

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
Alexander	Mark	Schobel	Whitehouse Station	NJ	US

Inventor 2

Remove

Given Name	Middle Name	Family Name	City	State	Country
Stephen	Paul	Wargacki	Annandale	NJ	US

Inventor 3

Remove

Given Name	Middle Name	Family Name	City	State	Country
Stephanie	M.	VARJAN	Oradell	NJ	US

Inventor 4

Remove

Given Name	Middle Name	Family Name	City	State	Country
Rajesh	Kumar	Kainthan	Tappan	NY	US

Inventor 5

Remove

Given Name	Middle Name	Family Name	City	State	Country
Malarvizhi		Durai	Clarksville	MD	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	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT
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Attorney Docket Number (if applicable)	18460.0039P1
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Correspondence Address

Direct all correspondence to (select one):

☒ The address corresponding to Customer Number	☐ Firm or Individual Name
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Customer Number	27890
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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	/Harold H. Fox, Reg.# 41498/			Date (YYYY-MM-DD)	2019-11-01
First Name	Harold	Last Name	Fox	Registration Number (If appropriate)	41498

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.**

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 a n other federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:				
Filing Date:				
Title of Invention:	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT			
First Named Inventor/Applicant Name:	Alexander Mark Schobel			
Filer:	Harold H. Fox			
Attorney Docket Number:	18460.0039P1			
Filed as Large Entity				
Filing Fees for Provisional				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
PROVISIONAL APPLICATION FILING	1005	1	280	280
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 (\$)				280

Electronic Acknowledgement Receipt

EFS ID:	37638916
Application Number:	62929737
International Application Number:	
Confirmation Number:	1064
Title of Invention:	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT
First Named Inventor/Applicant Name:	Alexander Mark Schobel
Customer Number:	27890
Filer:	Harold H. Fox
Filer Authorized By:	
Attorney Docket Number:	18460.0039P1
Receipt Date:	01-NOV-2019
Filing Date:	
Time Stamp:	21:12:49
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$280
RAM confirmation Number	E2019A1L14203293
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	Application Data Sheet	0039P1ADS.pdf	1823484	no	9
			aa7d1b6c53c2dc5cbc43f7d96d48cc9f0eb378bc		
Warnings:					
Information:					
2	Drawings-other than black and white line drawings	18460figures.pdf	565109	no	18
			ac592f94930c7a2f9e813cbafd0d7a93949fa86a		
Warnings:					
Information:					
3		18460application.pdf	903437	yes	107
			63fd57688344c19e312c12c4b44e5ecf56688111		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	100	
	Claims		101	106	
	Abstract		107	107	
Warnings:					
Information:					
4	Transmittal of New Application	0039P1Transmittal.pdf	1634097	no	4
			66d8176aa6f56ceba3708aadf436631c988b882b		
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30014	no	2
			67c498e289a961f5b5184e640826a9ad7bf501c6		

Warnings:	
Information:	
Total Files Size (in bytes):	4956141
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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.	

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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		
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.)
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Inventor Information:

Inventor	1				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Alexander	Mark	Schobel		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Whitehouse Station	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

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

Inventor	2				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Stephen	Paul	Wargacki		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Annandale	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	17 Indian Creek Rd				
Address 2					
City	Annandale	State/Province	NJ		
Postal Code	08801	Country	US		

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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

City	Oradell	State/Province	NJ	Country of Residence	US
------	---------	----------------	----	----------------------	----

Mailing Address of Inventor:

Address 1	151 Prospect Avenue				
Address 2					
City	Oradell	State/Province	NJ		
Postal Code	07649	Country	US		
Inventor	4				Remove
Legal Name					

Prefix	Given Name	Middle Name	Family Name	Suffix	
	Rajesh	Kumar	Kainthan		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Tappan	State/Province	NY	Country of Residence	US

Mailing Address of Inventor:

Address 1	15 Key Place				
Address 2					
City	Tappan	State/Province	NY		
Postal Code	10983	Country	US		
Inventor	5				Remove
Legal Name					

Prefix	Given Name	Middle Name	Family Name	Suffix	
	Malarvizhi		Durai		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Clarksville	State/Province	MD	Country of Residence	US

Mailing Address of Inventor:

Address 1	6409 Galway Drive				
Address 2					
City	Clarksville	State/Province	MD		
Postal Code	21029	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.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

Customer Number	27890		
Email Address	ipdocketing@step toe.com	Add Email	Remove Email
Email Address	hfox@step toe.com	Add Email	Remove Email

Application Information:

Title of the Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		
Attorney Docket Number	18460.0039P1	Small Entity Status Claimed	☐
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	18	Suggested Figure for Publication (if any)	

Filing By Reference:

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

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

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

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.			
Please Select One:	☒ Customer Number	US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	27890		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

Domestic Benefit/National Stage Information:

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

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			Add

Foreign Priority Information:

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

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)	Remove
Additional Foreign Priority Data may be generated within this form by selecting the Add button.				Add

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

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	18460.0039P1
	Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT	

Authorization or Opt-Out of Authorization to Permit Access:

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

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

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

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

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

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

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

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

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

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

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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

Applicant Information:

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

Applicant	1	Remove
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section. Clear		
☒ Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:		
Name of the Deceased or Legally Incapacitated Inventor:		
If the Applicant is an Organization check here. ☒		
Organization Name	AQUESTIVE THERAPEUTICS, INC.	
Mailing Address Information For Applicant:		
Address 1	30 TECHNOLOGY DRIVE	
Address 2		
City	WARREN	State/Province
Country	US	Postal Code
Phone Number		Fax Number
Email Address		
Additional Applicant Data may be generated within this form by selecting the Add button. Add		

