

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
 Stylesheet Version v1.2

EPAS ID: PAT4952334

SUBMISSION TYPE:	NEW ASSIGNMENT	
NATURE OF CONVEYANCE:	ASSIGNMENT	
CONVEYING PARTY DATA		
	Name	Execution Date
	LINDSAY HAYNES	10/12/2016
RECEIVING PARTY DATA		
Name:	IONO PHAMA LLC	
Street Address:	3133 HILL LAKE DR	
City:	BARTLETT	
State/Country:	TENNESSEE	
Postal Code:	38135	
PROPERTY NUMBERS Total: 1		
	Property Type	Number
	Application Number:	62421316
CORRESPONDENCE DATA		
Fax Number:		
<i>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.</i>		
Phone:	9013716664	
Email:	sfentress@veritaygroup.com	
Correspondent Name:	SUSAN B FENTRESS	
Address Line 1:	20 S DUDLEY, SUITE 803	
Address Line 4:	MEMPHIS, TENNESSEE 38103	
ATTORNEY DOCKET NUMBER:	24050.0001	
NAME OF SUBMITTER:	SUSAN B FENTRESS	
SIGNATURE:	/susan b fentress/	
DATE SIGNED:	05/08/2018	
	This document serves as an Oath/Declaration (37 CFR 1.63).	
Total Attachments: 2		
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source=assignment#page2.tif		

ASSIGNMENT

WHEREAS, Lindsay Haynes, an individual operating in Memphis, TN ("Assignor"), has invented an EPINEPHRINE FILM AND METHODS THEREOF ("Invention") that is described in U.S. Patent Application No. 62/421,316, filed 11-13-2016 ("Patent"); and

WHEREAS, Iono Pharma LLC, a limited liability company operating at 3133 Hill Lake Drive, Bartlett, TN ("Assignee"), desires to acquire the entire right, title, and interest in and to the Patent, the Invention and any improvements thereto, and any and all patents and patent applications therefor.

NOW, THEREFORE, in consideration of the payment of one (\$1.00) dollar, and for other good and valuable consideration, the receipt of which is hereby acknowledged, Assignor assigns to Assignee its entire right, title, and interest in and to the Patent, in and to the Invention and any improvements thereto, in and to all patents, reissue patents, certificates of inventorship, design registrations, utility models, and the like that have or may be granted in the United States or in any foreign country with respect to the Invention and any improvements thereto, and in and to all applications, including, without limitation, continuations, continuations-in-part, and divisions, that have or may be filed with respect to the Invention and any improvements thereto;

Assignor represents and warrants that it has not transferred, licensed, and/or assigned any of the rights assigned hereunder to anyone other than Assignee, or entered into any agreement that would otherwise conflict with this Assignment;

Assignor will, without additional charge to Assignee but at Assignee's expense, cooperate with and assist Assignee such that Assignee may realize and fully enjoy all the rights assigned hereunder, including the preparation and execution of all papers needed by Assignee, and providing such information and assistance as may reasonably be required by Assignee in any administrative or legal proceeding to obtain, maintain, protect, or enforce such rights; and

Assignor authorizes said Assignee, its successors and assigns, or anyone it may properly designate, to apply for Letters Patent, in its own name if desired, in the United States and in any foreign countries, and additionally to claim the filing date of the Patent and/or otherwise take advantage of the provisions of the International Convention.

Assignor hereby authorizes and requests that the law firm of Waller Lansden Dortch & Davis, LLP insert in this Assignment the application number and the filing date of the Patent when known.

This Assignment and each of its terms shall be binding on Assignor, and its representatives, heirs and assigns, and shall inure to the benefit of Assignee, its successors, and assigns.

IN WITNESS WHEREOF, Assignor and Assignee have executed this Assignment on the dates indicated below the undersigned names.

