claim 21, Bodor in view of Martino teaches the compound of claim l9, but neither Martino nor Bodor teaches wherein the compound is formulated in a unit dosage form as a rapidly dissolving film. However, Rawas-Qalaji teaches wherein the compound is formulated in a unit dosage form (para [0130], the unit dosage weight is typically 150 milligrams, although other suitable sizes may also be used and are within the scope of the invention), but Rawas-Qalaji does not teach wherein the compound is formulated as a rapidly dissolving film. However, it would have been obvious to a person having ordinary skill in the art to prepare the compound which is formulated as a rapidly dissolving film by routine experimentation in order to identify the formulation with the preferred physico-chemical properties for commercialization. It would have been further obvious to combine Rawas-Qalaji with Bodor because Bodor teaches a compound that is administered rectally specifically to increase stability of the compound upon delivery (col 1, ln 34-44, The compounds of the present invention are among other things characterized as stable at rectal pH) and Rawas-Qalaji teaches that sublingual administration avoids first pass metabolism (para [0004], The sublingual route usually produces a faster onset of action than traditional orally administered tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolic processes), which would enhance the bioavailability of drugs which are not stable in the digestive tract.

Regarding claim 22, Bodor in view of Martino, in further view of Rawas-Qalaji teaches the use of the pharmaceutical formulation of claim 21 (see above discussion). Rawas-Qalaji further teaches the use further comprising administering the formulation to a patient in need of anaphylactic treatment (para [0007], Epinephrine (EP) is the drug of choice for the treatment of anaphylaxis worldwide).

Claims 6-10, 12 meet the criteria set out under PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest the claimed invention.

Regarding claim 6, Bodor teaches the compound of claim 1. Bodor further teaches a compound of claim 1 and a pharmaceutically acceptable carrier (col 10, ln 15-17, claim 40, compound is topically co-administered with a nontoxic pharmaceutically acceptable rectal carrier), comprising; a compound similar to the compound as depicted in a formula 2B (col 5, preferred compound (7) 3-(trimethylaceloxy)-a-[(methylamino)methyl]benzyl alcohol), but Bodor does not teach wherein R2 is selected from the group consisting of: Cl or I. US 4,320,144 A to Resnick (hereinafter 'RESNICK') teaches a compound of formula similar to formula 2B and wherein R2 is Cl (col 3, ln 13-47, l,5-bis[(3-dichloropropanoyloxyphenyl)oxy] pentane), but the compound of Resnick does not teach the 2-methylamino-1-hydroxyethyl side chain of the claimed compound and there would be no reason for combining Resnick with Bodor as they teach significantly different types of treatment with unrelated compounds. Therefore the prior art does not teach or fairly suggest the claimed invention.

Regarding claim 7, Bodor teaches the compound of claim 1. Bodor further teaches a compound of claim 1 and a pharmaceutically acceptable carrier (col 10, ln 15-17, claim 40, compound is topically co-administered with a nontoxic pharmaceutically acceptable rectal carrier), comprising; a compound similar to the compound as depicted in a formula 3C (col 5, preferred compound (7) 3-(trimethylaceloxy)-a-[(methylamino)methyl]benzyl alcohol), but Bodor does not teach wherein R3 is selected from the group consisting of: CL or I. Resnick teaches a compound of formula similar to formula 3C and wherein R3 is Cl (col 3, ln 13-47, l,5-bis[(3-dichloropropanoyloxyphenyl)oxy] pentane), but the compound of Resnick has an additional methylene spacer between the chlorine atoms and the carbonyl group, and Resnick does not teach the 2-methylamino-1-hydroxyethyl side chain of the claimed compound and there would be no reason for combining Resnick with Bodor as they teach significantly different types of treatment with unrelated compounds. Therefore the prior art does not teach or fairly suggest the claimed invention.

Regarding claim 8, Bodor teaches the compound of claim 1. Bodor further teaches a compound of claim 1 and a pharmaceutically acceptable carrier (col 10, ln 15-17, claim 40, compound is topically co-administered with a nontoxic pharmaceutically acceptable rectal carrier), comprising; a compound similar to the compound as depicted in a formula 3D (col 5, preferred compound (7) 3-(trimethylaceloxy)-a-[(methylamino)methyl]benzyl alcohol), but Bodor does not teach wherein R4 is selected from the group consisting of: Cl or I. Resnick teaches a compound of formula similar to formula 3D and wherein R4 is Cl (col 3, ln 13-47, l,5-bis[(3-dichloropropanoyloxyphenyl)oxy] pentane), but the compound of Resnick has an additional methylene spacer between the chlorine atoms and the carbonyl group, and Resnick does not teach three halogen substituents, or the 2-methylamino-1-hydroxyethyl side chain of the claimed compound and there would be no reason for combining Resnick with Bodor as they teach significantly different types of treatment with unrelated compounds. Therefore the prior art does not teach or fairly suggest the claimed invention.

Regarding claim 9, Bodor teaches the compound of claim 1. Bodor further teaches a compound of claim 1 and a pharmaceutically acceptable carrier (col 10, ln 15-17, claim 40, compound is topically co-administered with a nontoxic pharmaceutically acceptable rectal carrier), comprising; a compound similar to the compound as depicted in a formula 4E (col 5, preferred compound (7) 3-(trimethylaceloxy)-a-[(methylamino)methyl]benzyl alcohol), but Bodor does not teach wherein R1 is selected from the group consisting of: Cl or I. Resnick teaches a compound of formula similar to formula 4E and wherein R1 is Cl (col 3, ln 13-47, l,5-bis[(3-dichloropropanoyloxyphenyl)oxy] pentane), but the compound of Resnick does not teach three halogen substituents with one halogen on the carbonyl alpha carbon, or the 2 -methylamino-1-hydroxyethyl side chain of the claimed compound and there would be no reason for combining Resnick with Bodor as they teach significantly different types of treatment with unrelated compounds. Therefore the prior art does not teach or fairly suggest the claimed invention.

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Supplemental Box

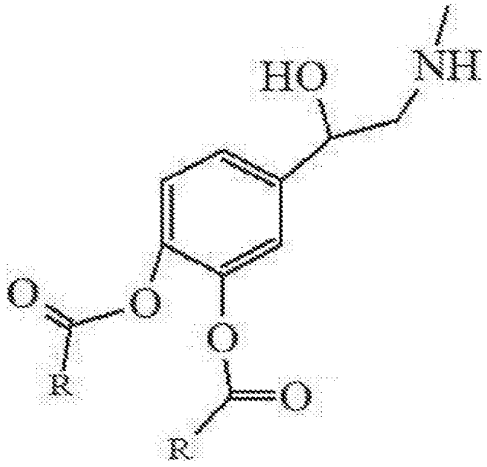
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Regarding claim 10, Bodor teaches the compound of claim 1. Bodor further teaches a compound of claim 1 and a pharmaceutically acceptable carrier (col 10, ln 15-17, claim 40, compound is topically co-administered with a nontoxic pharmaceutically acceptable rectal carrier), comprising; a compound similar to the compound as depicted in a formula 4F (col 5, preferred compound (7) 3-(trimethylaceloxy)-a-[(methylamino)methyl]benzyl alcohol), but Bodor does not teach wherein R2 is selected from the group consisting of: Cl or I. Resnick teaches a compound of formula similar to formula 4F and wherein R2 is Cl (col 3, ln 13-47, l,5-bis[(3-dichloropropanoyloxyphenyl)oxy] pentane), but the compound of Resnick does not teach four halogen substituents with two halogens on the carbonyl alpha carbon, or the 2 -methylamino-1-hydroxyethyl side chain of the claimed compound and there would be no reason for combining Resnick with Bodor as they teach significantly different types of treatment with unrelated compounds. Therefore the prior art does not teach or fairly suggest the claimed invention.

Regarding claim 12, Bodor teaches the compound of claim 1. Bodor further teaches a compound of claim 1 and a pharmaceutically acceptable carrier (col 10, ln 15-17, claim 40, compound is topically co-administered with a nontoxic pharmaceutically acceptable rectal carrier), comprising; a compound similar to the compound as depicted in a formula 6H (col 5, preferred compound (17) 3,4-di-2,5-hexadienoyloxy-a-[(methylamino)methyl]-benzyl alcohol), but Bodor does not teach wherein the ester side chain has unsaturation, or wherein R2 is selected from the group listed in the instant claim. Resnick teaches a compound of formula similar to formula 6H and wherein R2 is H (col 3, ln 13-47, l,5-bis[(4-acryloyloxy-2,6-dichlorophenyl)oxy] pentane), but the compound of Resnick does not teach the 2 -methylamino-1-hydroxyethyl side chain of the claimed compound and there would be no reason for combining Resnick with Bodor as they teach significantly different types of treatment with unrelated compounds. Therefore the prior art does not teach or fairly suggest the claimed invention.

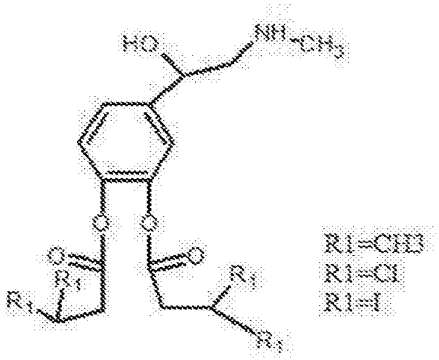
Claims 1-22 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used by industry.

FIG. 1

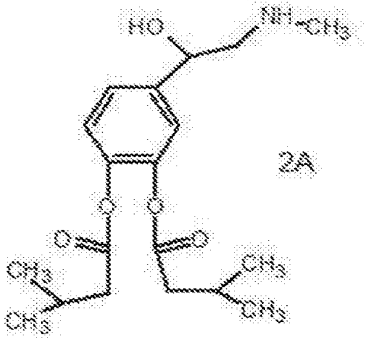


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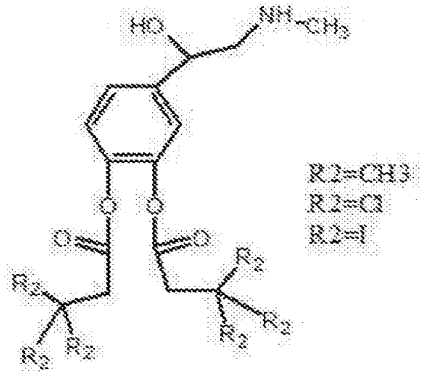
FIG. 2



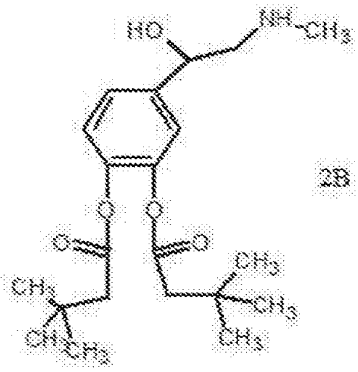
A



4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3-methylbutanoate)
CLogP: 2.0114



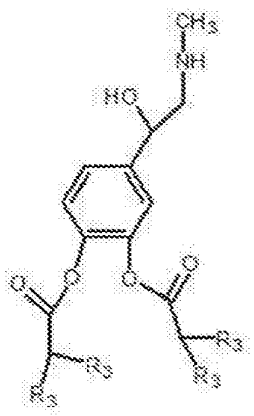
B



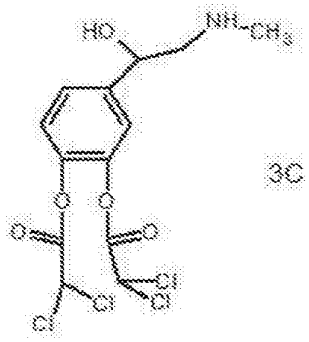
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3,3-dimethylbutanoate)
CLogP: 2.8094

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FIG. 3



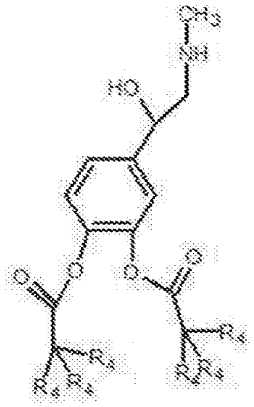
R3=CL
R3=I



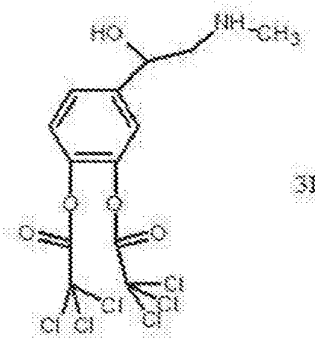
3C

C

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dichloroacetate)
CLogP: 1.4494



R4=Cl
R4=I



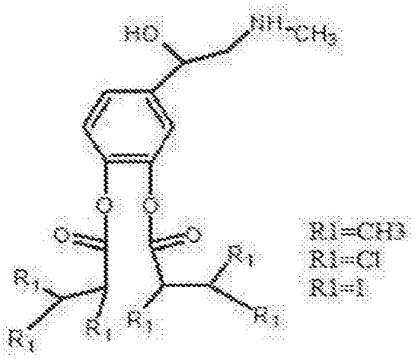
3D

D

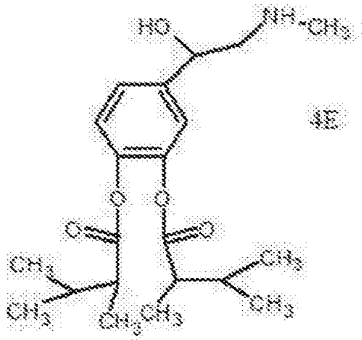
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,2-trichloroacetate)
CLogP: 2.8554

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FIG. 4

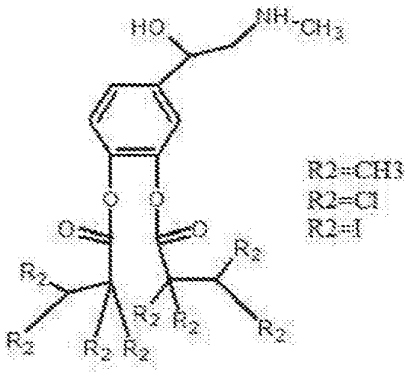


E

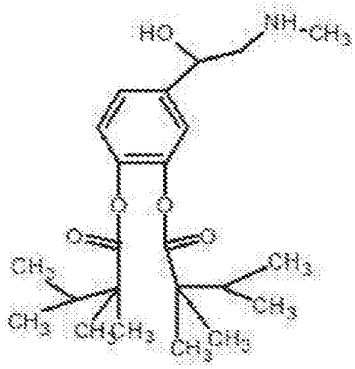


4E

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-dimethylbutanoate)
CLogP: 2.6294



F

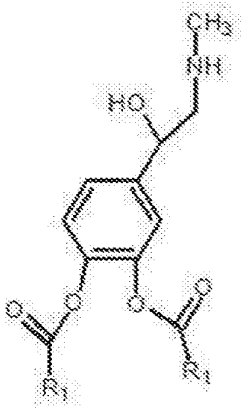


4F

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,3-trimethylbutanoate)
CLogP: 3.4274

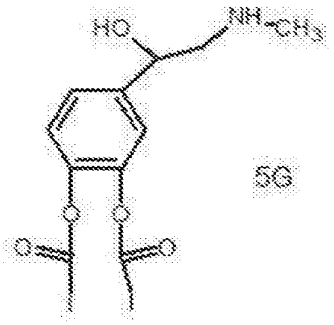
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FIG. 5