Assignee Information including Non-Applicant Assignee Information:

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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

Assignee	1		
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.			
			Remove
If the Assignee or Non-Applicant Assignee is an Organization check here.			☒
Organization Name	AQUESTIVE THERAPEUTICS, INC.		
Mailing Address Information For Assignee including Non-Applicant Assignee:			
Address 1	30 TECHNOLOGY DRIVE		
Address 2			
City	WARREN	State/Province	NJ
Country ⁱ	US	Postal Code	07059
Phone Number		Fax Number	
Email Address			
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.			Add

Signature:

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	/Harold H. Fox, Reg.# 41498/		Date (YYYY-MM-DD)	2019-11-01	
First Name	Harold	Last Name	Fox	Registration Number	41,498
Additional Signature may be generated within this form by selecting the Add button.				Add	

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

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.**

Privacy Act Statement

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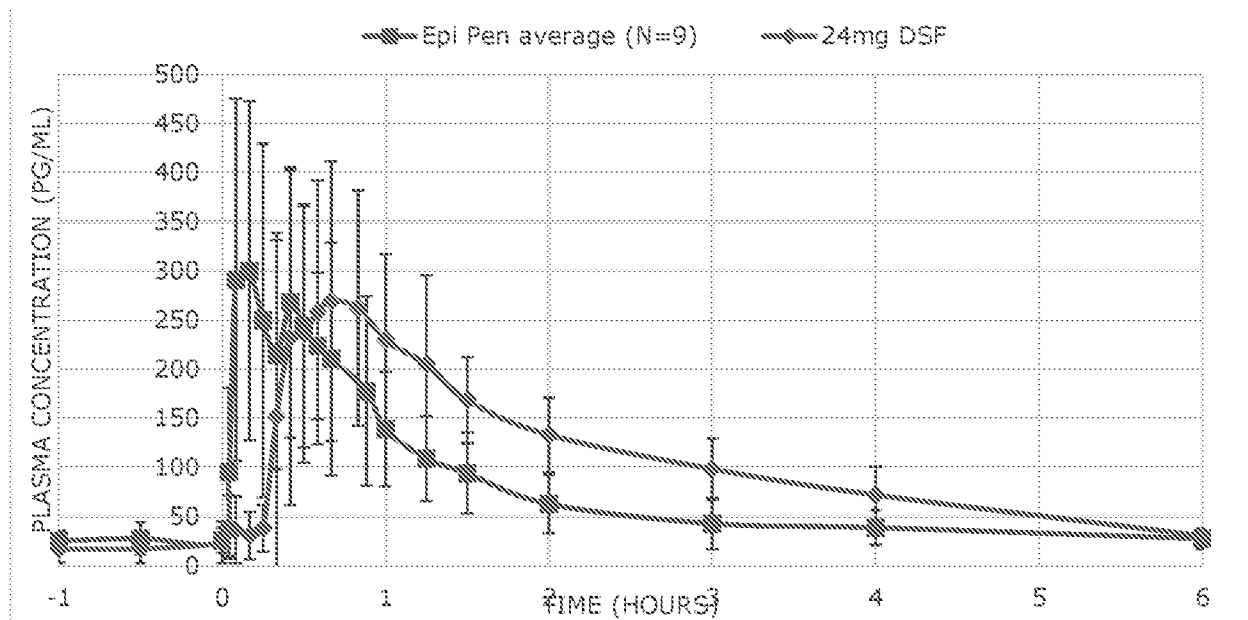