ASSIGNOR

By: Lindsay Haynes
Name: Lindsay Haynes
Date: 10/12/2016

ASSIGNEE

By: Hassan ALMOAZEN
Name: Hassan ALMOAZEN
Title: CSO Iono Pharma
Date: 9-27-2016



UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
62/421,316	11/13/2016		130	24050.0001		

CONFIRMATION NO. 8723

FILING RECEIPT



0000000087389368

76447

Susan B. Fentress
Harris, Shelton, Hanover and Walsh
40 S. Main St.
Suite 2700
Memphis, TN 38103

Date Mailed: 11/23/2016

Receipt is acknowledged of this provisional patent application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Hassan Almoazen, Bartlett, TN;

Applicant(s)

Iono Pharma, LLC, Bartlett, TN;

Power of Attorney:

Susan Fentress--31327

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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

If Required, Foreign Filing License Granted: 11/22/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 62/421,316**

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

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

PHARMACEUTICAL FORMULATION FOR RAPID DELIVERY OF EPINEPHRINE

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

page 1 of 3

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

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

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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

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

NOT GRANTED

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

SelectUSA

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

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

EPAS ID: PAT4140543

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT
CONVEYING PARTY DATA	
Name	Execution Date
HASSAN ALMOAZEN	11/13/2016
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:	62421316
CORRESPONDENCE DATA	
Fax Number:	(901)525-1455
<i>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.</i>	
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Correspondent Name:	SUSAN B FENTRESS
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Address Line 4:	MEMPHIS, TENNESSEE 38103
ATTORNEY DOCKET NUMBER:	24050.0001
NAME OF SUBMITTER:	SUSAN B FENTRESS
SIGNATURE:	/susan b fentress/
DATE SIGNED:	11/14/2016
This document serves as an Oath/Declaration (37 CFR 1.63).	
Total Attachments: 2	
source=HAlmoazenassignmenttolonoPharmaLLC#page1.tif	
source=HAlmoazenassignmenttolonoPharmaLLC#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 November 11, 2016 and has been assigned Serial No. 62/421,316 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

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: 11-13-2016
Hassan Almoazen

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
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:

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 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Susan B. Fentress/			Date (YYYY-MM-DD)	2016-11-08 ¹³
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-phenylene di-acetate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene 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-phenylene di-acetate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene 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-(methylamino) 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 sublingual 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-trichloroacetate) 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 $R_1 = H, CH_3, Cl$ or I . A representative molecule is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-dimethylbutanoate) having a CLogP: 2.6294. 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-

hydroxy-2-(methylamino-ethyl)-1,2-phenylene bis (2-iodoacetate) having a CLogP: 0.3834 and Structure G⁵ 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 R₂ = H, CH₃, 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 R₃ = H, CL, I or CH₃. 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-phenylene 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-phenylene 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

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 Levocetirizine 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 cm² 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).

[00031] 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

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 weights. 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.

[00038] Table 1: List of the compositions of the four FDFs formulations.

Ingredient (% w/w)	Use	F1	F2	F3	F4
<i>Epinephrine HCl</i>	Drug	5.9	5.9	5.9	5.9
<i>Sodium Metabisulfite</i>	Antioxidant	5.9	5.9	5.9	5.9
<i>Lycoat® RS720</i> (hydroxypropyl starch)	Film-forming polymer	20	25	27	30
<i>Glycerin</i>	Plasticizer	3	3	3	3
<i>Tween 80</i>	Surfactant	2	2	2	2
<i>Citric Acid</i> <i>Monohydrate</i>	Buffer; increases absorption in oral cavity	0.5	0.5	0.5	0.5
<i>Sodium Citrate</i> <i>Monobasic</i>	Buffer	0.5	0.5	0.5	0.5
<i>Xylitol</i>	Sweetener	10	10	10	10
<i>Tutti Frutti</i>	Flavor	6	6	6	6
<i>Water</i>		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 metabisulfite 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

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

disintegrates. Volunteers reported 10 -30 seconds disintegration time (Table 3). This comply with the regulations set by United State Pharmacopeia (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--**Epinephrine 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 mm² 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 release 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, 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 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.

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.

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 R₄ is selected for the group consisting of: H, CH₃, 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 R₁ is selected for the group consisting of: H, CH₃, 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.

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 dicarboniodate; 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.