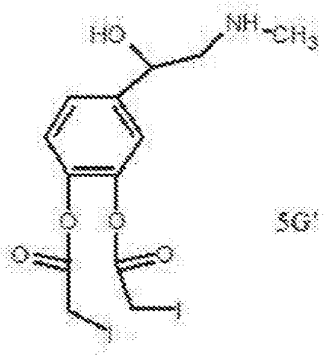
R1=H
R1=I
R1=Cl
R1=CH2CH2CH3
R1=CH2CH2CH2CH3
R1=CH2Cl
R1=CH2I
R1=CH2F

G



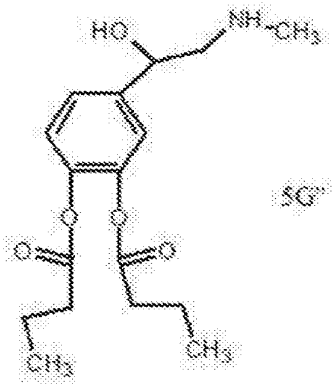
5G

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dicarbonodidate
CLogP: 1.0854



5G'

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-iodoacetate)
CLogP: 0.3834

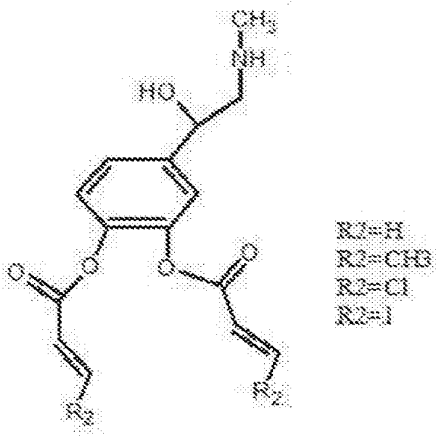


5G'

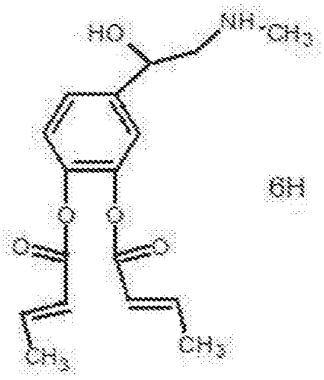
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate
CLogP: 1.2134

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FIG. 6

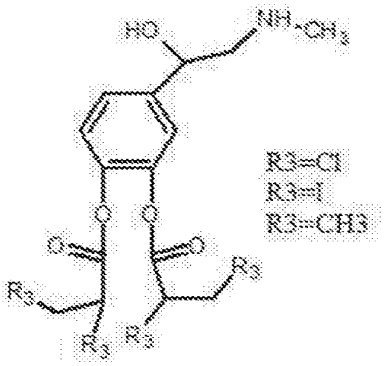


H

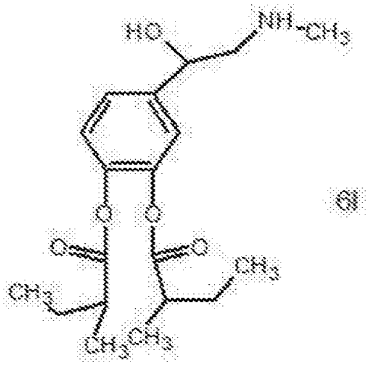


6H

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene (2*E*,2'*E*)-bis(but-2-enoate)
CLogP: 1.2054



I

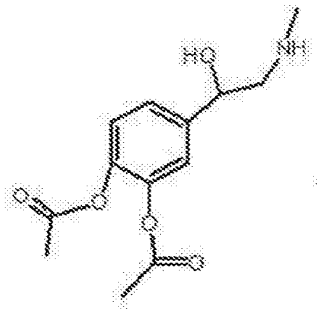


6I

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylbutanoate)
CLogP: 1.8314

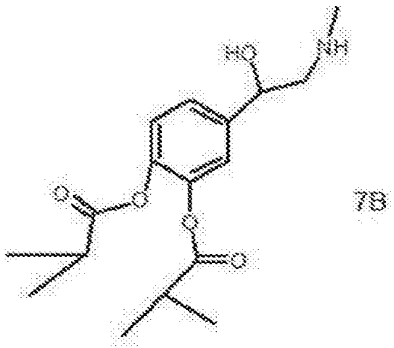
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FIG. 7



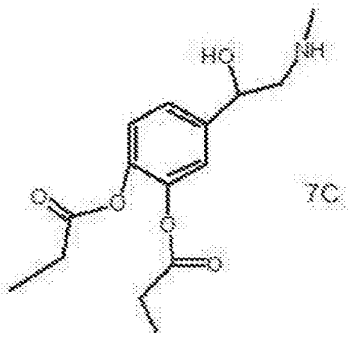
7A

4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate
CLogP: -0.9026



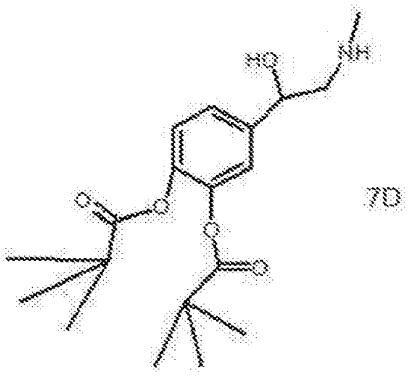
7B

4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2-methylpropanoate)
CLogP: 0.7733



7C

4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropanoate
CLogP: 0.1554

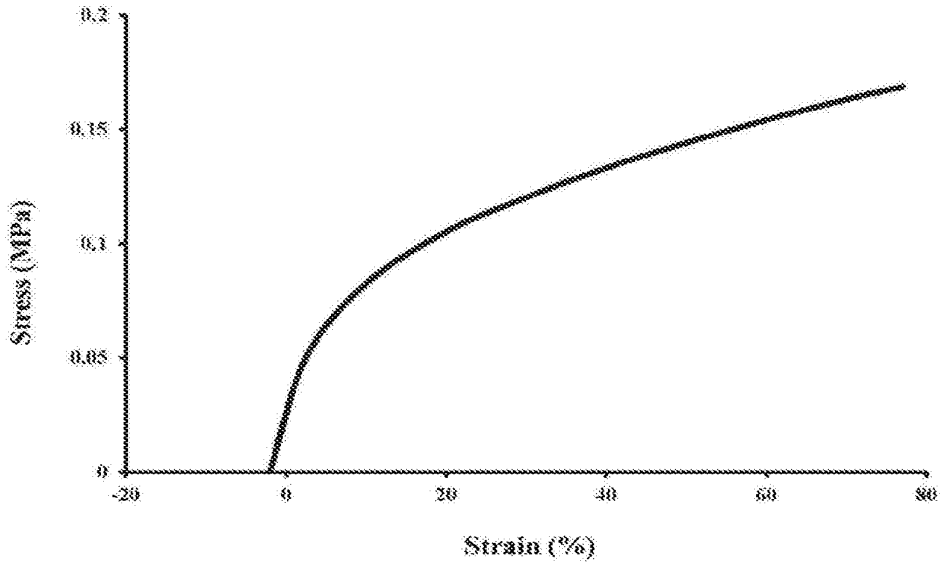


7D

4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate)
CLogP: 1.5714

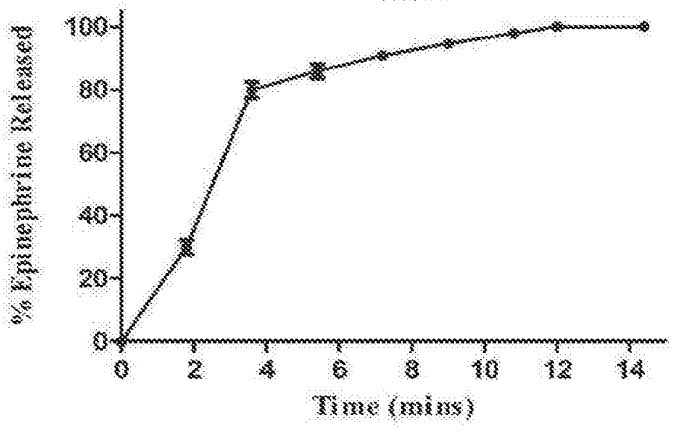
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FIG. 8



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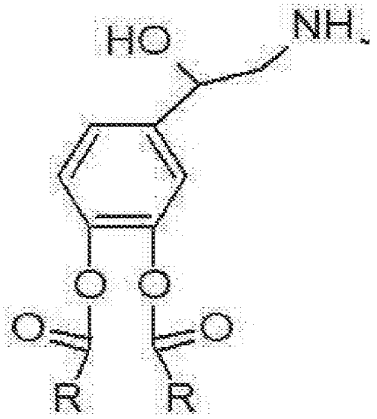
FIG. 9



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CLAIMS

1. A compound of a Formula:



wherein R is selected from the group consisting of: H, $CHCH_2$, $CHCHCH_3$, $CHCH_2CL$, $CHCH_2I$, $CHCLCH_2CL$, $CHICH_2I$, $CHCH_3CH_2CH_3$, $CH_2CCH_3CH_3CH_3$, $CH_2CH_2CH_3$, CH_2CL, CH_2I, CH_2F, CL, I, F, $CHCH_3CHCH_3CH_3$, CHCLCHCLCL, CHICHII, CHFCHFF, CH_2CHCH_2, CCLCLCHCLCL, CICHII, CCLCLCL, CIII, CH_2COCH_3, CH_2COCL CH_2COI, CH_2OCH_3, $CHICH_3$, $CCLCLCH_3$, $CH_2CHCH_3CH_3$, $CH_2CHCLCL$, CH_2CHII, $CH_2CCLCLCL$, CH_2CIII, CHCLCL, CHII, $CCH_3CH_3CHCH_3CH_3$, $NHCCH_3CH_3CH_3$, $NHCHCH_3CH_3$, $NHCH_2CH_3$, $NHCH_3$, SCH_3, SCH_2CH_3, $SCHCH_3CH_3$, $SCCH_3CH_3CH_3$, $CH_2C_6H_5$ and C_6H_5 or a pharmaceutically acceptable salt thereof.

2.The compound of claim 1, formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration.

3.The compound of claim 2, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

4.Use of the pharmaceutical composition of claims 2 or 3 in a patient in need of anaphylactic treatment.

5.The compound of claim 1 comprising: a compound as depicted in a formula **2A** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_2CH_3, $CH_2CH_2CH_3$, or $CH_2CH_2CH_2CH_3$, CL or I.

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6.The compound of claim 1 comprising: a compound as depicted in a formula **2B** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: CL or I.

7.The compound of claim 1 comprising: a compound as depicted in a formula **3C** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: CL and I.

8.The compound of claim 1 comprising: a compound as depicted in a formula **3D** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_4 is selected for the group consisting of: Cl and I.

9.The compound of claim 1 comprising: a compound as depicted in a formula **4E** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: Cl and I.

10.The compound of claim 1 comprising: a compound as depicted in a formula **4F** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: Cl and I.

11.The compound of claim 1 comprising: a compound as depicted in a formula **5G** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: H, I, Cl, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, CH_2Cl, CH_2I and CH_2F.

12. The compound of claim 1 comprising: a compound as depicted in **6H** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3, Cl and I.

13.The compound of claim 1 comprising: a compound as depicted in a formula **6I** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: Cl, I and CH_3.

14. A method to deliver epinephrine or a prodrug of epinephrine comprising: the steps of: providing epinephrine in a unit dosage form, formulated for sublingual or buccal administration, wherein the unit dosage form is a rapidly dissolving film, to a patient in need of treatment thereof.

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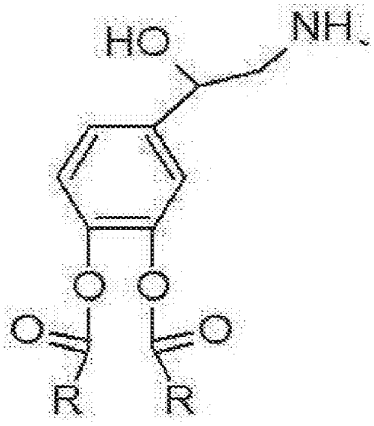
15.The method of claim 14 wherein the prodrugs of epinephrine has a Log P value in the range of about 0.5-6.0.

16. The method of claim 14 wherein the prodrugs of epinephrine has a Log P value in the range of about 1.0-5.0.

17. The method of claim 14 further comprising: providing said epinephrine or the prodrug of epinephrine in a unit dosage form to a patient in need of anaphylactic treatment.

18.The method of claim 14 further comprising: providing said prodrug of epinephrine in a unit dosage form to a patient in need of anaphylactic treatment.

19. A compound of a Formula:



wherein R is selected from the group consisting of: H, CH_3, CH_2CH_3, $CHCH_3CH_3$ and $CCH_3CH_3CH_3$, and wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration.

20. The compound of claim 19, wherein the compound is selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

21.The compound of claim 19, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

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22. Use of the pharmaceutical formulation of claim 21 in a patient in need of anaphylactic treatment.

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TITLE OF THE INVENTION: PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE

Field of the Invention:

[0001] The present invention relates to pharmaceutical compositions for the treatment of anaphylaxis formulated for rapid sublingual or buccal delivery, *i.e.*, compounds that dissolves in the oral cavity. In one embodiment, the delivery vehicle is a rapidly dissolving film. The films contain an epinephrine, or a novel epinephrine pro-drug formulated for the rapid delivery of the drug to a patient in need of treatment, such as for example, a patient in need of treatment for anaphylaxis.

Description of Related Art Including Information

[0002] Epinephrine is considered the primary choice for the treatment of anaphylaxis which is a life threatening allergic reaction that might lead to death if untreated especially in children. A study reported that one in every 10,000 children has an anaphylactic attack per year. Epinephrine is the drug of choice for the treatment of anaphylactic shock in children and adults. It is highly soluble in water, highly hydrophilic (log P -0.68) and can be oxidized readily. Based on the current physicochemical properties of epinephrine, the only delivery available in the market is intramuscular injection. The administration of proper therapeutic agents, such as, epinephrine must be prompt. This is usually performed through the usage of auto-injectors such as EPIPEN (MYLAN) or TWINJECT (SHIONOGI PHARMA, INC.) that deliver the required dose in the mid-outer thigh either subcutaneously or intramuscularly. However, many disadvantages are reported with the usage of these injectors such as high cost, inaccurate administration, short half-life, patient's fear of needles, accidental injections, and unavailability of a sufficient number of fixed prefilled doses.

[0003] These shortcomings affect greatly the patient compliance and adherence to these injectors. In addition, it is very challenging to adjust the dose to different children ages as there are only two premeasured fixed epinephrine doses (0.15 and 0.3 mg). Recent study showed that only 17% of pediatric patients who have experienced anaphylactic symptoms have used prescribed auto injectors. Other available delivery systems such as syringes or inhalers are also underused due to their

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lack of rapid and accurate dosing. Therefore, there is growing interest in the development of an alternative non-invasive delivery system that can easily provide accurate doses of epinephrine.