Fig. 1A

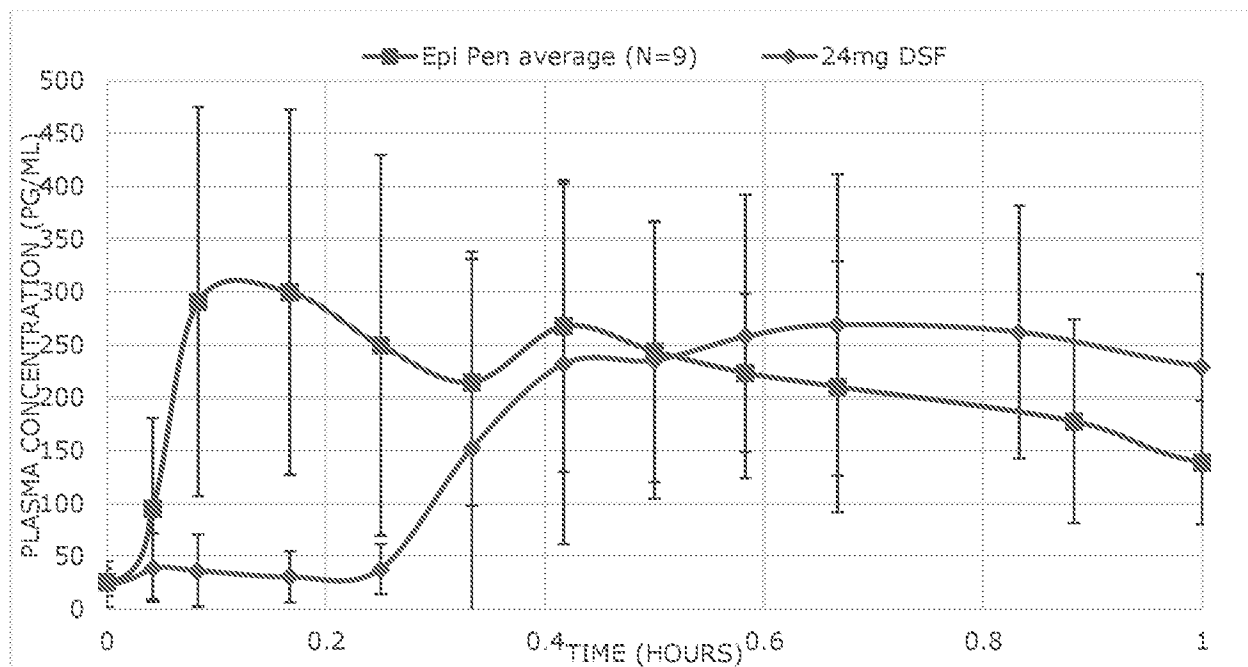


Fig. 1B

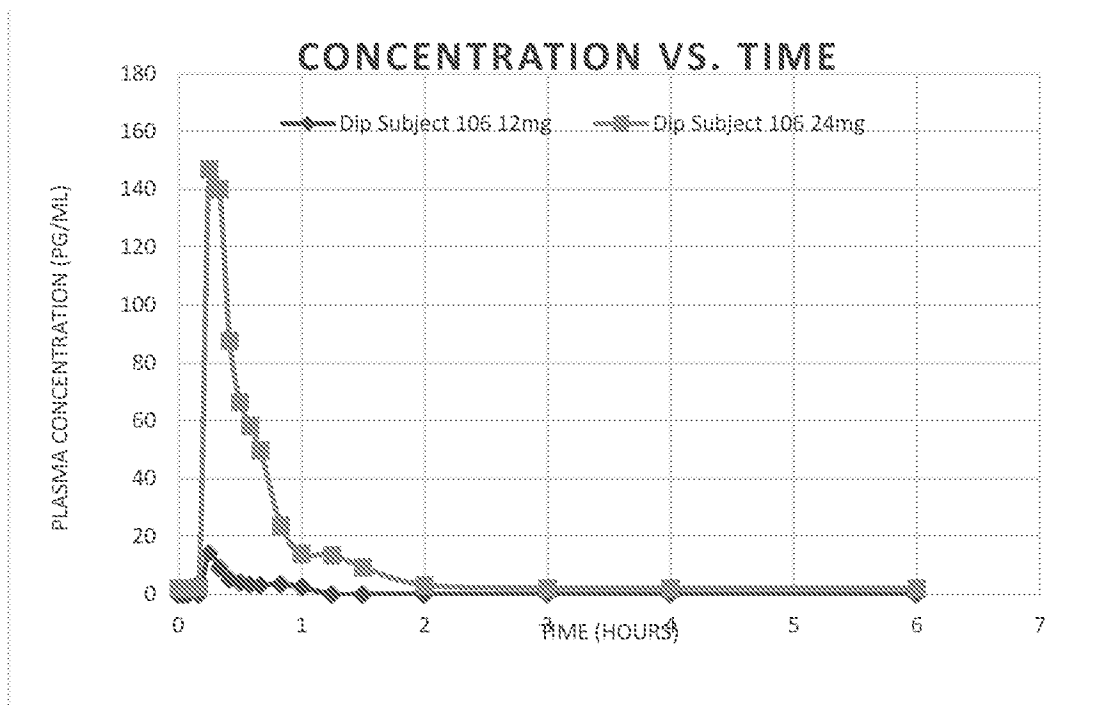


Fig. 2A

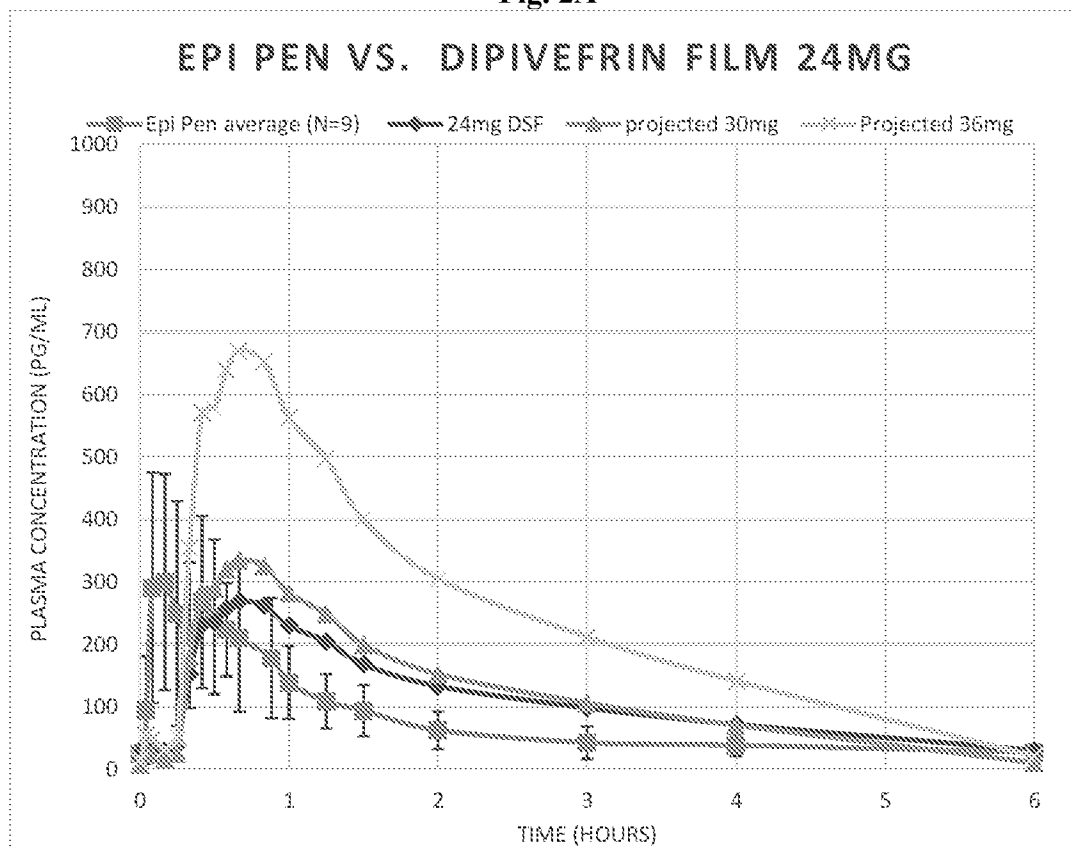


Fig. 2B

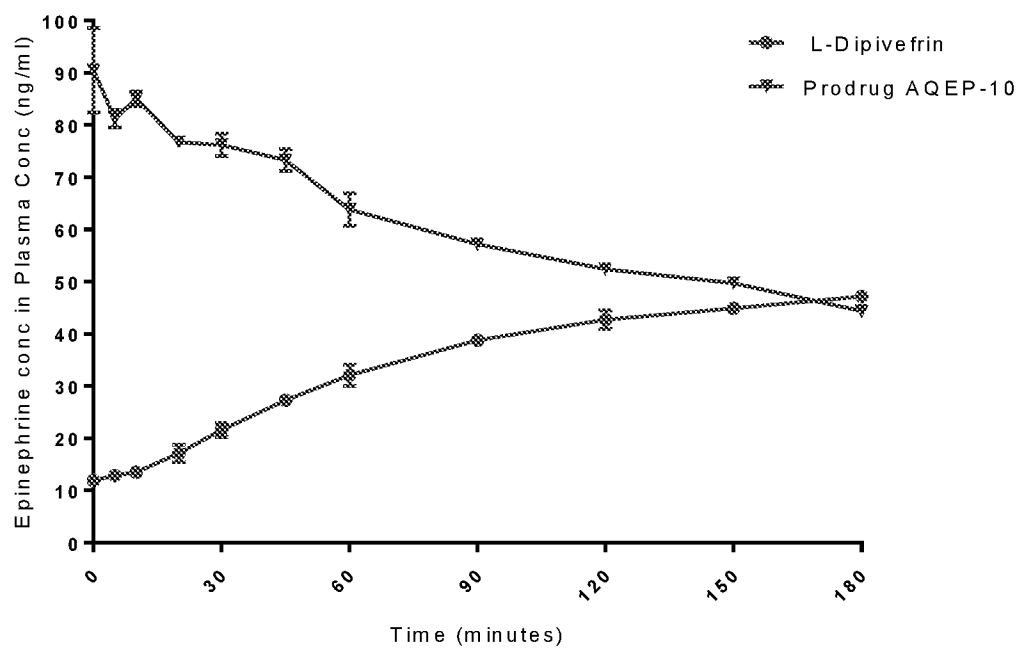