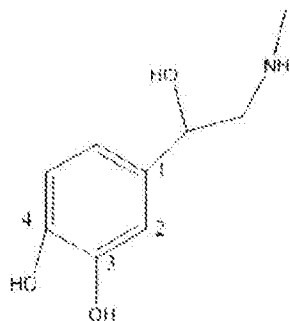
29. A pharmaceutical formulation comprising: a compound as depicted in **6H** and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H, CH_3 , Cl and I.
30. The pharmaceutical formulation of claim 29 wherein said compound 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-phenylene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate; 4-(1-hydroxy-2-

- (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-phenylene di-acetate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene 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.

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).

FIG. 3



4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol
(LogP: 0.6846)

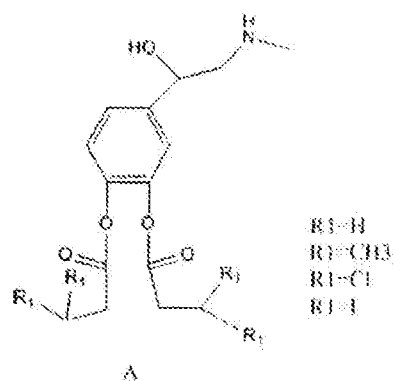


FIG. 2

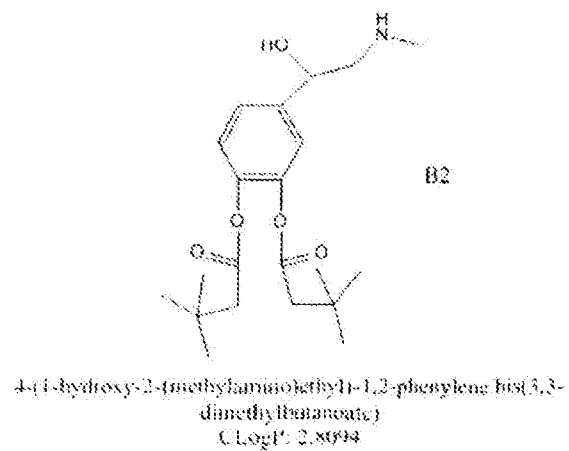
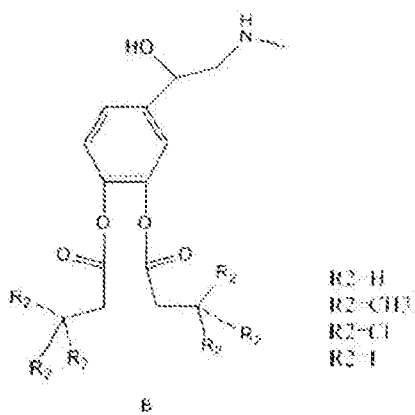
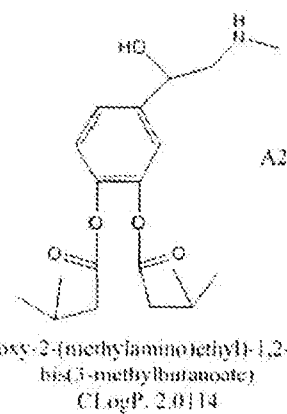
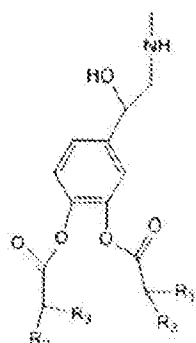
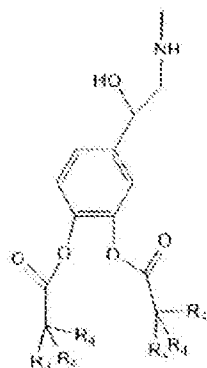


FIG. 3



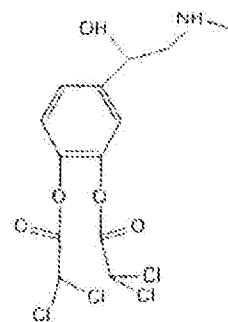
R3=H
R3=CH3
R3=Cl
R3=F

C



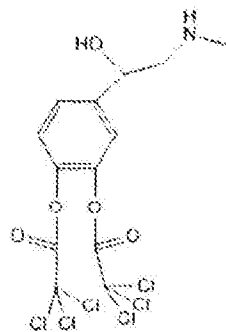
R4=H
R4=CH3
R4=Cl
R4=F

D



4-(1-hydroxy-2-methylaminoethyl)-1,2-phenylene bis(2,2-dichloroacetate)
CLogP: 1.4494