[0004] Anwar A. Hussain and James E. Truelove were granted patents related to the synthesis of novel esters of [(methylamino)methyl] benzyl alcohol which is epinephrine. The purpose of the Hussain's *et. al.* invention was to develop a prodrug of epinephrine HCl with superior lipid solubility to enhance penetration through the cornea of the eye to treat glaucoma. Hussain *et. al.* synthesized four different prodrugs for this purpose (see structures 7A, 7B, 7C, 7D). These four molecules were tested in human, rabbit and horse plasmas and found that 3, 4 – dipivalyl-α-[(methylamino) methyl] benzyl alcohol hydrochloride (structure 7D) shows the best penetration profile into the eye. Hussain's et. al. didn't evaluate the log P of these molecules nor did they evaluate the sublingual or buccal permeability or absorption. Their main focus was to develop a prodrug specifically for the eye. Since the initial publishing of Anwar's patents in 1974 and 1975, no one has followed up or even published any new data on structures 7A, 7B, and 7C. Dipivalyl-α-[(methylamino)] benzyl alcohol hydrochloride (7D) was further developed into a drug delivery system for glaucoma (Dipivefrin or Propine). Hussain and Truelove selected this prodrug for further development because of several physicochemical and biological qualities. The first quality was estimating the delay before onset of seizure for this prodrug was about 8-10 minutes, the second quality was the rate of hydrolysis expressed as $t_{1/2}$ in human plasma was about 1,800 seconds and the third quality was the $t_{1/2}$ hydrolysis and oxidation *in vitro* was 700 and 300 days respectively. In a separate publication (Journal of Pharmaceutical Sciences, Vol. 65, No. 10, October 1976, p: 1510-1512), Hussain *et. al.* shared the graphs for the *in vitro* hydrolysis of this particular prodrug using rabbit eye homogenate and compared the hydrolysis among three different plasmas (human, rabbit, rabbit eye homogenate).

[0005] Films that incorporate a pharmaceutically active ingredient are disclosed in U.S. Pat. No. 4,136,145 to Fuchs, *et al.* ("Fuchs"). These films can be formed into a sheet, dried and then cut into individual doses. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas. A drug delivery vehicle must provide a high level of uniformity with respect to the dosage delivered.

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BRIEF SUMMARY OF THE INVENTION

[0006] This invention relates to pharmaceutical compositions made by modifying the physicochemical properties of epinephrine in order to enhance its permeability through biological membranes (sublingual and buccal membranes). Several prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring, by chemically reacting the two groups with several acid moieties to form an ester bond with different alkyl chains. The addition of an alkyl group will enhance the lipophilicity of epinephrine (increase log P) and will consequently increase its permeability through the biological membranes (sublingual and buccal tissues in the oral cavity). The 3 and 4 positions represent meta and para locations with respect to the carbon in position 1 on the phenolic ring of epinephrine. Once the prodrug penetrates biological membranes (sublingual and buccal), the biological enzyme carboxyesterase will degrade the ester bond and release epinephrine for therapeutic activity. A prodrug is a biologically inactive compound that can be metabolized in the body to produce a drug. On characteristic of the selected prodrug compounds is fast hydrolysis in plasma.

[0007] In another embodiment, the subject matter includes a method to deliver epinephrine involving the steps of: providing epinephrine in a unit dosage form formulated for sublingual or buccal administration, wherein the unit dosage form is a rapidly dissolving film and the unit dosage form provides the pharmaceutical pro-drug of epinephrine. More specifically, this method involves providing pharmaceutical pro-drug compositions epinephrine in a unit dosage form to patients in need of anaphylactic treatment.

[0008] The subject matter includes a pharmaceutical formulation made of: a compound as depicted in a formula 2A and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, CL and I. A pharmaceutical formulation made of: a compound as depicted in a formula 2B and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: CL and I. A pharmaceutical formulation made of: a compound as depicted in a formula 3C and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_4 is selected for the group consisting of: CL and I. A pharmaceutical formulation made of: a compound as depicted in a formula 3D and a pharmaceutically acceptable carrier or a

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pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula 4E and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula 4F and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula 5G and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: H, I, Cl, $CH_2CH_2CH_3$ & $CH_2CH_2CH_2CH_3$, CH_2Cl, CH_2I and CH_2F A pharmaceutical formulation made of: a compound as depicted in a formula 6H and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3, Cl and I. A pharmaceutical formulation made of: a compound as depicted in a formula 6I and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: Cl, I and CH_3. The compound is formulated in a unit dosage form as a rapidly dissolving film. The invention further provides use of the pharmaceutical formulation in a patient in need of anaphylactic treatment.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWING(S):

[00010] The invention can be best understood by those having ordinary skill in the art by reference to the following detailed description when considered in conjunction with the accompanying drawings in which:

[00011] FIG. 1 shows the generic chemical structure of a biologically inactive compound of this invention.

[00012] FIG. 2 shows exemplary compounds of the present invention.

[00013] FIG. 3 shows exemplary compounds of the present invention.

[00014] FIG. 4 shows exemplary compounds of the present invention.

[00015] FIG. 5 shows exemplary compounds of the present invention.

[00016] FIG. 6 shows exemplary compounds of the present invention.

[00017] FIG. 7 shows Anwar A. Hussain and James E. Truelove compounds.

[00018] FIG. 8 shows a stress-strain profile of the optimized epinephrine fast dissolving film.

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[00019] FIG. 9 shows a release profile of the epinephrine from the optimized fast dissolving film in 500 ml Simulated Saliva at 37 °C.

DETAILED DESCRIPTION OF THE INVENTION:

[00020] The present invention may be understood more readily by reference to the following detailed description of the invention. It is to be understood that this invention is not limited to the specific devices, methods, conditions or parameters described herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed invention. Also, as used in the specification including the appended claims, the singular forms "a," "an," and "the" include the plural, and reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise. Ranges may be expressed herein as from "about" or "approximately" one particular value and/or to "about" or "approximately" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment.

[00021] These and other aspects, features and advantages of the invention will be understood with reference to the detailed description herein, and will be realized by means of the various elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description of the invention are exemplary and explanatory of preferred embodiments of the inventions, and are not restrictive of the invention as claimed. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Reference will now be made in detail to the presently preferred embodiments of the invention, examples of which are illustrated in the accompanying drawings. Throughout the following detailed description, the same reference numerals refer to the same elements in all figures.

[00022] The present invention provides a novel biologically inactive compound that can be metabolized in the body to produce a drug that has the biological activity of epinephrine. Epinephrine acts on nearly all body tissues. Its actions vary by tissue type and tissue expression of adrenergic receptors. For example, high levels of

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epinephrine cause smooth muscle relaxation in the airways but cause contraction of the smooth muscle that lines most arterioles. The present subject matter relates to modifying the physicochemical properties of epinephrine in order to enhance its permeability through biological membranes (sublingual and buccal membranes. **FIG. 1** shows the generic chemical structure of a biologically inactive compound of this invention, while **Table 1** shows exemplary prodrugs of epinephrine made by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring along with Log P values or a pharmaceutically acceptable salt thereof. The prodrugs of epinephrine preferably have a Log P value in the range of about 0.5-6.0. and more preferably between 1.0-5.0. This range was listed as a table of marketed sublingual tablets and films in Ashraf et. al "Considerations in developing sublingual tablets-An overview", Pharmaceutical Technology, 2014, 38(11). Log P is the logarithmic value of the ratio of two concentrations of a compound in a mixture of two immiscible liquids such as water and octanol at equilibrium. Log P values can be calculated mathematically by the use of PERCEPTA PLATFORM software (ACD Labs, Toronto, Ontario, Canada).

TABLE 1

R	Log P	R	Log P
R= $CHCH_2$	-0.20	R= CH_2COCH_3	-1.44
R= $CHCHCH_3$	+0.84	R= CH_2COCL	-0.21
R= $CHCH_2CL$	+0.05	R= CH_2COI	+1.10
R= $CHCH_2I$	+1.36	R= CH_2OCH_3	-1.29
R= $CHCLCH_2CL$	+0.78	R= $CHICH_3$	+1.82
R= $CHICH_2I$	+4.0	R= $CCLCLCH_3$	+1.36
R= $CHCH_3CH_2CH_3$	+1.85	R= $CH_2CHCH_3CH_3$	+1.85
R= $CH_2CCH_3CH_3CH_3$	+2.55	R= $CH_2CHCLCL$	+1.06
R= $CH_2CH_2CH_3$	+0.8	R= CH_2CHII	+4.09
R= CH_2CL	-0.51	R= $CH_2CCLCLCL$	+2.97
R= CH_2I	+1.12	R= CH_2CHI	+7.68
R= CH_2F	-0.85	R= CHCLCL	+0.66
R= CHI	+8.13	R= CHII	+4.03
R= CL	+1.24	R= $CCH_3CH_3CHCH_3CH_3$	+3.24
R= I	+2.55	R $NHCCH_3CH_3CH_3$	+1.63
R= F	+0.72	R= $NHCHCH_3CH_3$	+1.28
R= $CHCH_3CHCH_3CH_3$	+2.54	R= $NHCH_2CH_3$	+0.93
R= CHCLCHCLCL	+2.08	R= $NHCH_3$	+0.40

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R= CHICHII	+7.09	R= SCH_3	+1.92
R= CHFCHFF	+0.80	R=SCH_2CH_3	+2.45
R= CH_2CHCH_2	+0.07	R=$SCHCH_3CH_3$	+2.80
R= CCLCLCHCLCL	+4.18	R= $SCCH_3CH_3CH_3$	+3.15
R= CHCHII	+11.29	R= $CH_2C_6H_5$	+2.52
R= CCLCLCL	+2.90	R= C_6H_5	+3.10

[00023] A pro-drug is a derivative of epinephrine selected for fast permeability through sub-lingual and buccal membranes (*ie* a compound that dissolves in the oral cavity) and fast hydrolysis (half-life $t_{1/2}$ range from 1-6 minutes) by plasma enzymes to form epinephrine when delivered. These characteristics are physical properties of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film. Now referring to **FIG. 2,** derivatives of epinephrine are shown. Structure **2A** represents di-ester derivatives of epinephrine where the R_1 can be a short alkyl chain of CH_3, CH_2CH_3, $CH_2CH_2CH_3$, or $CH_2CH_2CH_2CH_3$, CL or I. A representative molecule of this group compounds is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3-methylbutanoate) having a CLogP: 2.0114. Structure **2B** represents derivatives of epinephrine where R_2 = CH_3, CL or I. A representative molecule of this group of compounds is 4-(1-hydroxy-2-(methyllamino) ethyl)-1,2-phenylene bis(3,3-dimethylbutanoate) having a CLogP: 2.8094. Adding H, CH_3, Cl or I change the Log P of the prodrug and adds a non-toxic moiety to the molecule. The rate of hydrolysis of each ester can increase or decrease depending on how the atom in position R_4 influences the ester group

[00024] Now referring to **FIG. 3,** derivatives of epinephrine are shown. Structure **3C** represents a derivative of epinephrine where R_3 = Cl or I. A representative molecule of the group is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dichloroacetate) having a CLogP: 1.4494. Structure **3D** represents a derivative of epinephrine where R_4 = Cl or I. A representative molecule of the groups is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,2-trichloroacetae) having a CLogP: 2.8554. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

[00025] Now referring to **FIG. 4** derivatives of epinephrine are shown. Structure **4E** represents a derivative of epinephrine where R1 = CH3, CL or I. A representative molecule is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-

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dimethylbutanoate) having a CLogP: 2.6294. Structure 4F represents a derivative of epinephrine where $R_2 = CH_3$, CL or I. A representative molecule is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,3-trimethylbutanoate) having a CLogP: 3.4274. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

[00026] Now referring to FIG. 5, derivatives of epinephrine are shown. Structure G represents a derivative epinephrine where R_1 = H, I, Cl, $CH_2CH_2CH_3$ & $CH_2CH_2CH_2CH_3$, CH_2Cl, CH_2I or CH_2F. Representative molecules are: 5G 4- (1-hydroxy-2-(methylamino) ethyl) 1,2-phenylene dicarboniodidate having a Clog: 1.084;. 5G' 4-(1-hydroxy-2-(methylamino-ethyl)-1,2-phenylene bis (2-iodoacetate) having a CLogP: 0.3834 and Structure 5G'' 4-(1-hydroxy-2-methylamino)ethyl)-1,2-phenylene dibutyrate) having a CLogP: 1.2134.

[00027] Now referring to FIG. 6, a derivative epinephrine is shown. Structure H6 represents a derivative of epinephrine where R_2 = H, CH_3, CL or I. A representative example is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene (2*E*,2'*E*)-bis(but-2-enoate) having a CLogP: 1.2054. Structure I6 represents a derivative of epinephrine where R_3 = CL, I or CH_3. A representative example is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylbutanoate) having a CLogP: 1.8314.

[00028] Now referring to FIG. 7, the compounds of the invention as shown in US patent 3,809,714 and US patent 3,825,583 hereby incorporated by reference. Representative molecules include: 7A 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene diacetate having a DLogP: -0.9026. 7B 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate) having a CLogP: 0.773300. 7C 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate having a CLogP: 0.1554. 7D 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate) having a CLogP: 1.5714. If these molecules show fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme (half-life 1-6 minutes) a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film. The subject matter includes: uses of a pharmaceutical formulation in a patient in need of anaphylactic treatment, wherein the pharmaceutical formulation is made of a compound selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-

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2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient. A pharmaceutical formulation made of a compound selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

TABLE 2

R	Log P
Structure 7A R= CH_3	-0.97
Structure 7C R= CH_2CH_3	+0.09
Structure 7B R= $CHCH_3CH_3$	+0.79
Structure 7D R= $CCH_3CH_3CH_3$	+1.49

[00029] The present invention further provides a pharmaceutical composition made of at least one compound or mixture of compounds of the invention in a pharmaceutically acceptable carrier thereof. The invention features a pharmaceutical composition in unit dosage form formulated for sublingual or buccal administration. The delivery systems include: fast dissolving films, oral dissolving tablets, inhalation, and nasal delivery. In one embodiment, the unit dosage form of the present invention is a film for the delivery of epinephrine hydrochloride, as an anaphylactic treatment in a patient, such as for a pediatric or geriatric patient. A typical rapidly dissolving film is made of a drug, a water-soluble polymer, a plasticizer, a saliva stimulating agent, a surfactant and other fillers such as sweetening agents and flavors in case of bitter taste drugs. *See e.g.* A. Arya, A. Chandra, V. Sharma, and K. Pathak, "Fast dissolving oral films: An innovative drug delivery system and dosage form," *Int. J. ChemTech Res.*, vol. 2, no. 1, pp. 576–583, 2010.D. P. Lettre, "Formulation and Evaluation of Rapidly Disintegrating Film of Levocetrizine Hydrochloride," *Pharmacia*, vol. 2, no. 2, pp. 208–220, 2010.

[00030] For the present invention, the drug is epinephrine, a prodrug of epinephrine or a salt thereof. The typical dose of epinephrine for anaphylactic treatment

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is 0.3 to 0.5 mg in adults and 0.01 mg/kg up to a maximum of 0.3 mg in children administered through intramuscular route. In this study, 13mg/9 cm^2 of epinephrine (5.9 % w/w) are used as the dose size. This quantity is calculated for 6-7-year-old child according to Clark's rule Pediatric dose = Adult dose x (child's weight/150).