Fig. 3A

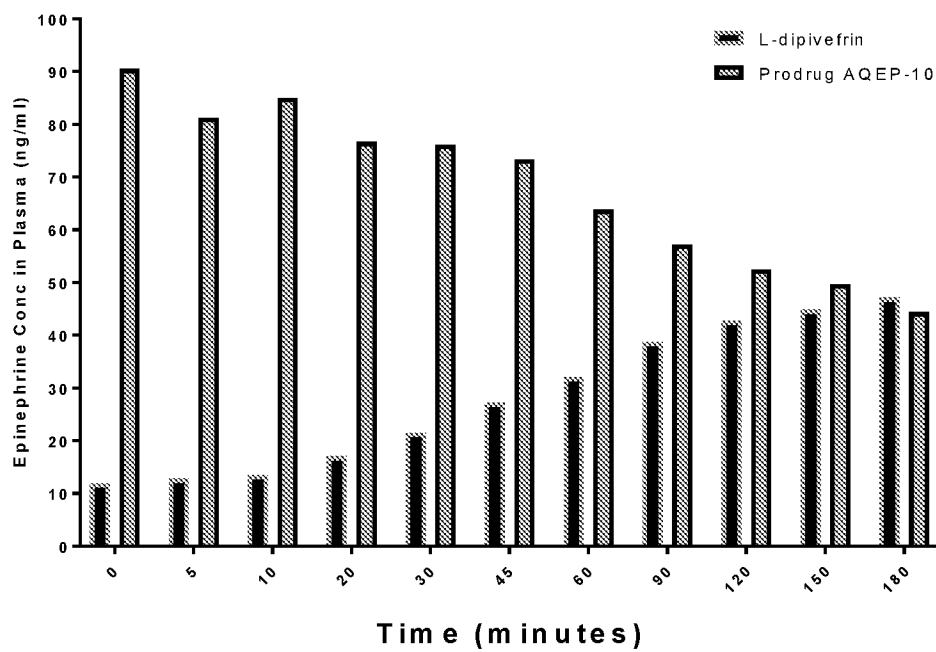


Fig. 3B

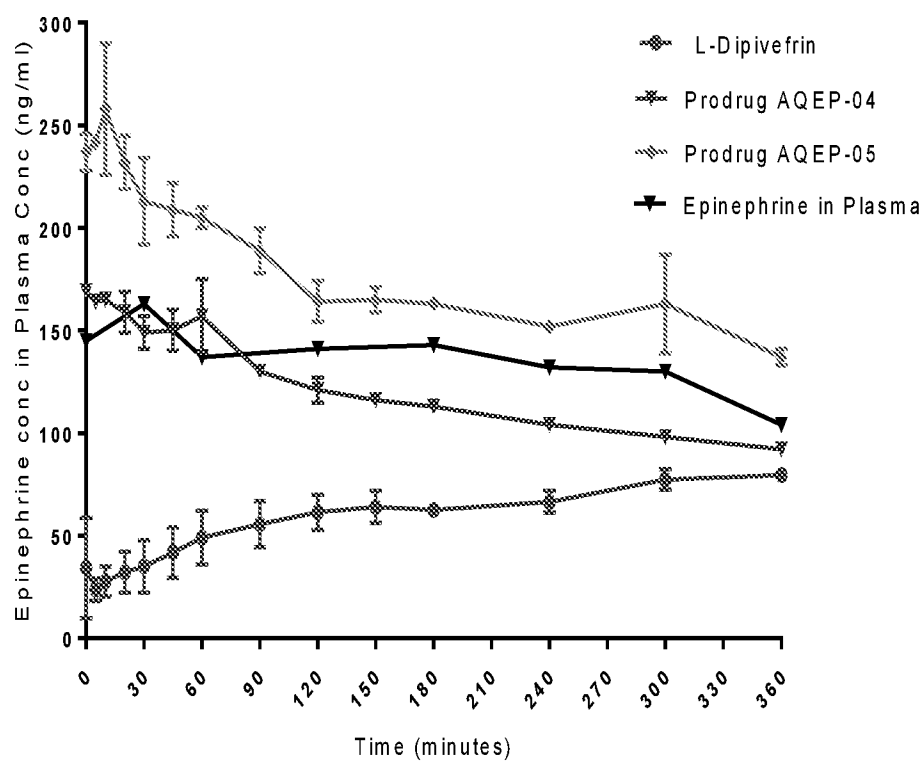


Fig. 4

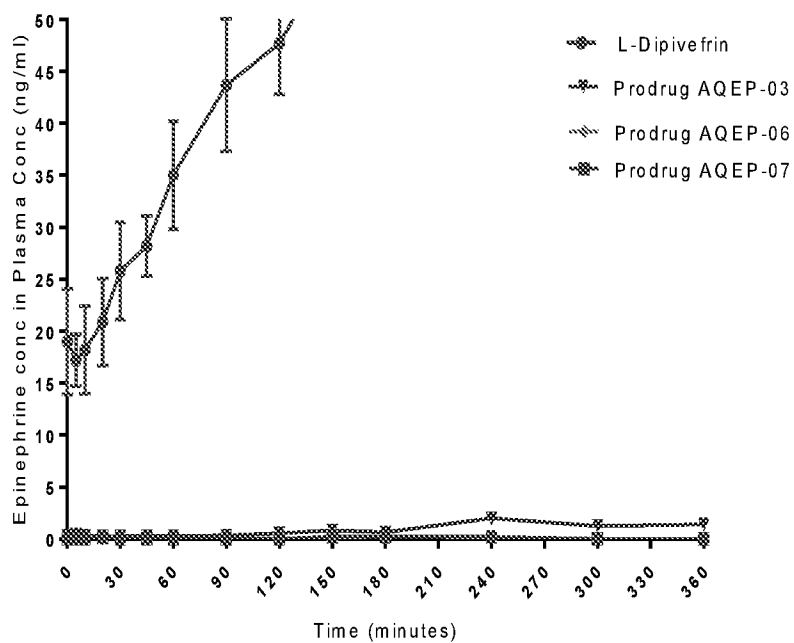


Fig. 5