C3



4-(1-hydroxy-2-methylaminoethyl)-1,2-phenylene bis(2,2,2-trichloroacetate)
CLogP: 2.8554

D3

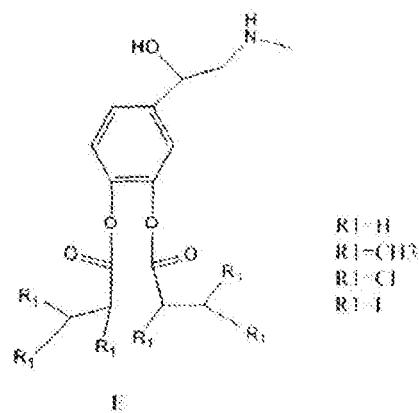
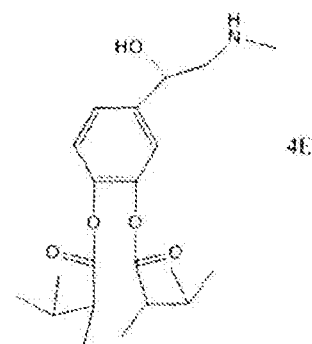
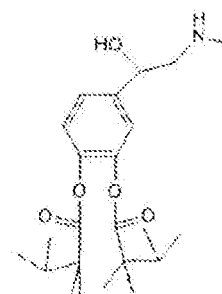
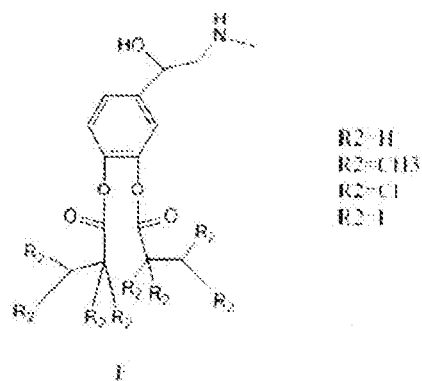


FIG. 4

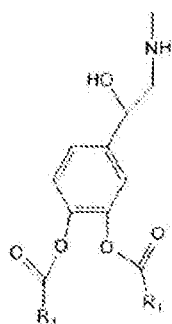


4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-dimethylbutanoate)
 CLogP: 2.6294



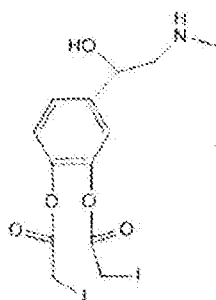
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-trimethylbutanoate)
 CLogP: 3.4274

FIG. 5



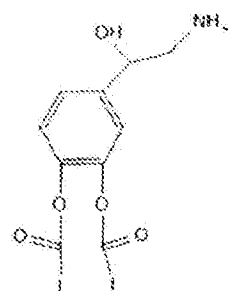
G

R1=H
 R1=I
 R1=Cl
 R1=CH3
 R1=CH2CH3
 R1=CH2CH2CH3
 R1=CH2CH2CH2CH3
 R1=CH2Cl
 R1=CH2I
 R1=CH2F



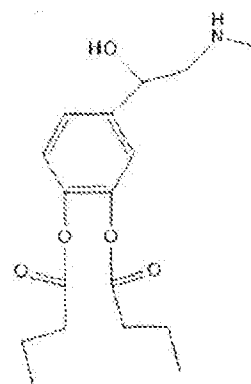
G5

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-iodoacetate)
 CLogP: 0.3834



G5

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dicarbonodidate
 CLogP: 1.0854