[00031] A typical dose of 40 mg was based on a study in rabbits that showed a dose bioequivalence between a 40mg epinephrine tablet administered sublingually and 0.3 mg epinephrine administered intramuscularly using Epi pen. Injectors, Rawas-Qalaji et. al. Biopharm Drug Dispos. 27: 427-435 (2006). Furthermore, the time to reach maximum epinephrine concentration after a 0.3 mg EPIPEN (Mylan Specialty L.P.) injection in children is reported at 8±2 minutes. In another study, maximum plasma epinephrine concentration is reached within 34±14 minutes using 0.01 mg/kg dose injection of epinephrine subcutaneously in the deltoid region.

[00032] The polymer and the optimal amount of polymer are selected to obtain a non-sticky and functional film. A film-forming polymer should have good wetting property, high spread ability, good feeling in the mouth and should be safe and non-irritant. Many studies have showed that polymer content of at least 10 -15 % is needed in order to formulate proper film of proper thickness after drying in order to peel the film off from the release line. In one exemplary embodiment, the polymer is a water soluble modified hydroxypropyl starch that is specifically manufactured for aqueous film coating in immediate release solid oral dosage forms.

[00033] A plasticizer is used to form the rapidly dissolving film. The plasticizer enhances the flow of the polymer and improve the tensile strength and elongation of the fill. Several plasticizers are commonly used in rapidly dissolving film preparation such as glycerol, di-butylphthalate, and polyethylene glycols and they are usually used up to 20 % concentration of dry polymer weight.

[00034] The function of the surfactant is to facilitate the solubilization or wetting of the film and subsequently causing the film to disintegrate quickly, releasing the drug to be absorbed through the buccal cavity. Surfactants can include Tween 80, which is a complex mixture of polyoxyethylene ethers used as emulsifiers or dispersing agents in pharmaceuticals.

[00035] A saliva stimulating agent used to facilitate the delivery of the drug using a rapidly dissolving film to the patient. Other fillers, such as sweetening agents and flavors in case of bitter taste drugs and colors are added to the rapidly

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dissolving film to facilitate the delivery of the drug using a rapidly dissolving film to the patient. Typically, acids such as citric acid, malic acid, lactic acid and ascorbic acid are used as chemical stimulants of saliva secretion. However, citric acid is the most preferred among them. Xylitol and Tutti Frutti flavor are used for taste masking. Xylitol is an effective sweetening agent which has equal sweetness to sucrose.

[00037] Examples :Four formulations are prepared in this example. Epinephrine is soluble in Lycoat 720 (modified hydroxypropyl starch) water mixture. This hydrophilic polymer solubilizes epinephrine HCl, form a high viscosity gel that spreads well as we cast the film and lead to a non-sticky dry film after water evaporation. This polymer doesn't have any oxyethylene groups that can promote the oxidation of epinephrine nor it has glucose units that promotes water adsorption. The other ingredients added such as tween, glycerin decreased the rigidity of the film and improved elasticity. sodium metabisulfite was added to prevent and long-term oxidation of epinephrine HCl in the film. The citric acid brings the pH of the gel to the maximum stability range for epinephrine. The percentages of the polymer are shown in (Table 3). The polymer percentages are (20, 25, 27 and 30 %) of the total formulation weights. The polymer used in this example is LYCOAT (Ferromet). LYCOAT is a water soluble modified hydroxypropyl starch that is specifically manufactured for aqueous film coating in immediate release solid oral dosage forms.

[00038] **Table 3: List of the compositions of the four FDFs formulations.**

Ingredient (% w/w)	Use	F1	F2	F3	F4
Epinephrine HCl	Drug	5.9	5.9	5.9	5.9
Sodium Metabisulfite	Antioxidant	5.9	5.9	5.9	5.9
Lycoat 720 (hydroxypropyl starch)	Film-forming polymer	20	25	27	30
Glycerin	Plasticizer	3	3	3	3
Tween 80	Surfactant	2	2	2	2
Citric Acid Monohydrate	Buffer; increases absorption	0.5	0.5	0.5	0.5

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	in oral cavity				
Sodium Citrate Monobasic	Buffer	0.5	0.5	0.5	0.5
Xylitol	Sweetener	10	10	10	10
Tutti Frutti	Flavor	6	6	6	6
Water		46.2	41.2	39.2	36.2

[00039] Glycerin is used as a plasticizer to provide the proper elasticity for the film (Table 1). A plasticizer imparts a certain level of flexibility to the film by decreasing its brittleness. Films in this example are prepared using 3% glycerol which is equivalent to 10-15 % of the amount of polymer used.

[00040] Tween 80 is used as a surfactant (Table 2). Citric acid is used to adjust the pH and can be used in rapidly dissolving film as a saliva simulating agent to increase the secretion rate of saliva which will further improve the disintegration time of the film. Finally, the addition of an antioxidant is very important for the stability of epinephrine. Prompt oxidation of epinephrine in aqueous solutions results in a colored inactive product which has been reported. Therefore, different types of antioxidants are used in the commercial injectors such as sodium metabisulfite, EDTA and ascorbic acid achieving shelf life of two years. In this exemplary embodiment, the addition of sodium metabisuflite stabilizes the film.

[00041] However, films formed by formulations 1, 2 and 3 are too sticky after drying rendering them unusable. Formulation 4, having 30 % polymer content, formed a smooth, transparent, flexible and uniform film and therefore it is selected for further testing. The difference in stickiness is clearly related to the variation of the polymer content. This comes in agreement with a previous study that showed that using 22.5% of LYCOAT polymer formed a thin and flexible but sticky film at that concentration concluding that a higher percentage of polymer is needed.

[00042] Physical properties of the film prepared by formulation 4 are evaluated such as elastic modulus, thickness, content uniformity and dissolution time. Assessing these parameters is essential to determine the efficiency and usability of the film by patients. Elastic modulus is first studied as it represents a clear measure of the

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stiffness level of the film. It is calculated as the ratio of the applied stress over strain on a specific section.

[00043] Elastic's modulus= (Force at corresponding strain/cross section area) ×1/ (corresponding strain).

[00044] Now referring to FIG. 8, the profile of the film is illustrated showing a small increase in the applied strain to the film causes a quick increase in stress reaching a value of 0.1 MPa at 20 % strain level. As the strain increases further above 20 %, the increase magnitude in stress decreases gradually until it reaches a semi-plateau at value 0.16 MPa where % stress is 80 %. The value of elastic modulus is determined at 1.325 MPa which is an indication of very good flexibility of the film (Table 3).

[00045] **Table 4: List of physical properties of the optimized film**

Test	Results
Elastic Modulus	1.325±0.2 MPa
Thickness	0.29±0.01 mm
Content Uniformity	93% ± 10%

[00046] The thickness of the film at different locations is measured at 0.29 mm with very small margin of variability which is an indication of the high uniformity of the film (Table 4). A maximum thickness variation of 5 % is permitted in the preparation of the rapidly dissolving film. A uniform thickness across the film as it directly correlates with the accuracy of the dose in the film. Drug content in film is measured at 93 % ±10 indicating high level of consistency of epinephrine dose within the film (Table 2), as a limit of 85 -115 % of content uniformity is acceptable according to USP.

[00047] Now referring to FIG. 9, the dissolution profile of epinephrine from the film in terms of rate and extent in simulated saliva is determined on six samples of the optimized film. More than 90 % of epinephrine is released from the film within 7.2 minutes.

[00048] Taste and disintegration time of the optimized film are evaluated on 6 volunteers (Table 3). The disintegration time is the time when the film starts to break

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or disintegrates. Volunteers reported 10 -30 seconds disintegration time (Table 3). This complies with the regulations set by United State Pharmecopeia (USP) for disintegration time of oral films (not exceeding 30 seconds). Bitterness of epinephrine is masked efficiently according to volunteer's comments (Table 5). Four volunteers sensed no bitterness of the film while the other two volunteers reported slight to very slight sensation of bitterness. Moreover, no tongue constriction is reported by any of the volunteers. This data presents clear proof of the efficiency of rapidly dissolving film in taste masking the bitterness of epinephrine and an indication of strong potential for using a rapidly dissolving film as a replacement therapy of epinephrine injections for children.

[00049] **Table 5**: *In vivo* taste and disintegration time evaluation of the optimized epinephrine FDF.

Volunteer	Bitterness	Tongue Constriction	Disintegration Time
1	None	None	~10 seconds
2	None	None	~10 seconds
3	Slight	None	~20 seconds
4	None	None	~30 seconds
5	Very slight	None	~20 seconds
6	None	None	~30 seconds

[00050] Materials--Epinpherine hydrochloride, sodium metabisulfite, citric acid monohydrate and sodium citrate monobasic are purchased from Sigma Aldrich (St. Louis, MO). Lycoat® RS720 is obtained from Roquette (Lestrem, France). Glycerin and tween 80 are purchased from Fisher Chemicals (Pittsburg, PA). Xylitol is purchased from Gallipot (St. Paul, MN). Tutti Frutti is obtained from LorAnn Oils (Lansing, MI). Film Preparation--Several rapidly dissolving films are prepared by a solvent casting technique to choose the optimum film formulation. The formulation compositions of the rapidly dissolving film are mentioned in Table 3. LYCOAT and Xylitol are dissolved in warm water. The solution is then placed in a sonicator for

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two hours and then the solution is left overnight to ensure the removal of all entrapped air bubbles. Other excipients and Epinephrine HCl are added to the solution on the next day at room temperature. The mixture is then placed again in a sonicator for 40 minutes. The mixture is then spread onto a checkered paper covered by plastic sheet using a stainless-steel bar applicator. The film is left to dry overnight and is cut into 9 mm^2 small film strips.

[00053] Physical properties-The thickness and elastic modulus of the optimized film is evaluated using Dynamic Mechanical Analyzer (Q800 DMA, TA instruments, New Castle, DE). This is important to evaluate tensile properties of the films. Three strips of the optimized films are tested at 25 °C according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02). Each film is positioned between the grips of the instrument. The preload force is set at 0.01 N and the final force at 15N. The initial grip separation is set to 60 mm and crosshead speed is set to 500 mm/min. The test is terminated when the film breaks. Elastic modulus is determined as the slope of the straight-line part of the stress-strain curve and it is expressed in force per unit area (MPa).

[00054] Drug content uniformity: Specific areas are cut from six different films and weighted to calculate the estimated amount of drug in each area. Films are then dissolved in 100 ml of citric acid buffer. The media are stirred and then filtered using 0.45 um filters (Millipore Corporation, Millipore, Vimodron, Italy) and epinephrine content is assessed using UVmini-1240 UV-Vis Spectrophotometer (Shimadzu, Japan) at wavelength 280 nm. Epinephrine content is determined by calculating the percentage of the measured epinephrine to the estimated amount in each film.

[00055] *In vitro* dissolution test: For the dissolution test, rapidly dissolving film are evaluated using USP dissolution apparatus II, paddle (Distek Evolution 6100, North Brunswick, NJ). Six strips are placed in different 1 L vessels containing 500 ml Simulated Saliva. The temperature of the dissolution media is set to 37 C and rpm is set to 50 rpm. Samples are taken at different time points throughout the time of the experiment (15 mins), and the amount of epinephrine released in the media is determined by UVmini-1240 UV-Vis Spectrophotometer (Shimadzu, Japan) at 280 nm.

[00056] Human taste panel--To evaluate the palatability of optimized epinephrine film, a taste evaluation study is performed on six healthy volunteers. The study is

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carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), and all volunteers are informed in advance of the related details and the goal of the study and their consents are obtained. Volunteers are asked to place the film on the interior surface of their buccal cavity until the film is fully disintegrated. Volunteers then rinsed their mouths with drinking water. Volunteers have to report their findings of the presence of bitterness or not, any tongue restriction and how long it took for full disintegration of the film.

[00057] Equivalent elements can be substituted for the ones set forth above such that they perform in substantially the same manner in substantially the same way for achieving substantially the same result. It is believed that the system and method of the present invention and many of its attendant advantages will be understood by the foregoing description. It is also believed that it will be apparent that various changes may be made in the form, construction and arrangement of the components thereof without departing from the scope and spirit of the invention or without sacrificing all of its material advantages. The form herein before described being merely exemplary and explanatory embodiment thereof. It is the intention of the following claims to encompass and include such changes.

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62/421,316 13 November 2016 (13.11.2016) US

(71) Applicant: **IONO PHARMA, LLC** [US/US]; 3133 Hilllake Drive, Bartlett, TN 38135 (US).

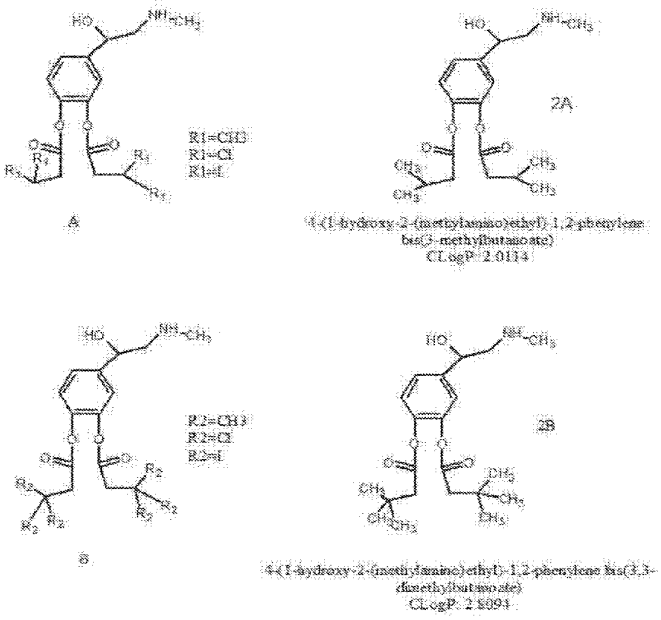
(72) Inventors: **ALMOAZEN, Hassan**; 3133 Hill Lake Drive, Bartlett, TN 38135 (US). **HAYNES, Lindsay**; 2068 Horizons Dr, Ooltewah, TN 37363 (US).

(74) Agent: **FENTRESS, Susan, B.**; Veritay Group, IP, 20 Dudley Suite 803, Memphis, TN 38103 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(54) Title: PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE

FIG. 2



(57) Abstract: The present invention relates to a pharmaceutical composition for the treatment of anaphylaxis formulated for rapid delivery, in one embodiment, the delivery vehicle is a rapidly dissolvmg film. The films contain an epinephrine or a novel epinephrine pro-drag for fee rapid treatment of anaphylaxis in a patient. This invention relates to pharmaceutical compositions made by modifying the physicoehemieal properties of epinephrine in order to enhance its permeability through biological membranes (sublingual and buccal membranes). Several prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring, by chemically reacting the two groups with several acid moieties to form an ester bond with different alkyl chains. The addition of an alkyl group will enhance the lipophilicity of epinephrine (increase log P) and will consequently increase its permeability through the biological membranes (sublingual and buccal tissues in the oral cavity).

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[continued on next page]

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/US17/60761
International Application No.

09 NOV 2017 (09.11.17)
International Filing Date

PCT INTERNATIONAL APPLICATION
RO/US
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum)

Box No. I TITLE OF INVENTION

PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Iono Pharma, LLC
3133 Hill Lake Drive
Bartlett, TN 38135
USA

Telephone No.

Facsimile No.

Applicant's registration No. with the Office

E-mail authorization: Marking one of the check-boxes below authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send, notifications issued in respect of this international application to that e-mail address if those offices are willing to do so.

☐ as advance copies followed by paper notifications; or ☐ exclusively in electronic form (no paper notifications will be sent).