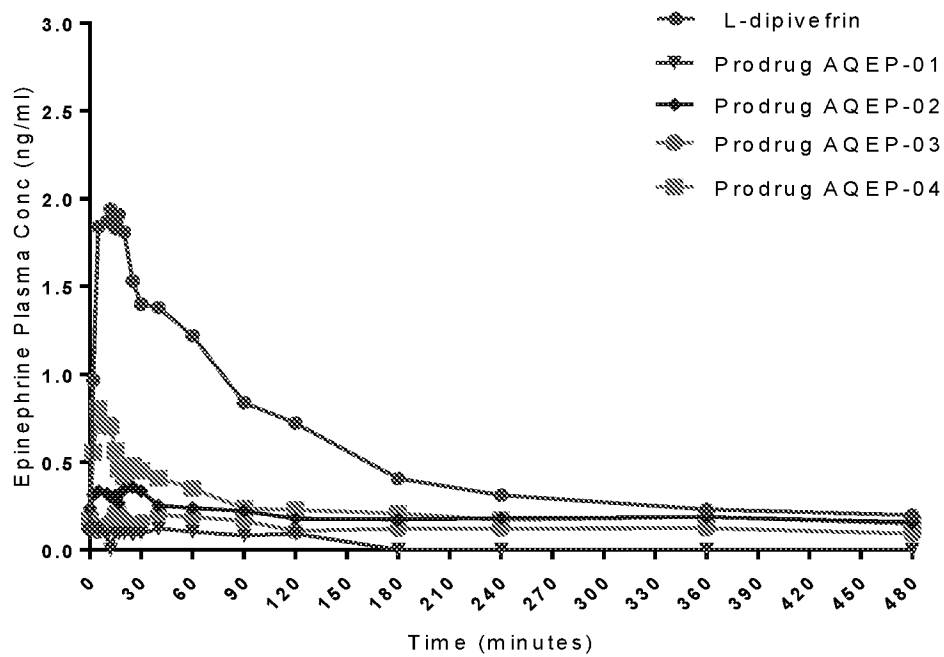


Fig. 6A

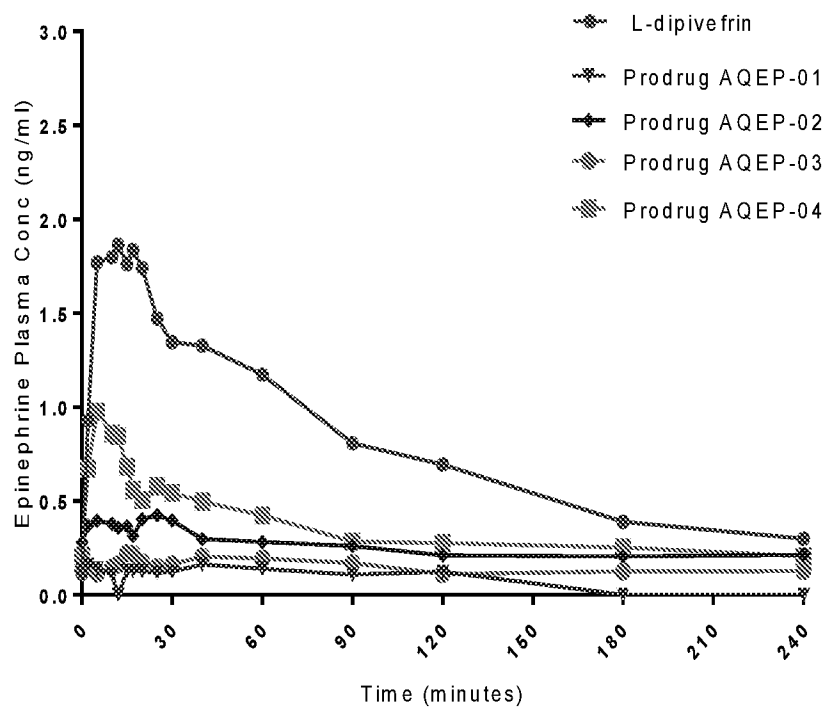


Fig. 6B

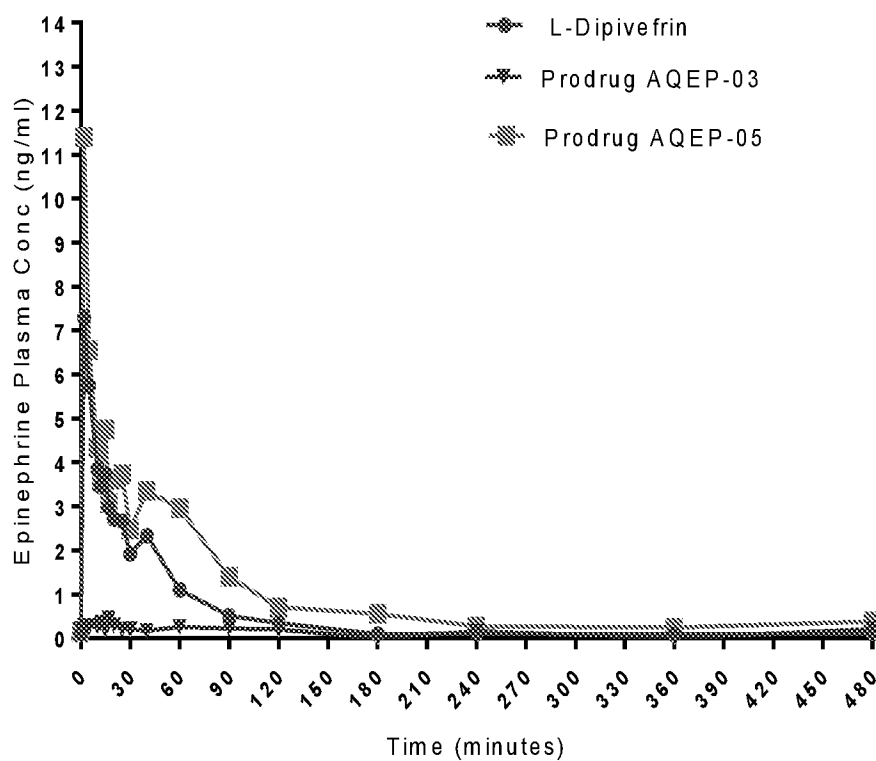


Fig. 7A

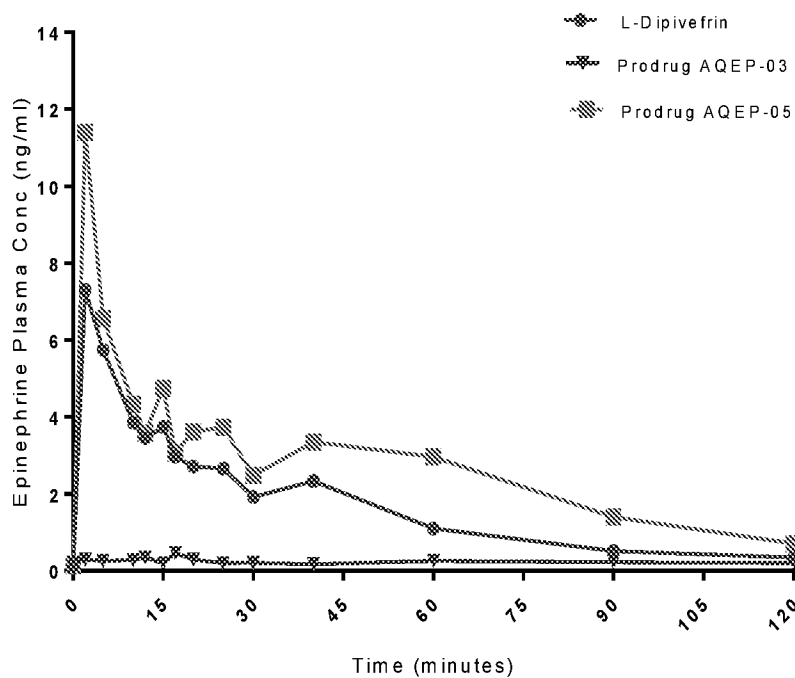


Fig. 7B