G5

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrates
 CLogP: 1.2134

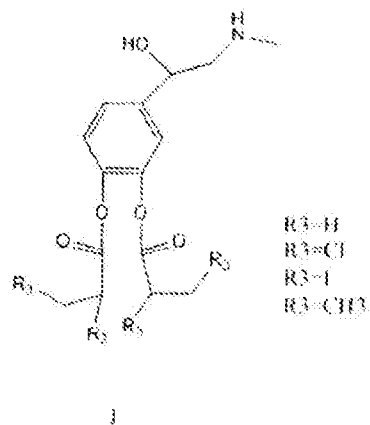
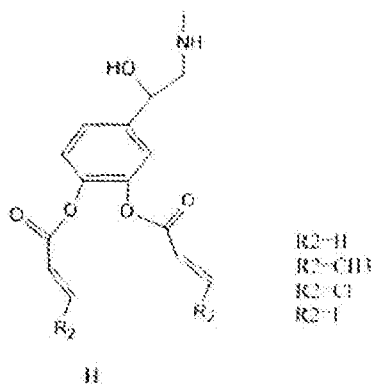
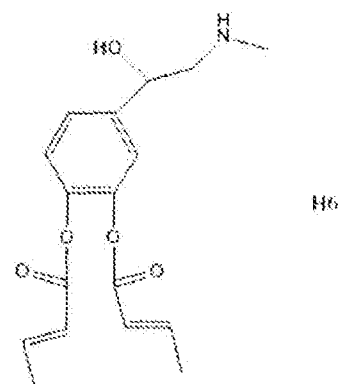
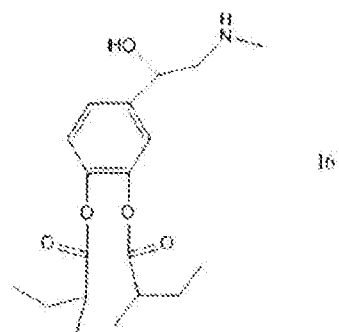


FIG. 6

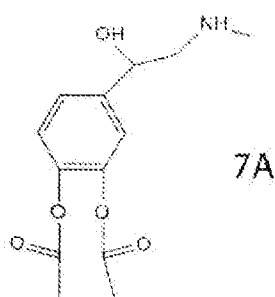


4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene (2*E*,2'*E*)-bis(but-2-enate)
 CLogP: 1.2054



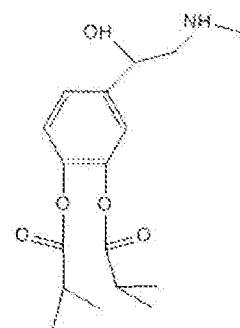
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylbutan-2-ate)
 CLogP: 1.8314

FIG. 7



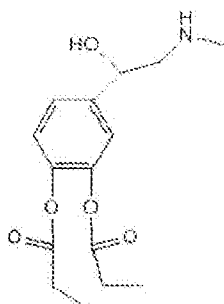
7A

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene diacetate
CLogP: -0.9026