E-mail address:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☒ all designated States ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Susan B Fentress
Veritay Group, IP
20 Dudley Suite 803
Memphis, TN 38103
USA

Telephone No.
9013716683

Facsimile No.
9018661656

Agent's registration No. with the Office
31327

E-mail authorization: Marking one of the check-boxes below authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send, notifications issued in respect of this international application to that e-mail address if those offices are willing to do so.

☒ as advance copies followed by paper notifications; or ☐ exclusively in electronic form (no paper notifications will be sent).

E-mail address: sfentress@veritaygroup.com

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
Hassan Almoazen
3133 Hill Lake Drive
Bartlett, TN 38135
USA

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
Lindsay Haynes
2068 Horizons Dr
Ooltewah, TN 37363
USA

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
☐ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
☐ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet

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Box No. V DESIGNATIONS

The filing of this request **constitutes under Rule 4.9(a) the designation** of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany **is not designated** for any kind of national protection

☐ JP Japan **is not designated** for any kind of national protection

☐ KR Republic of Korea **is not designated** for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing or subsequently under Rule 26bis.1, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application.)

Box No. VI PRIORITY CLAIM AND DOCUMENT

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application: regional Office	international application: receiving Office
item (1) 13/11/2016 13 NOV 2016	62/421,316	US		
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

Furnishing the priority document(s):

☒ The **receiving Office** is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application(s) was filed with the receiving Office which, for the purposes of this international application, is the receiving Office)* identified above as:

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

☐ The **International Bureau** is requested to obtain from a digital library a certified copy of the earlier application(s) identified above, using, where applicable, the access code(s) indicated below *(if the earlier application(s) is available to it from a digital library)*:

☐ item (1) access code _____ ☐ item (2) access code _____ ☐ item (3) access code _____ ☐ other, see Supplemental Box

Restore the right of priority: the receiving Office is requested to restore the right of priority for the earlier application(s) identified above or in the Supplemental Box as item(s) (_____). *(See also the Notes to Box No. VI. further information must be provided to support a request to restore the right of priority.)*

Incorporation by reference: where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if more than one International Searching Authority is competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA/ US

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Continuation of Box No. VII USE OF EARLIER SEARCH AND CLASSIFICATION RESULTS

1. Request by the applicant under Rule 4.12

1.1 ☐ The ISA indicated in Box No. VII **is requested to take into** account **the results of the earlier search(es)** indicated below (*see also Notes to Continuation of Box No. VII, item 1, use of results of more than one earlier search*)

Filing date *(day/month/year)* | Application Number | Country *(or regional Office)*

☐ **Statement (Rule 4.12(ii))**: this international application is the same, or substantially the same, as the application in respect of which the earlier search was carried out except, where applicable, that it is filed in a different language.

1.2 **Submission of the earlier search results, where necessary***

☐ **Availability of documents (Rules 12*bis*.1(c) and (d) and 12*bis*.2(b))**: the following documents are **available to the ISA** in a form and a manner acceptable to it, and therefore **DO NOT need** to be submitted by the applicant to the receiving Office, or to the ISA.

- ☐ a copy of the results of the earlier search,
- ☐ a copy of the earlier application,
- ☐ a translation of the earlier application into a language which is accepted by the ISA,
- ☐ a translation of the results of the earlier search into a language which is accepted by the ISA,
- ☐ a copy of any document cited in the earlier search results *(if known, please indicate below the documents available to the ISA)*:

☐ **Request from the applicant to the receiving Office to transmit to the ISA a copy of the earlier search results (Rule 12*bis*.1(b) and (d))**: *(where the earlier search was not carried out by the ISA indicated in Box No. VII but by the same Office as that which is acting as receiving Office; or where the earlier search results are otherwise available to the receiving Office)*: the applicant **requests** the receiving Office **to prepare and transmit** to the ISA a copy of the earlier search results.

* The applicant **only** needs to furnish a copy of the earlier search results to the receiving Office, or the ISA, if none of the scenarios mentioned under item 1 applies. *(See item 10 in the check-list and also Notes to Continuation of Box No. VII, item 1).*

☐ Further earlier searches are indicated on a continuation sheet.

2. Transmission of the earlier search and classification results to the ISA by the receiving Office where the applicant DID NOT make a request under Rule 4.12

2.1 Where the international application claims priority of an earlier application, subject to Article 30(2)(a) and (3), **the receiving Office**:

- **shall transmit** a copy of the earlier search and classification results to the ISA (unless such copy is already available to the ISA), where the earlier application(s) was filed with the **same Office** as that which is acting as **the receiving Office** and that Office **has carried out** the earlier search in respect of the earlier application (Rule 23*bis*.3(a));
- **may transmit** such a copy if the earlier application was filed with a different Office, but where the results of that earlier search and classification are nevertheless available to the receiving Office (Rule 23*bis*.2(c)).

However, where the applicant did not request the receiving Office to transmit to the ISA a copy of the earlier search results under Rule 4.12 (see above item 1), in respect of an earlier search carried out on the following earlier application, the priority of which is subsequently claimed in this international application, the applicant may consider (*see also Notes to Continuation of Box No. VII, item 2, use of more than one earlier search*):

Filing date *(day/month/year)* | Application Number | Country *(or regional Office)*

2.2 **Request not to transmit the earlier search results by the receiving Office to the ISA (Rule 23*bis*.2(b))**

☐ **to request** that the receiving Office **DOES NOT transmit** the results of the earlier search to the ISA (Rule 23*bis*.2(b)) *(may only be checked where the international application is filed with the following receiving Offices: DE, FI and SE)*

2.3 **Authorization to transmit the earlier search and classification results by the receiving Office to the ISA (Rule 23*bis*.2(a) and (c))**

☐ **to authorize** the receiving Office **to transmit** the results of the earlier search and classification to the ISA (Rule 23*bis*.2(c)) *(may only be checked where the international application is filed with the following receiving Offices: AU, CH, CZ, EI, HU, IL, JP, NO, SE, SG and US)*

☐ **to authorize** the receiving Office **to transmit** the results of the earlier international search and classification to the ISA (Rule 23*bis*.2(a) and Article 30(2)(a) and (3)) *(may only be checked where the earlier search concerns an international application, the priority of which is subsequently claimed in this international application and where the earlier international search was carried out by a different ISA than the ISA chosen in Box No. VII)*

☐ Further earlier searches are indicated on a continuation sheet.

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:

			Number of declarations
☐	Box No. VIII (i)	Declaration as to the identity of the inventor :	
☒	Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :	1
☐	Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :	
☐	Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America) :	
☐	Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :	

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Box No. IX CHECK LIST for EFS-Web filings - this sheet is only to be used when filing an international application with RO/US via EFS-Web

This international application contains the following:	Number of sheets
(a) request form PCT/RO/101 (including any declarations and supplemental sheets)	6
(b) description (excluding any sequence listing part of the description, see (f), below)	16
(c) claims	4
(d) abstract	1
(e) drawings (if any)	9
(f) sequence listing part of the description in the form of an image file (e.g. PDF)	
Total number of sheets (including the sequence listing part of the description if **filed as an image file**)	36

(g) sequence listing part of the description

- ☐ filed in the form of an **Annex C/ST.25 text file**
- ☐ WILL BE filed separately on physical data carrier(s), on the same day and in the form of an **Annex C/ST.25 text file**

Indicate type and number of physical data carrier(s)

This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*	Number of items
1. ☐ fee calculation sheet	1
2. ☐ original separate power of attorney	
3. ☐ original general power of attorney	
4. ☐ copy of general power of attorney; reference number:	
5. ☐ priority document(s) identified in Box No. VI as item(s)	
6. ☐ Translation of international application into *(language)*:	
7. ☐ separate indications concerning deposited microorganism or other biological material	
8. ☐ *(only where item (f) is marked in the left column)* copy of the sequence listing in electronic form (Annex C/ST.25 text file) not forming part of the international application but **furnished only for the purposes of international search** under Rule 13*ter*	
9. ☐ *(only where item (f) (in the left column) and item 8 (above) are marked)* a statement confirming that "the information recorded in electronic form submitted under Rule 13*ter* is identical to the sequence listing as contained in the international application" as filed via EFS-Web	
10. ☐ copy of results of earlier search(es) (Rule 12*bis*.1(a))	
11. ☐ other *(specify)*:	

Figure of the drawings which should accompany the abstract:	2	**Language of filing** of the international application:	ENGLISH

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

/susan b fentress/
Veritay Group, IP
20 Dudley 803
Memphis, TN 38103
US
31327
Agent for Applicant

09-11-2017

For receiving Office use only

1. Date of actual receipt of the purported international application:	09 NOV 2017 (09.11.17)
2. Drawings: ☐ received: ☐ not received:	
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA / US	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

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Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

In relation to this international application Iono Pharma, LLC is entitled to apply for and be granted a patent by virtue of the following assignments: an assignment of Hassan Almoazen dated 13 NOV 2016 and Lindsay Haynes dated 12 OCT 2016.

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

890729

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

November 19, 2017

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *62/421,316*
FILING DATE: *November 13, 2016*
RELATED PCT APPLICATION NUMBER: *PCT/US17/60761*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US62/421,316*

Certified by

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
Approved for use through 05/31/2015. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

Provisional Application for Patent Cover Sheet

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

Inventor(s)

Inventor 1 — Remove

Given Name	Middle Name	Family Name	City	State	Country i
Hassan		Almoazen	Bartlett	TN	US

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

Title of Invention	Pharmaceutical Formulation for Rapid Delivery of Epinephrine
Attorney Docket Number (if applicable)	24050.0001

Correspondence Address

Direct all correspondence to (select one):

(●) The address corresponding to Customer Number	( ) Firm or Individual Name
Customer Number	76447

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 United States Government. The U.S. Government agency name is:
- ( ) Yes, the invention was under a contract with an agency of the United States Government. The name of the U.S. Government agency and Government contract number are:

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
Approved for use through 05/31/2015. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

Entity Status
Applicant asserts small entity status under 37 CFR 1.27 or applicant certifies micro entity status under 37 CFR 1.29

- (●) Applicant asserts small entity status under 37 CFR 1.27
- ( ) Applicant certifies micro entity status under 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
- ( ) No

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 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 CFR1.14). 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

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Susan B. Fentress/			Date (YYYY-MM-DD)	2016-11-[illegible]3
First Name	Susan	Last Name	Fentress	Registration Number (If appropriate)	31327

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 8 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. **This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.**

TITLE OF THE INVENTION: PHARMACEUTICAL FORMULATION FOR RAPID DELIVERY OF EPINEPHRINE

CROSS-REFERENCE TO RELATED APPLICATIONS: Not applicable.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT: Not Applicable.

THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT: Not Applicable

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC OR AS A TEXT FILE VIA THE OFFICE ELECTRONIC FILING SYSTEM (EFS-WEB): Not Applicable.

STATEMENT REGARDING PRIOR DISCLOSURES BY THE INVENTOR OR A JOINT INVENTOR: Not Applicable.

BACKGROUND OF THE INVENTION

Field of the Invention:

[0001] The present invention relates to a pharmaceutical composition for the treatment of anaphylaxis formulated for rapid delivery. In one embodiment, the delivery vehicle is a rapidly dissolving film. The films contain an epinephrine or a novel epinephrine pro-drug for the rapid treatment of anaphylaxis in a patient.

Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.

[0002] Epinephrine is considered the primary choice for the treatment of anaphylaxis which is a life threatening allergic reaction that might lead to death if untreated especially in children. A study reported that one in every 10,000 children has an anaphylactic attack per year. Epinephrine is the drug of choice for the treatment of

anaphylactic shock in children and adults. It is highly soluble in water, highly hydrophilic (log P -0.68) and can be oxidized readily. Based on the current physicochemical properties of epinephrine, the only delivery available in the market is intramuscular injection. The administration of proper therapeutic agents, such as, epinephrine must be prompt. This is usually performed through the usage of auto-injectors such as EPIPEN (MYLAN) or TWINJECT (SHIONOGI PHARMA, INC.) that deliver the required dose in the mid-outer thigh either subcutaneously or intramuscularly. However, many disadvantages are reported with the usage of these injectors such as high cost, inaccurate administration, short half-life, patient's fear of needles, accidental injections, and unavailability of a sufficient number of fixed prefilled doses.

[0003] These shortcomings affect greatly the patient compliance and adherence to these injectors. In addition, it is very challenging to adjust the dose to different children ages as there are only two premeasured fixed epinephrine doses (0.15 and 0.3 mg). Recent study showed that only 17% of pediatric patients who have experienced anaphylactic symptoms, have used prescribed auto injectors. Other available delivery systems such as syringes or inhalers are also underused due to their lack of rapid and accurate dosing. Therefore, there is growing interest in the development of an alternative non-invasive delivery system that can easily provide accurate doses of epinephrine.

[0004] Anwar A. Hussain and James E. Truelove were granted patents related to the synthesis of novel esters of [(methylamino)methyl] benzyl alcohol which is epinephrine. The purpose of the Hussain's *et. al.* invention was to develop a prodrug of epinephrine HCl with superior lipid solubility to enhance penetration through the cornea

of the eye to treat glaucoma. Hussain *et. al.* synthesized four different prodrugs for this purpose (see structures 7A, 7B, 7C, 7D). These four molecules were tested in human, rabbit and horse plasmas and found that 3, 4 – dipivalyl-α-[(methylamino) methyl] benzyl alcohol hydrochloride (structure 7D) shows the best penetration profile into the eye. Hussain's et. al. didn't evaluate the log P of these molecules nor did they evaluate the sublingual or buccal permeability or absorption. Their main focus was to develop a prodrug specifically for the eye. Since the initial publishing of Anwar's patents in 1974 and 1975, no one has followed up or even published any new data on structures 7A, 7B, and 7C, Dipivalyl-α-[(methylamino)] benzyl alcohol hydrochloride (7D) was further developed into a drug delivery system for glaucoma (Dipivefrin or Propine). Hussain and Truelove picked this particular prodrug for further development because of several physicochemical and biological qualities. The first quality was estimating the delay before onset of seizure for this prodrug to be about 8-10 minutes, the second quality was the rate of hydrolysis expressed as $t_{1/2}$ in human plasma was about 1,800 seconds and the third quality was evaluating the hydrolysis and oxidation $t_{1/2}$ in vitro to be 700 and 300 days respectively. In a separate publication (Journal of Pharmaceutical Sciences, Vol. 65, No. 10, October 1976, p: 1510-1512), Hussain *et. al.* shared the graphs for the vitro hydrolysis of this particular prodrug using rabbit eye homogenate and compared the hydrolysis among three different plasmas (human, rabbit, rabbit eye homogenate).

[0005] Films that incorporate a pharmaceutically active ingredient are disclosed in U.S. Pat. No. 4,136,145 to Fuchs, *et al.* ("Fuchs"). These films can be formed into a sheet, dried and then cut into individual doses. Examples of specific uses disclosed by Fuchs

include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas. A drug delivery vehicle must provide a high level of uniformity with respect to the dosage delivered.