Average Epinephrine Plasma Concentration vs Time

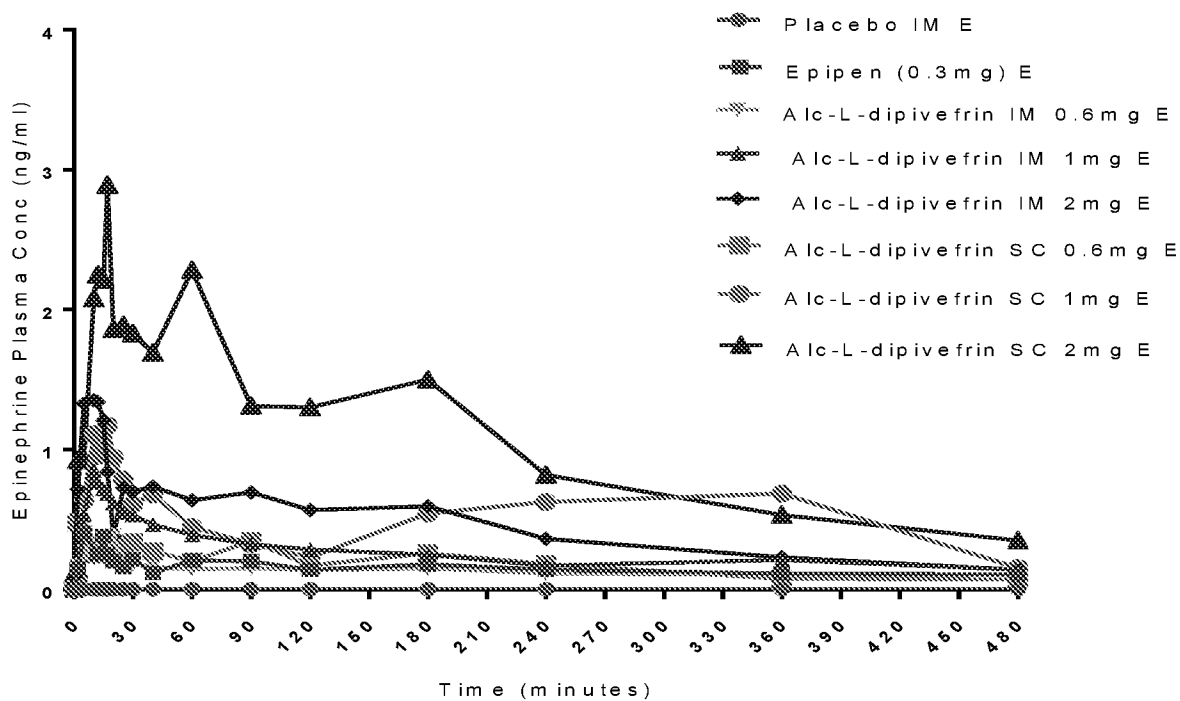


Fig. 8A

IM administration-Average Epinephrine Plasma Concentration

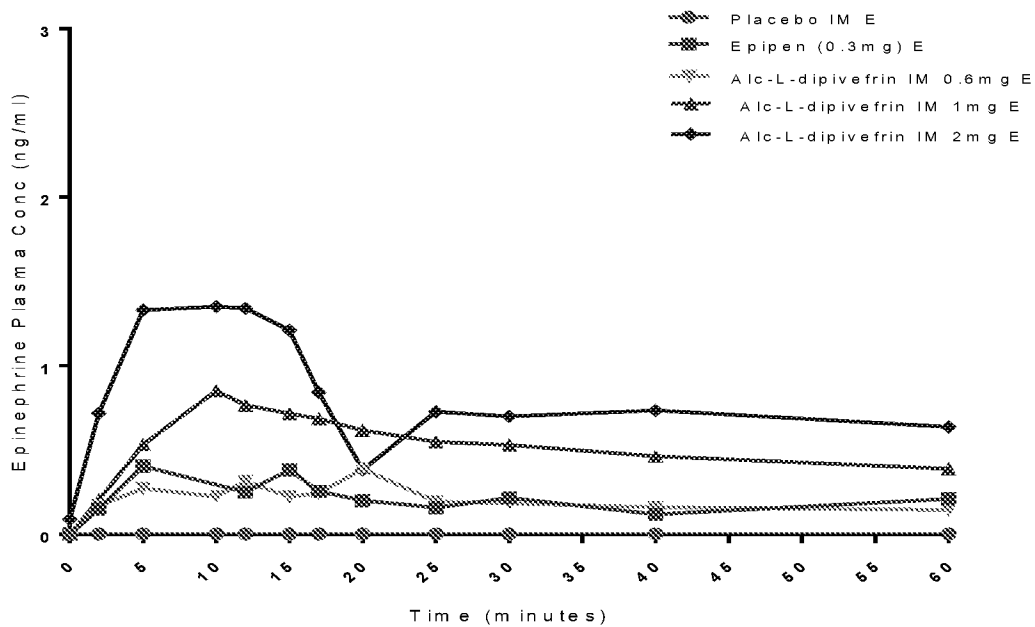