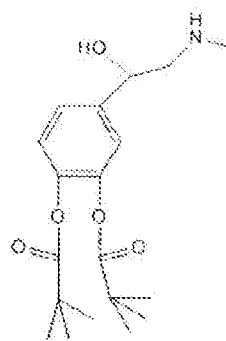
7B

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate)
CLogP: 0.773399



7C

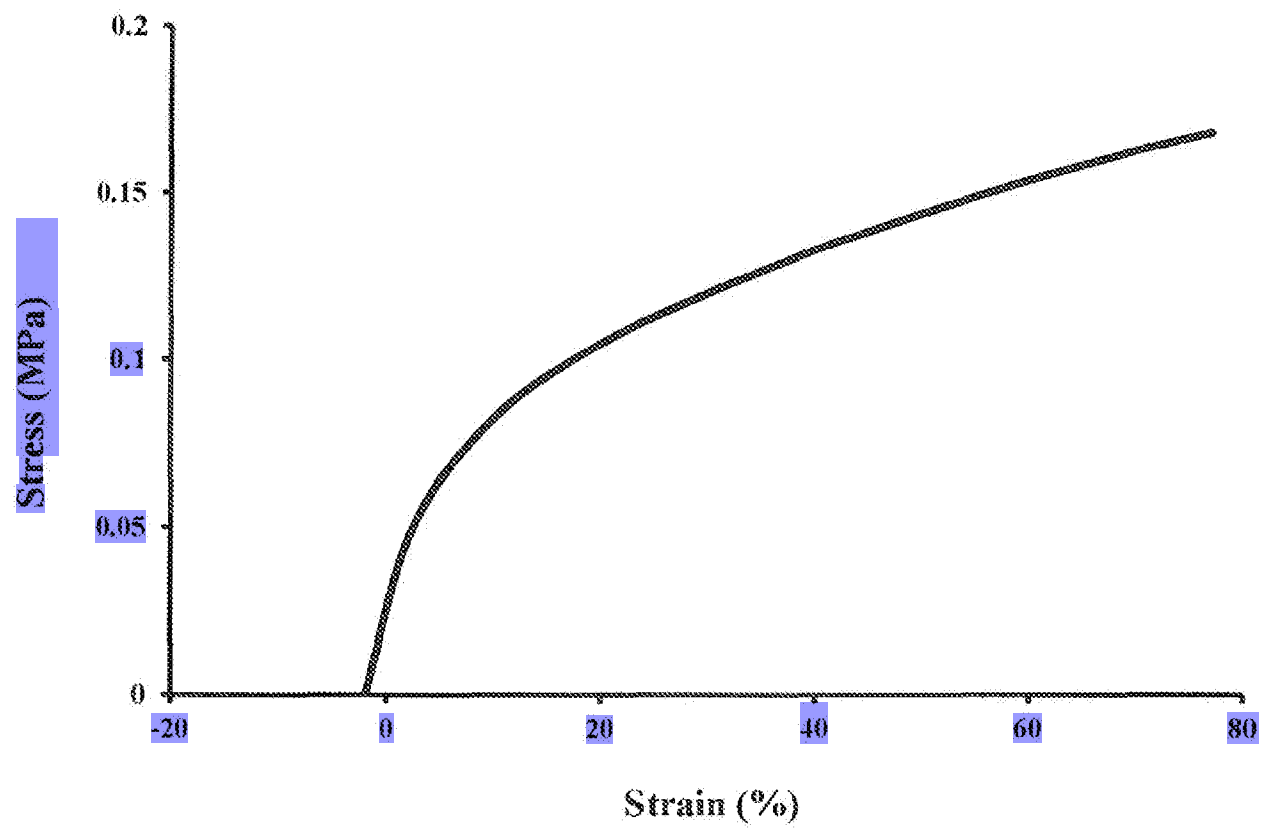
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate
CLogP: 0.1554