BRIEF SUMMARY OF THE INVENTION

[0006] This invention relates to pharmaceutical compositions made by modifying the physicochemical properties of epinephrine in order to enhance its permeability through biological membranes (sublingual and buccal membranes). Several prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring, by chemically reacting the two groups with several acid moieties to form an ester bond with different alkyl chains. The addition of an alkyl group will enhance the lipophilicity of epinephrine (increase log P) and will consequently increase its permeability through the biological membranes (sublingual and buccal tissues in the oral cavity). The 3 and 4 positions represent meta and para locations with respect to the carbon in position 1 on the phenolic ring of epinephrine. Once the prodrug penetrates biological membranes (sublingual and buccal), the biological enzyme carboxyesterase will degrade the ester bond and release epinephrine for therapeutic activity.

[0007] In another embodiment, the subject matter includes a method to deliver epinephrine involving the steps of: providing epinephrine in a unit dosage form formulated for sublingual or buccal administration, wherein the unit dosage form is a rapidly dissolving film and the unit dosage form provides the pharmaceutical pro-drug compositions of epinephrine. More specifically, this method involves providing pharmaceutical pro-drug compositions epinephrine in a unit dosage form to patients in need of anaphylactic treatment.

[0008] The subject matter includes a pharmaceutical formulation comprising: a compound as depicted in a formula 2A and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: H, CH_3, CL and I. A pharmaceutical formulation comprising: a compound as depicted in a formula 2B and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3, CL and I. A pharmaceutical formulation comprising: a compound as depicted in a formula 3C and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: H, CH_3, CL and I. A pharmaceutical formulation comprising: a compound as depicted in a formula 3D and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_4 is selected for the group consisting of: H, CH_3, Cl and I. A pharmaceutical formulation comprising: a compound as depicted in a formula 4E and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: H, CH_3, Cl and I. A pharmaceutical formulation comprising: a compound as depicted in a formula 4F and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3, Cl and I. A pharmaceutical formulation comprising: a compound as depicted in a formula 5G and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: H, I, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$ & $CH_2CH_2CH_2CH_3$, CH_2Cl, CH_2I and CH_2F A pharmaceutical formulation comprising: a compound as depicted in a

formula 6H and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3, Cl and I. A pharmaceutical formulation comprising: a compound as depicted in a formula 6I and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: H, Cl, I and CH_3. The compound is formulated in a unit dosage form as a rapidly dissolving film. The invention further provides use of the pharmaceutical formulation in a patient in need of anaphylactic treatment.

[0009] The subject matter includes: uses of a pharmaceutical formulation in a patient in need of anaphylactic treatment, wherein the pharmaceutical formulation is made of a compound selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient. A pharmaceutical formulation made of a compound selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWING(S):

[00010] The invention can be best understood by those having ordinary skill in the art by reference to the following detailed description when considered in conjunction with the accompanying drawings in which:

[00011] **FIG. 1** shows the chemical structure of epinephrine.

[00012] **FIG. 2** shows exemplary compounds of the present invention.

[00013] **FIG. 3** shows exemplary compounds of the present invention.

[00014] **FIG. 4** shows exemplary compounds of the present invention.

[00015] **FIG. 5** shows exemplary compounds of the present invention.

[00016] **FIG. 6** shows exemplary compounds of the present invention.

[00017] **FIG. 7** shows exemplary compounds of the present invention.

[00018] **FIG. 8** shows a stress-strain profile of the optimized epinephrine fast dissolving film.

[00019] **FIG. 9** shows a release profile of the epinephrine from the optimized fast dissolving film in 500 ml Simulated Saliva at 37 °C.

DETAILED DESCRIPTION OF THE INVENTION:

[00020] The present invention may be understood more readily by reference to the following detailed description of the invention. It is to be understood that this invention is not limited to the specific devices, methods, conditions or parameters described herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed invention. Also, as used in the specification including the appended claims, the singular

forms "a," "an," and "the" include the plural, and reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise. Ranges may be expressed herein as from "about" or "approximately" one particular value and/or to "about" or "approximately" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment.

[00021] These and other aspects, features and advantages of the invention will be understood with reference to the detailed description herein, and will be realized by means of the various elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description of the invention are exemplary and explanatory of preferred embodiments of the inventions, and are not restrictive of the invention as claimed. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Reference will now be made in detail to the presently preferred embodiments of the invention, examples of which are illustrated in the accompanying drawings. Throughout the following detailed description, the same reference numerals refer to the same elements in all figures.

[00022] The present invention provides novel biologically inactive compound that can be metabolized in the body to produce a drug that has the biological activity of epinephrine. Epinephrine acts on nearly all body tissues. Its actions vary by tissue type

and tissue expression of adrenergic receptors. For example, high levels of epinephrine causes smooth muscle relaxation in the airways but causes contraction of the smooth muscle that lines most arterioles. The present subject matter relates to modifying the physicochemical properties of epinephrine **(FIG. 1)** in order to enhance its permeability through biological membranes (sublingual and buccal membranes). Several exemplary prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring.

[00023] Now referring to **FIG. 2,** derivatives of epinephrine are shown. Structure **2A** represents di-ester derivatives of epinephrine where the R_1 can be H, short alkyl chain of CH_3, CH_2CH_3, $CH_2CH_2CH_3$, or $CH_2CH_2CH_2CH_3$, CL or I. A representative molecule of this group compounds is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3-methylbutanoate) having a CLogP: 2.0114. Structure **2B** represents derivatives of epinephrine where R_2 = H, CH_3, CL or I. A representative molecule of this group of compounds is 4-(1-hydroxy-2-(methyllamino) ethyl)-1,2-phenylene bis(3,3-dimethylbutanoate) having a CLogP: 2.8094. Adding H, CH_3, Cl or I change the Log P of the prodrug and adds a non-toxic moiety to the molecule. The rate of hydrolysis of each ester can increase or decrease depending on how the atom in position R_4 influences the ester group. A pro-drug is selected for fast permeability through sub-lingual and buccal membranes and fast hydrolysis by the enzyme. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

[00024] Now referring to **FIG. 3,** derivatives of epinephrine are shown. Structure **3C** represents a derivative of epinephrine where R_3 = H, CH_3 Cl or I. A representative molecule of the group is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dichloroacetate) having a CLogP: 1.4494. Structure **3D** represents a derivative of epinephrine where R_4 = H, CH_3 Cl or I. A representative molecule of the groups is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,2-trichloroacetae) having a CLogP: 2.8554. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

[00025] Now referring to **FIG. 4** derivatives of epinephrine are shown. Structure **4E** represents a derivative of epinephrine where R1 = H, CH3, CL or I. A representative molecule is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-dimethylbutanoate) having a CLogP: 2.6294. Structure **4F** represents a derivative of epinephrine where R_2 =H, CH_3, CL or I. A representative molecule is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,3-trimethylbutanoate) having a CLogP: 3.4274. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

[00026] Now referring to **FIG. 5,** derivatives of epinephrine are shown. Structure **G** represents a derivative epinephrine where R_1 = H, I, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$ & $CH_2CH_2CH_2CH_3$, CH_2Cl, CH_2I or CH_2F. Representative molecules are: 4- (1-hydroxy-2-(methylamino) ethyl) 1,2-phenylene dicarboniodidate having a Clog: 1.084;. 4-(1-

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hydroxy-2-(methylamino-ethyl)-1,2-phenylene bis (2-iodoacetate) having a CLogP: 0.3834 and Structure G"5 4-(1-hydroxy-2-methylamino)ethyl)-1,2-phenylene dibutyrate) having a CLogP: 1.2134.

[00027] Now referring to **FIG. 6,** a derivative epinephrine is shown. Structure **H6** represents a derivative of epinephrine where R_2 = H, CH_3, CL or I. A representative example is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene (2*E*,2'*E*)-bis(but-2-enoate) having a CLogP: 1.2054.Structure **I6** represents a derivative of ephinephrine where R_3 = H, CL, I or CH_3. A representative example is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylbutanoate) having a CLogP: 1.8314.

[00028] Now referring to **FIG. 7,** the compounds of the invention as shown in US patent 3,809,714 and US patent 3,825,583 hereby incorporated by reference. Representative molecules include: **7A** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene diacetate having a DLogP: -0.9026. **7B** 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate) having a CLogP: 0.773300. **7C** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate having a CLogP: 0.1554. **7D** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate) having a CLogP: 1.5714. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

[00029] The present invention further provides a pharmaceutical composition made of at least one compound or mixture of compounds of the invention in a pharmaceutically acceptable carrier thereof. The invention features a pharmaceutical composition in unit

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dosage form formulated for sublingual or buccal administration. The delivery systems include: fast dissolving films, oral dissolving tablets, inhalation, and nasal delivery. In one embodiment, the unit dosage form of the present invention is a film for the delivery of epinephrine hydrochloride, as an anaphylactic treatment in a patient, such as for example a pediatric or geriatric patient. A typical rapidly dissolving film is made of a drug, a water-soluble polymer, a plasticizer, a saliva stimulating agent, a surfactant and other fillers such as sweetening agents and flavors in case of bitter taste drugs and colors. *See e.g.* A. Arya, A. Chandra, V. Sharma, and K. Pathak, "Fast dissolving oral films: An innovative drug delivery system and dosage form," *Int. J. ChemTech Res.*, vol. 2, no. 1, pp. 576–583, 2010.D. P. Lettre, "Formulation and Evaluation of Rapidly Disintegrating Film of Levocetrizine Hydrochloride," *Pharmacia*, vol. 2, no. 2, pp. 208–220, 2010.

[00030] For the present invention, the drug is epinephrine or prodrug of epinephrine or a salt thereof. The typical dose of epinephrine for anaphylactic treatment is 0.3 to 0.5 mg in adults and 0.01 mg/kg up to a maximum of 0.3 mg in children administered through intramuscular route. In this study, 13mg/9 cm^2 of epinephrine (5.9 % w/w) are used as the dose size (Table 1). This quantity is calculated for 6-7-year-old child according to Clark's rule Pediatric dose = Adult dose x (child's weight/150).

[000031] A typical dose of 40 mg was based on a study in rabbits that showed a dose bioequivalence between 40 mg epinephrine tablet administered sublingually and 0.3 mg epinephrine administered intramuscularly using Epi pen. Injectors, Rawas-Qalaji et. al. Biopharm Drug Dispos. 27: 427-435 (2006). Furthermore, the time to reach maximum epinephrine concentration after 0.3 mg EPIPEN (Mylan Specialty L.P.) Injection of children is reported at 8±2 minutes. In another study, maximum plasma epinephrine

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concentration is reached within 34±14 minutes using 0.01 mg/kg dose injection of epinephrine subcutaneously in the deltoid region.

[00032] The polymer and the optimal amount of polymer are selected to obtain a non-sticky and functional film. A film-forming polymer should have good wetting property, high spread ability, good feeling in the mouth and should be safe and non-irritant. Many studies have showed that polymer content of at least 10 -15 % is needed in order to formulate proper film of proper thickness after drying in order to peel the film off from the release line. In one exemplary embodiment, the polymer is a water soluble modified hydroxypropyl starch that specifically manufactured for aqueous film coating in immediate release solid oral dosage forms.

[00033] A plasticizer is used to form the rapidly dissolving film. The plasticizer enhances the flow of the polymer and improve the tensile strength and elongation of the fill. Several plasticizers are commonly used in rapidly dissolving film preparation such as glycerol, di-butylphthalate, and polyethylene glycols and they are usually used up to 20 % concentration of dry polymer weight.

[00034] The function of the surfactant is to facilitate the solubilization or wetting of the film and subsequently causing the film to disintegrate quickly, releasing the drug to be absorbed through the buccal cavity. Surfactants can include Tween 80, which is a complex mixture of polyoxyethylene ethers used as emulsifiers or dispersing agents in pharmaceuticals.

[00035] A saliva stimulating agent used to facilitate the delivery of the drug using a rapidly dissolving film to the patient. Other fillers, such as sweetening agents and flavors in case of bitter taste drugs and colors are added to the rapidly dissolving film to

facilitate the delivery of the drug using a rapidly dissolving film to the patient. Typically, acids such as citric acid, malic acid, lactic acid and ascorbic acid are used as chemical stimulants of saliva secretion. However, citric acid is the most preferred among them Xylitol and tutti frutti flavor are used for taste masking (Table 1). Xylitol is an effective sweetening agent which has equal sweetness to sucrose.

[00036] Examples:

[00037] Four formulations are prepared in this example. The percentages of the polymer are shown in (Table 1). The polymer percentages are (20, 25, 27 and 30 %) of the total formulation weighs. The polymer used in this example is LYCOAT (Ferromet). LYCOAT is a water soluble modified hydroxypropyl starch that specifically manufactured for aqueous film coating in immediate release solid oral dosage forms.

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[00038] Table 1: List of the compositions of the four FDFs formulations.

Ingredient (% w/w)	Use	F1	F2	F3	F4
Epinephrine HCl	Drug	5.9	5.9	5.9	5.9
Sodium Metabisulfite	Antioxidant	5.9	5.9	5.9	5.9
Lycoat® RS720 (hydroxypropyl starch)	Film-forming polymer	20	25	27	30
Glycerin	Plasticizer	3	3	3	3
Tween 80	Surfactant	2	2	2	2
Citric Acid Monohydrate	Buffer; increases absorption in oral cavity	0.5	0.5	0.5	0.5
Sodium Citrate Monobasic	Buffer	0.5	0.5	0.5	0.5
Xylitol	Sweetener	10	10	10	10
Tutti Frutti	Flavor	6	6	6	6
Water		46.2	41.2	39.2	36.2

[00039] Glycerin is used as a plasticizer to provide the proper elasticity for the film (Table 1). A plasticizer imparts certain level of flexibility to the film by decreasing its brittleness. Films in this example are prepared using 3% glycerol which is equivalent to 10-15 % of the amount of polymer used.

[00040] Tween 80 is used as a surfactant (Table 1). Citric acid is use to adjust the pH and can be used in rapidly dissolving firm as saliva simulating agent to increase the secretion rate of saliva which will further improve the disintegration time of the film. Finally, the addition of antioxidant is very important for the stability of epinephrine.

Prompt oxidation of epinephrine in aqueous solution results in a colored inactive product which has been reported. Therefore, different types of antioxidants are used in the commercial injectors such as sodium metabisulfite, EDTA and ascorbic acid achieving shelf life of two years. The addition of sodium metabisuflite to the film, herein, will ensure the stability of epinephrine in the film (Table 1). However, further stability studies should be performed to assess this claim.

[00041] However, films formed by formulations 1, 2 and 3 are too sticky after drying rendering them unusable. While formulation 4 that has 30 % polymer content formed smooth, transparent, flexible and uniform film and therefore it is selected for further testing. The difference in stickiness is clearly related to the variation of the polymer content. This comes in agreement with previous study that showed that using 22.5% of LYCOAT polymer formed a thin and flexible but sticky film at that concentration concluding that higher percentage of polymer is needed.

[00042] Physical properties of the film prepared by formulation 4 are evaluated such as elastic modulus, thickness, content uniformity and dissolution time. Assessing these parameters is essential to determine the efficiency and usability of the film by patients. Elastic modulus is first studied as it represents clear measure of the stiffness level of the film. It is calculated as the ratio of the applied stress over strain on specific section.

[00043] Elastic 's modulus= (Force at corresponding strain/cross section area) ×1/ (corresponding strain).

[00044] Now referring to **FIG. 8**, the profile of the film is illustrated showing a small increase in the applied strain to the film causes a quick increase in stress reaching a

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value of 0.1 MPa at 20 % strain level. As the strain increases further above 20 %, the increase magnitude in stress decreases gradually until it reaches semi-plateau at value 0.16 MPa where % stress is 80 %. The value of elastic modulus is determined at 1.325 MPa which is indication of very good flexibility of the film (Table 2).