Fig. 8B

SC administration-Average Epinephrine Plasma Concentration

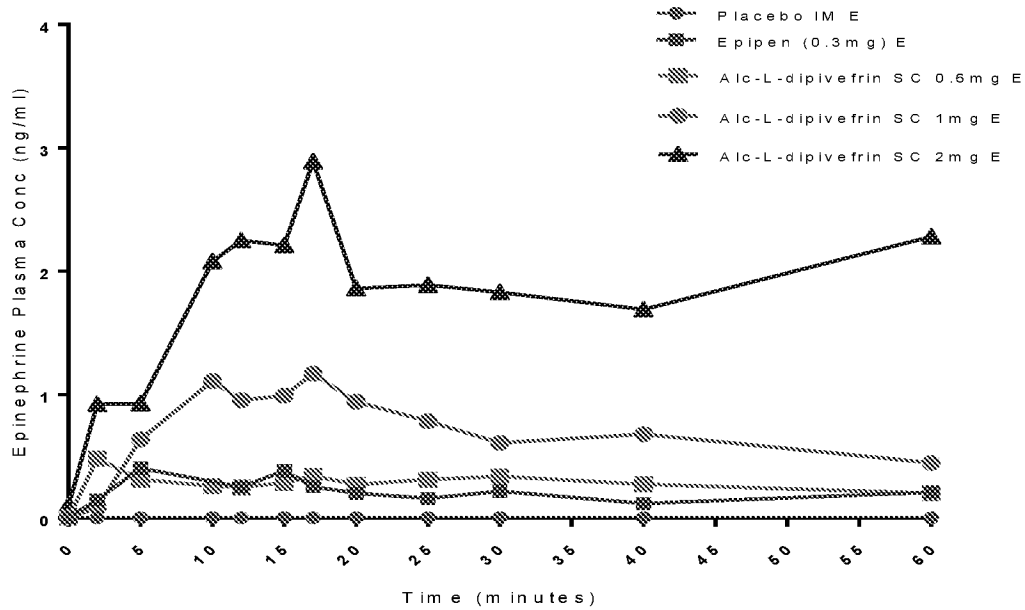


Fig. 8C

Comparison of IM & SC administration L-dipivefrin 0.6 