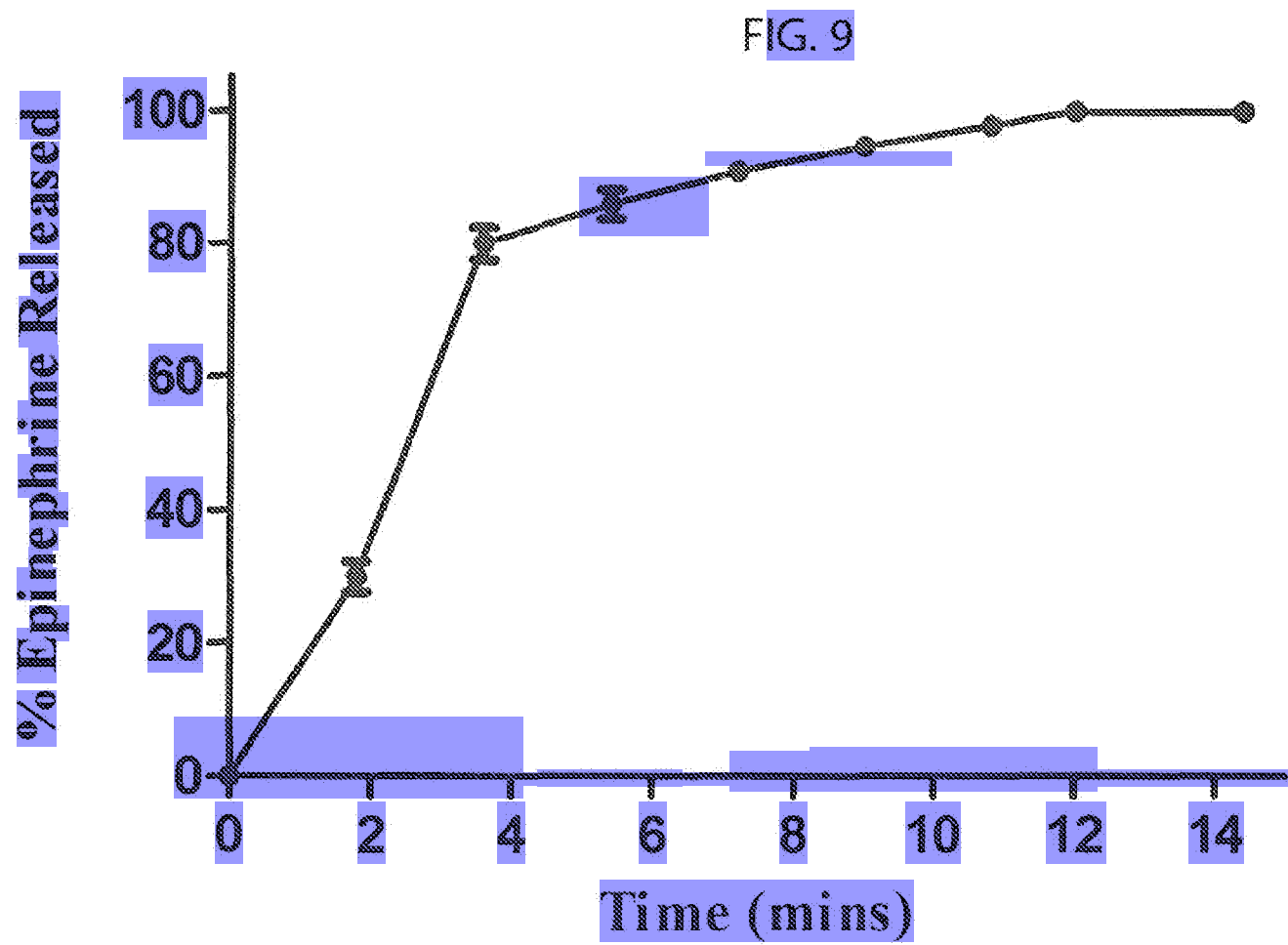


7D

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate)
CLogP: 1.5714

FIG. 8





Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	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.			

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
	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	sfentress@harrisskelton.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)	

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	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.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	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).

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.

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.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	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.

- ☒ 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

Country¹ 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.

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	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)	2016-11-13	
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 Patent Application Fee Transmittal

Application Number:				
Filing Date:				
Title of Invention:	PHARMACEUTICAL FORMULATION FOR RAPID DELIVERY OF EPINEPHRINE			
First Named Inventor/Applicant Name:	Hassan Almoazen			
Filer:	Susan Bennett Fentress			
Attorney Docket Number:				
Filed as Small Entity				
Filing Fees for Provisional				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
PROVISIONAL APPLICATION FILING FEE	2005	1	130	130
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

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

Electronic Acknowledgement Receipt

EFS ID:	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	

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File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	transmital.pdf	766309	no	2
			70bc784db72a8047a397adc264984d056a7b0c8f		
Warnings:					
Information:					
2	Specification	spec.pdf	6990454	no	21
			9f425738d8fd66f15ea655247a2eb5ed244ba752		
Warnings:					
Information:					
3	Claims	claims.pdf	1516757	no	5
			cadcf8d0a132dba39ab8fb7ed885a83dbf2a1fb4b		
Warnings:					
Information:					
4	Abstract	abstract.pdf	178172	no	1
			a55b7db4edf62f7a8c9039672c3c833f7261e8df		
Warnings:					
Information:					
5	Drawings-only black and white line drawings	figs.pdf	815860	no	9
			adc3a613b19ef50a0b0f2cab9bdde5c9e3d13c8d		
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Information:					
6	Application Data Sheet	ads.pdf	3033750	no	7
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Warnings:					
Information:					

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7	Fee Worksheet (SB06)	fee-info.pdf	29274	no	2
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Warnings:

Information:

Total Files Size (in bytes):	13330576
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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.