[00045] Table 2: List of physical properties of the optimized film

Test	Results
Elastic Modulus	1.325±0.2 MPa
Thickness	0.29±0.01 mm
Content Uniformity	93% ± 10%

[00046] The thickness of the film at different locations is measured at 0.29 mm with very small margin of variability which is an indication of the high uniformity of the film (Table 2). A maximum thickness variation of 5 % is permitted in the preparation of the rapidly dissolving film. A uniform thickness across the film as it directly correlates with the accuracy of the dose in the film. Drug content in film is measured at 93 % ±10 indicating high level of consistency of epinephrine dose within the film (Table 2), as a limit of 85 -115 % of content uniformity is acceptable according to USP.

[00047] Now referring to **FIG. 9**, the dissolution profile of epinephrine from the film in terms of rate and extent in simulated saliva is determined on six samples of the optimized film. More than 90 % of epinephrine is released from the film within 7.2 minutes.

[00048] Taste and disintegration time of the optimized film are evaluated on 6 volunteers (Table 3). The disintegration time is the time when the film starts to break or

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disintegrates. Volunteers reported 10 -30 seconds disintegration time (Table 3). This comply with the regulations set by United State Pharmecopeia (USP) for disintegration time of oral films (not exceeding 30 seconds). Bitterness of epinephrine is masked efficiently according to volunteer's comments (Table 3). Four volunteers sensed no bitterness of the film while the two others volunteers reported slight to very slight sensation of bitterness. Moreover, no tongue constriction is reported by any of the volunteers. This data presents clear proof of the efficiency of rapidly dissolving film in taste masking the bitterness of epinephrine and an indication of strong potential for using a rapidly dissolving film as a replacement therapy of epinephrine injections for children.

[00049] **Table 3**: In vivo taste and disintegration time evaluation of the optimized epinephrine FDF.

Volunteer	Bitterness	Tongue Constriction	Disintegration Time
1	None	None	~10 seconds
2	None	None	~10 seconds
3	Slight	None	~20 seconds
4	None	None	~30 seconds
5	Very slight	None	~20 seconds
6	None	None	~30 seconds

[00050] Materials--Epinpherine hydrochloride, sodium metabisulfite, citric acid monohydrate and sodium citrate monobasic are purchased from Sigma Aldrich (St.

Louis, MO). Lycoat® RS720 is obtained from Roquette (Lestrem, France). Glycerin and tween 80 are purchased from Fisher Chemicals (Pittsburg, PA). Xylitol is purchased from Gallipot (St. Paul, MN). Tutti frutti is obtained from LorAnn Oils (Lansing, MI).

[00051] Film Preparation--Several rapidly dissolving films are prepared by solvent casting technique to choose the optimum film formulation. The formulations compositions of the rapidly dissolving film are mentioned in **table 1.**

[00052] LYCOAT and xylitol are dissolved in warm water. The solution is then placed in a sonicator for two hours and then the solution is left overnight to ensure the removal of all entrapped air bubbles. Other excipients and Epinephrine HCl are added to the solution on the next day at room temperature. The mixture is then placed again in a sonicator for 40 minutes. The mixture is then spread onto a checkered paper covered by plastic sheet using a stainless-steel bar applicator. The film is left to dry overnight and is cut into 9 mm^2 small film strips.

[00053] Physical properties-The thickness, and elastic modulus of the optimized film is evaluated using Dynamic Mechanical Analyzer (Q800 DMA, TA instruments, New Castle, DE). This is important to evaluate tensile properties of the films. Three strips of the optimized films are tested at 25 °C according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02). Each film is positioned between the grips of the instrument. The preload force is set at 0.01 N and the final force at 15N. The initial grip separation is set to 60 mm and crosshead speed is set to 500 mm/min. The test is terminated when the film breaks. Elastic modulus is determined as the slope of the straight-line part of the stress-strain curve and it is expressed in force per unit area (MPa).

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[00054] Drug content uniformity: Specific areas are cut from six different films and weighted to calculate the estimated amount of drug in each area. Films are then dissolved in 100 ml of citric acid buffer. The media are stirred and then filtered using 0.45 um filters (Millipore Corporation, Millipore, Vimodron, Italy) and epinephrine content is assessed using UVmini-1240 UV-Vis Spectrophotometer (Shimadzu, Japan) at wavelength 280 nm. Epinephrine content is determined by calculating the percentage of the measured epinephrine to the estimated amount in each film.

[00055] In vitro dissolution test: For the dissolution test, rapidly dissolving film are evaluated using USP dissolution apparatus II, paddle (Distek Evolution 6100, North Brunswick, NJ). Six strips are placed in different 1 L vessels containing 500 ml Simulated Saliva. The temperature of the dissolution media is set to 37 C and rpm is set to 50 rpm. Samples are taken at different time points throughout the time of the experiment (15 mins), and the amount of epinephrine release in the media is determined by UVmini-1240 UV-Vis Spectrophotometer (Shimadzu, Japan) at 280 nm.

[00056] Human taste pane/--To evaluate the palatability of optimized epinephrine film, taste evaluation study is performed on six healthy volunteers. The study is carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), and all volunteers are informed in advance of the related details and the goal of the study and their consents are obtained. Volunteers are asked to place the film on the interior surface of their buccal cavity until film is fully disintegrated. Volunteers then rinsed their moths with drinking water. Volunteers have to report their findings of the presence of bitterness or not, any tongue restriction and how long it took for full disintegration of the film.

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[00057] Equivalent elements can be substituted for the ones set forth above such that they perform in substantially the same manner in substantially the same way for achieving substantially the same result. It is believed that the system and method of the present invention and many of its attendant advantages will be understood by the foregoing description. It is also believed that it will be apparent that various changes may be made in the form, construction and arrangement of the components thereof without departing from the scope and spirit of the invention or without sacrificing all of its material advantages. The form herein before described being merely exemplary and explanatory embodiment thereof. It is the intention of the following claims to encompass and include such changes.

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CLAIMS

1. A pharmaceutical formulation comprising: a compound as depicted in a formula **2A** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: H, CH_3, CL and I.
2. The pharmaceutical formulation of claim 1 wherein said compound is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3-methylbutanoate).
3. The pharmaceutical formulation of claim 1 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.
4. Use of the pharmaceutical formulation of claim 1 in a patient in need of anaphylactic treatment.
5. A pharmaceutical formulation comprising: a compound as depicted in a formula **2B** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3, CL and I.
6. The pharmaceutical formulation of claim 5 wherein said compound is 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3,3-dimethylbutanoate).
7. The pharmaceutical formulation of claim 5 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.
8. Use of the pharmaceutical formulation of claim 5 in a patient in need of anaphylactic treatment.
9. A pharmaceutical formulation comprising: a compound as depicted in a formula **3C** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: H, CH_3, CL and I.

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10. The pharmaceutical formulation of claim 9 wherein said compound is 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dichloroacetate).

11. The pharmaceutical formulation of claim 9 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

12. Use of the pharmaceutical formulation of claim 9 in a patient in need of anaphylactic treatment.

13. A pharmaceutical formulation comprising: a compound as depicted in a formula **3D** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_4 is selected for the group consisting of: H, CH_3, Cl and I.

14. The pharmaceutical formulation of claim 13 wherein said compound is 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,2-trichloroacetate).

15. The pharmaceutical formulation of claim 13 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

16. Use of the pharmaceutical formulation of claim 13 in a patient in need of anaphylactic treatment.

17. A pharmaceutical formulation comprising: a compound as depicted in a formula **4E** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: H, CH_3, Cl and I.

18. The pharmaceutical formulation of claim 17 wherein said compound is 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-dimethylbutanoate).

19. The pharmaceutical formulation of claim 17 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

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20. Use of the pharmaceutical formulation of claim 17 in a patient in need of anaphylactic treatment.

21. A pharmaceutical formulation comprising: a compound as depicted in a formula **4F** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3, Cl and I.

22. The pharmaceutical formulation of claim 21 wherein said compound is 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,3-trimethylbutanoate).

23. The pharmaceutical formulation of claim 21 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

24. Use of the pharmaceutical formulation of claim 21 in a patient in need of an anaphylactic treatment.

25. A pharmaceutical formulation comprising: a compound as depicted in a formula **5G** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: H, I, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, CH_2Cl, CH_2I and CH_2F

26. The pharmaceutical formulation of claim 25 wherein said compound is selected from the group consisting of: 4- (1-hydroxy-2-(methylamino) ethyl) 1,2-phenylene dicarboniodidate; 4-(1-hydroxy-2-(methylamino-ethyl)-1,2-phenylene bis(2-iodoacetate; and 4-(1-hydroxy-2-methylamino)ethyl)-1,2-phenylene dibutyrate.

27. The pharmaceutical formulation of claim 25 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

28. Use of the pharmaceutical formulation of claim 25 in a patient in need of anaphylactic treatment.

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29. A pharmaceutical formulation comprising: a compound as depicted in **6H** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3, Cl and I.

30. The pharmaceutical formulation of claim 29 wherein said compound is 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene (2*E*,2'*E*)-bis(but-2-enoate).

31. The pharmaceutical formulation of claim 29 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

32. Use of the pharmaceutical formulation of claim 29 in a patient in need of anaphylactic treatment.

33. A pharmaceutical formulation comprising: a compound as depicted in a formula **6I** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: H, Cl, I and CH_3.

34. The pharmaceutical formulation of claim 33 wherein said compound is 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2--methylbutanoate).

35. The pharmaceutical formulation of claim 33 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

36. Use of the pharmaceutical formulation of claim 33 in a patient in need of anaphylactic treatment.

37. Use of a pharmaceutical formulation in a patient in need of anaphylactic treatment, wherein said pharmaceutical formulation comprises a compound selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; 4-(1-hydroxy-2-

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(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient.

38. A pharmaceutical formulation comprising a compound selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

39. A method to deliver epinephrine comprising the steps of: providing epinephrine in a unit dosage form formulated for sublingual or buccal administration, wherein the unit dosage form is a rapidly dissolving film.

40. The method of claim 39 further comprising providing said epinephrine in a unit dosage form to a pediatric patient in need of anaphylactic treatment.

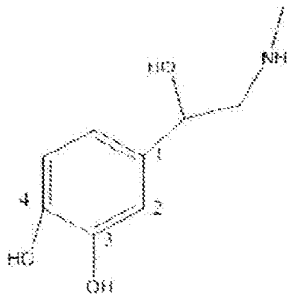
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ABSTRACT

This invention relates to pharmaceutical compositions made by modifying the physicochemical properties of epinephrine in order to enhance its permeability through biological membranes (sublingual and buccal membranes). Several prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring, by chemically reacting the two groups with several acid moieties to form an ester bond with different alkyl chains. The addition of an alkyl group will enhance the lipophilicity of epinephrine (increase log P) and will consequently increase its permeability through the biological membranes (sublingual and buccal tissues in the oral cavity).

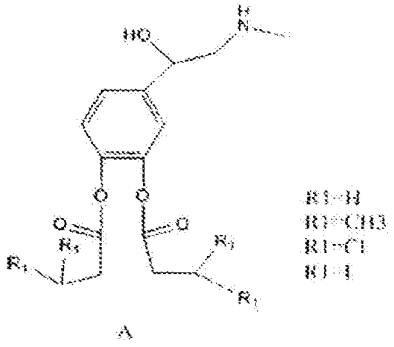
AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1005 pdf Page 380

FIG. 1



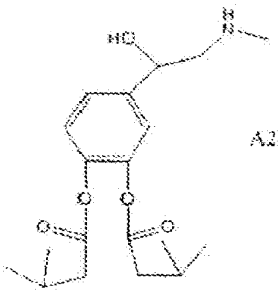
4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol
CLogP: -0.0846

FIG. 2



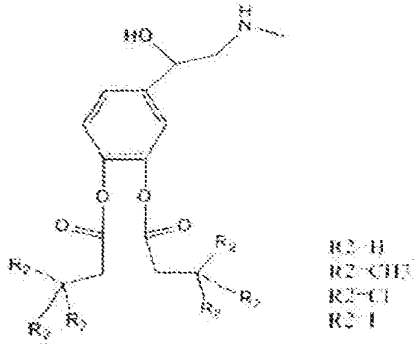
R1=H
R1=CH3
R1=Cl
R1=I

A



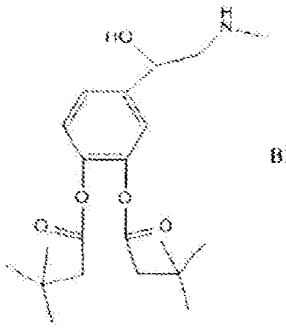
A2

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3-methylbutanoate)
CLogP: 2.0114



R2=H
R2=CH3
R2=Cl
R2=I

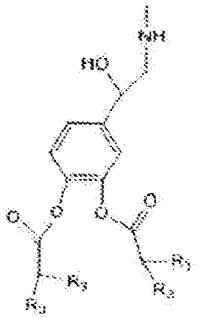
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B2

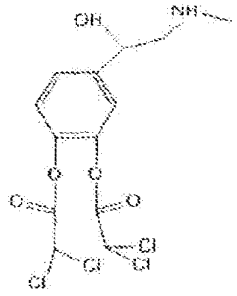
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3,3-dimethylbutanoate)
CLogP: 2.8094

FIG. 3



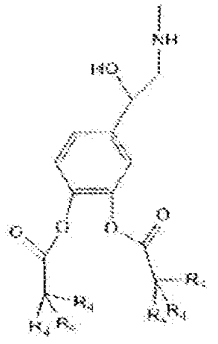
R3=H
R3=CH3
R3=CL
R3=I

C



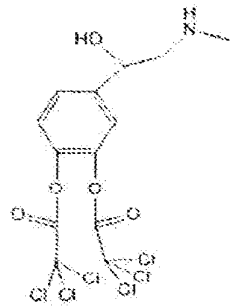
C3

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dichloroacetate)
CLogP: 1.4494



R4=H
R4=CH3
R4=CL
R4=I

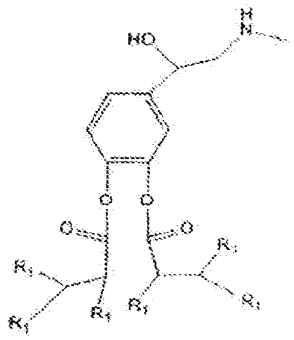
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D3

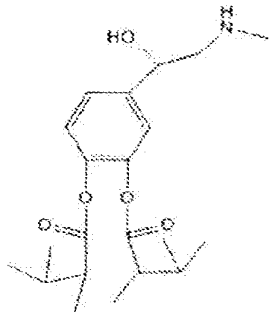
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,2-trichloroacetate)
CLogP: 2.8554

FIG. 4



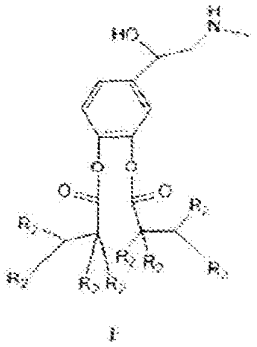
R1=H
R1=CH3
R1=Cl
R1=I

E



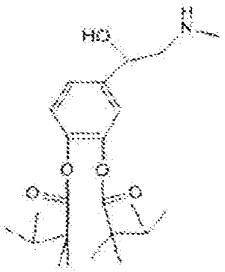
4E

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-dimethylbutanoate)
CLogP: 2.6294



R2=H
R2=CH3
R2=Cl
R2=I

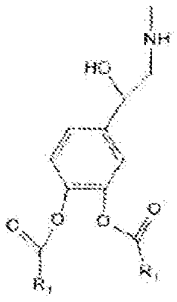
F



4F

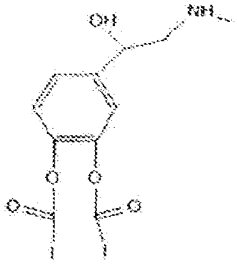
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,3-trimethylbutanoate)
CLogP: 3.4274

FIG. 5



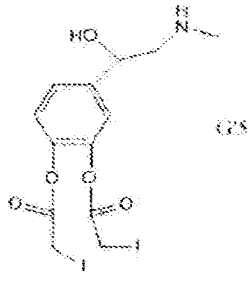
G

R1=H
R1=I
R1=Cl
R1=CH3
R1=CH2CH3
R1=CH2CH2CH3
R1=CH2CH2CH2CH3
R1=CH2Cl
R1=CH2I
R1=CH2F



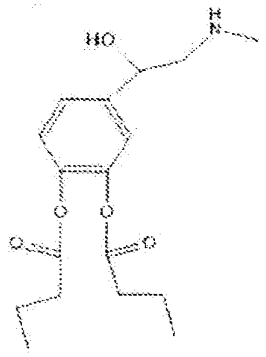
G3

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dicarbonodidate
CLogP: 1.0854



G5

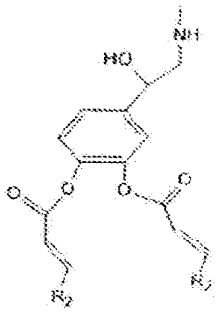
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-iodoacetate)
CLogP: 0.3834



G*5

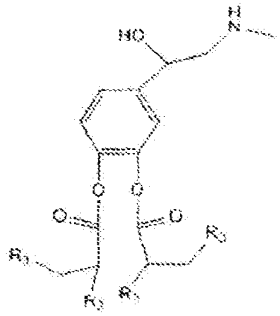
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate
CLogP: 1.2134

FIG. 6



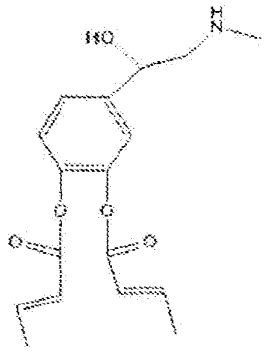
R2=H
R2=CH3
R2=Cl
R2=I

II



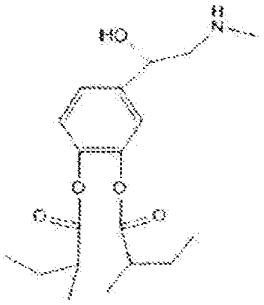
R3=H
R3=Cl
R3=I
R3=CH3

I



II6

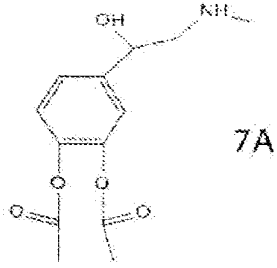
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene (2E,2'E)-bis(but-2-enoate)
CLogP: 1.2054



I6

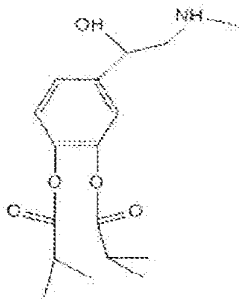
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylbutanoate)
CLogP: 1.8314

FIG. 7



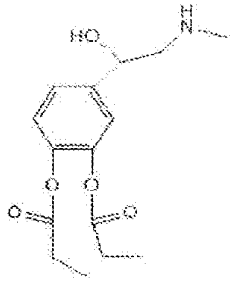
7A

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene diacetate
CLogP: -0.9026



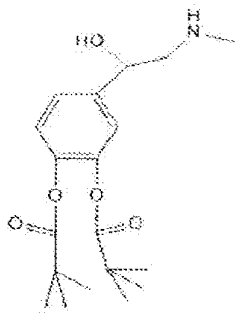
7B

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate)
CLogP: 0.773399



7C

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate
CLogP: 0.1554



7D

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate)
CLogP: 1.5714

FIG. 8

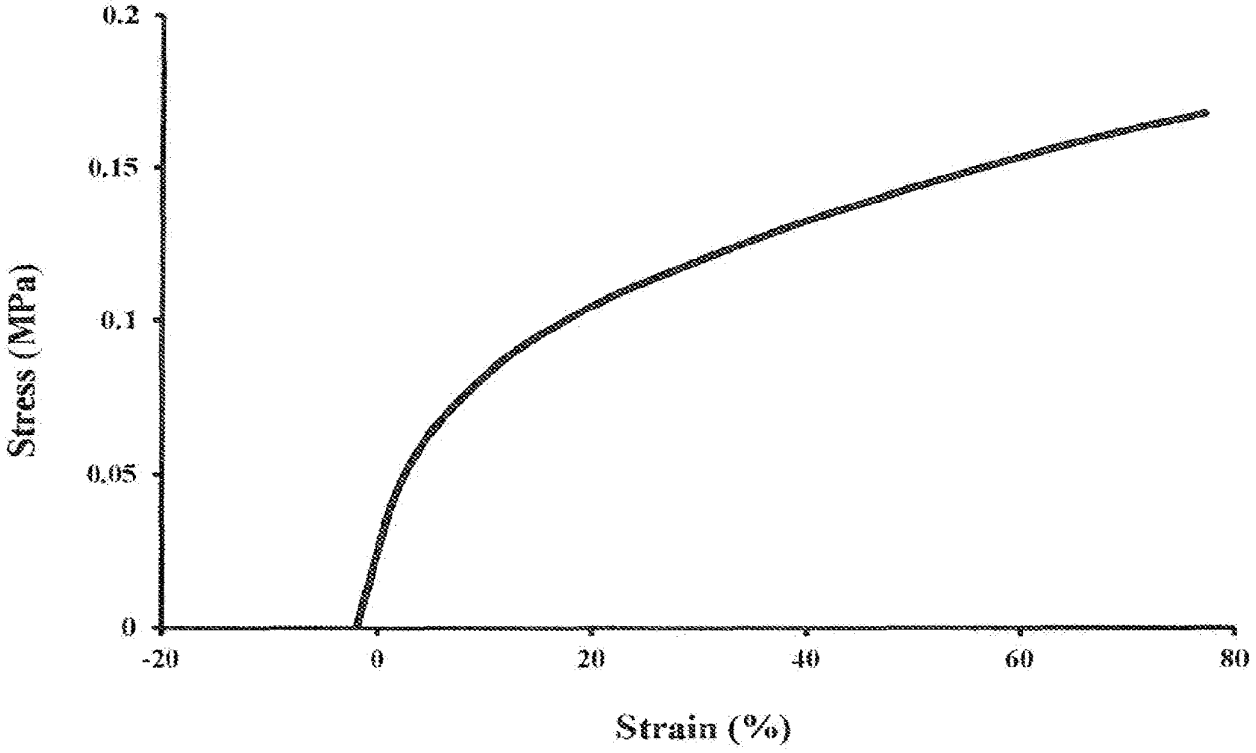
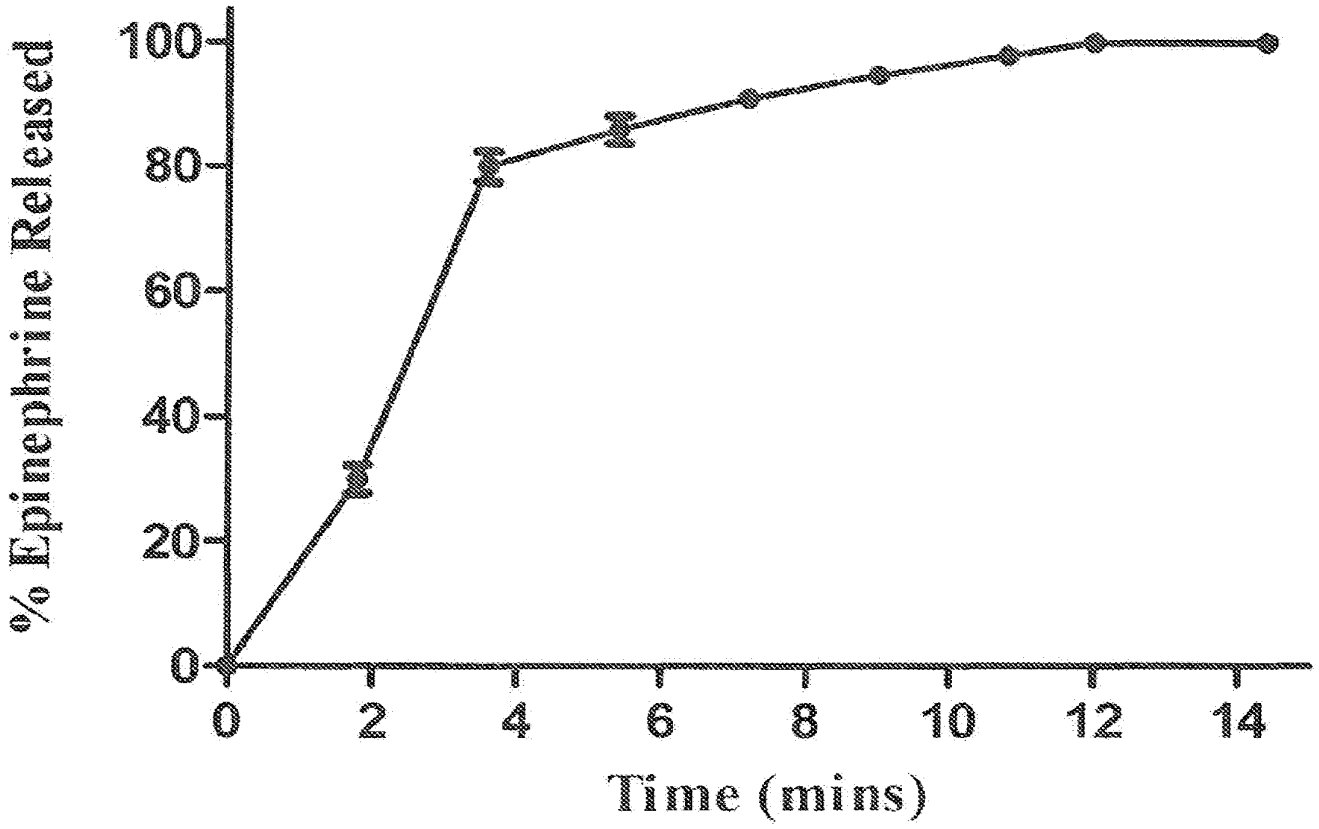


FIG. 9


% Epinephrine Released
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Time (mins)

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001
	Application Number	
Title of Invention	Pharmaceutical Formulation for Rapid Delivery of Epinephrine	

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.

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

Inventor Information:

Inventor 1 Remove

Legal Name

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	Hassan		Almoazen	

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Address 2			
City	Bartlett	State/Province	TN
Postal Code	38135	Country i	US

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

Correspondence Information:

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For further information see 37 CFR 1.33(a).

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

Customer Number	76447		
Email Address	sfentress@harrisshelton.com	Add Email	Remove Email

Application Information:

Title of the Invention	Pharmaceutical Formulation for Rapid Delivery of Epinephrine		
Attorney Docket Number	24050.0001	Small Entity Status Claimed	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	9	Suggested Figure for Publication (if any)	

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001
	Application Number	
Title of Invention	Pharmaceutical Formulation for Rapid Delivery of Epinephrine	

Filing By Reference:

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

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

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

Publication Information:

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

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

Representative Information:

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

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	76447		

Domestic Benefit/National Stage Information:

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

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

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001
	Application Number	
Title of Invention	Pharmaceutical Formulation for Rapid Delivery of Epinephrine	

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)[1] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[1]	Filing Date (YYYY-MM-DD)	Access Code[1] (if applicable)

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

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

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001
	Application Number	
Title of Invention	Pharmaceutical Formulation for Rapid Delivery of Epinephrine	

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001
	Application Number	
Title of Invention	Pharmaceutical Formulation for Rapid Delivery of Epinephrine	

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

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	Iono Pharma, LLC		
Mailing Address Information For Applicant:			
Address 1	3133 Hill Lake Drive		
Address 2			
City	Bartlett	**State/Province**	TN
Country	US	Postal Code	38135
Phone Number		Fax Number	
Email Address			

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

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001
	Application Number	
Title of Invention	Pharmaceutical Formulation for Rapid Delivery of Epinephrine	

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.

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

Organization Name	Iono Pharma, LLC

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	3133 Hill Lake Drive		
Address 2			
City	Bartlett	**State/Province**	TN
Country i	US	Postal Code	38135
Phone Number		Fax Number	
Email Address			

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

Signature:

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

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

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

Signature	/Susan B. Fentress/			Date (YYYY-MM-DD)	2016-11-1[illegible]
First Name	Susan	Last Name	Fentress	Registration Number	31327

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24050.0001
	Application Number	
Title of Invention	Pharmaceutical Formulation for Rapid Delivery of Epinephrine	

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

Electronic Acknowledgement Receipt	
EFS ID:	27492915
Application Number:	62421316
International Application Number:	
Confirmation Number:	8723
Title of Invention:	PHARMACEUTICAL FORMULATION FOR RAPID DELIVERY OF EPINEPHRINE
First Named Inventor/Applicant Name:	Hassan Almoazen
Customer Number:	76447
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	13-NOV-2016
Filing Date:	
Time Stamp:	11:48:06
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$130
RAM confirmation Number	111416INTEFSW12004000
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	transmital.pdf	766309 70bc784db72a8047a397adc264984d056a7b0c8f	no	2
Warnings:					
Information:					
2	Specification	spec.pdf	6990454 9f425738d8fd66f15ea65524 7a2eb5ed244b a752	no	21
Warnings:					
Information:					
3	Claims	claims.pdf	1516757 cadcf8d0a132dba39ab8fb7ed885a83dbf2a fb4b	no	5
Warnings:					
Information:					
4	Abstract	abstract.pdf	178172 a55b7db4edf62f7a8c9039672c3c833f7261 e8df	no	1
Warnings:					
Information:					
5	Drawings-only black and white line drawings	figs.pdf	815860 adc3a613b19ef50a0b0f2cab9bdde5c9e3d 13c8d	no	9
Warnings:					
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6	Application Data Sheet	ads.pdf	3033750 6cd57e0bea8d708980 1f437 15e29643fd8e b2bb7	no	7
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7	Fee Worksheet (SB06)	fee-info.pdf	29274 93941cd81ef59c40ad53b1b03e015a758a8c6b0c	no	2
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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

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DOCUMENT MADE AVAILABLE UNDER THE PATENT COOPERATION TREATY (PCT)

International application number:		**PCT/US2017/060761**
International filing date:		**09 November 2017 (09.11.2017)**
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Document details:	Country/Office:	**US**
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Date of receipt at the International Bureau:		**20 November 2017 (20.11.2017)**

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-*bis*)

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