mg-Average Epinephrine Plasma Concentration

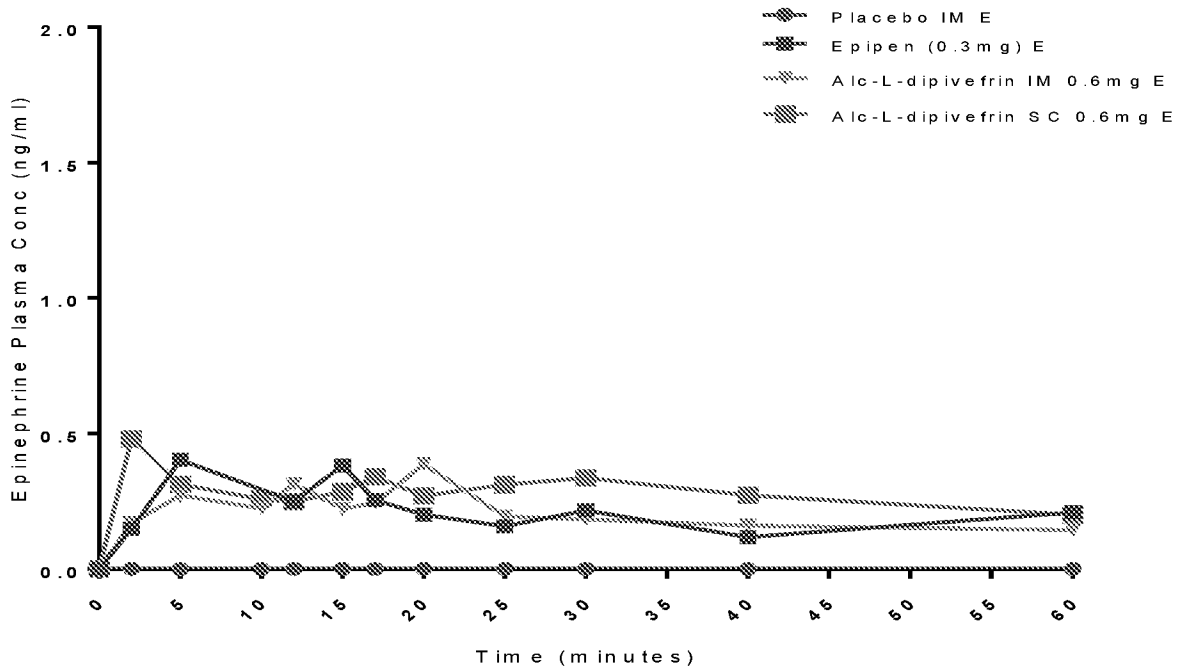


Fig. 9A

Comparison of IM & SC administration L-dipivefrin 1 mg-Average Epinephrine Plasma Concentration

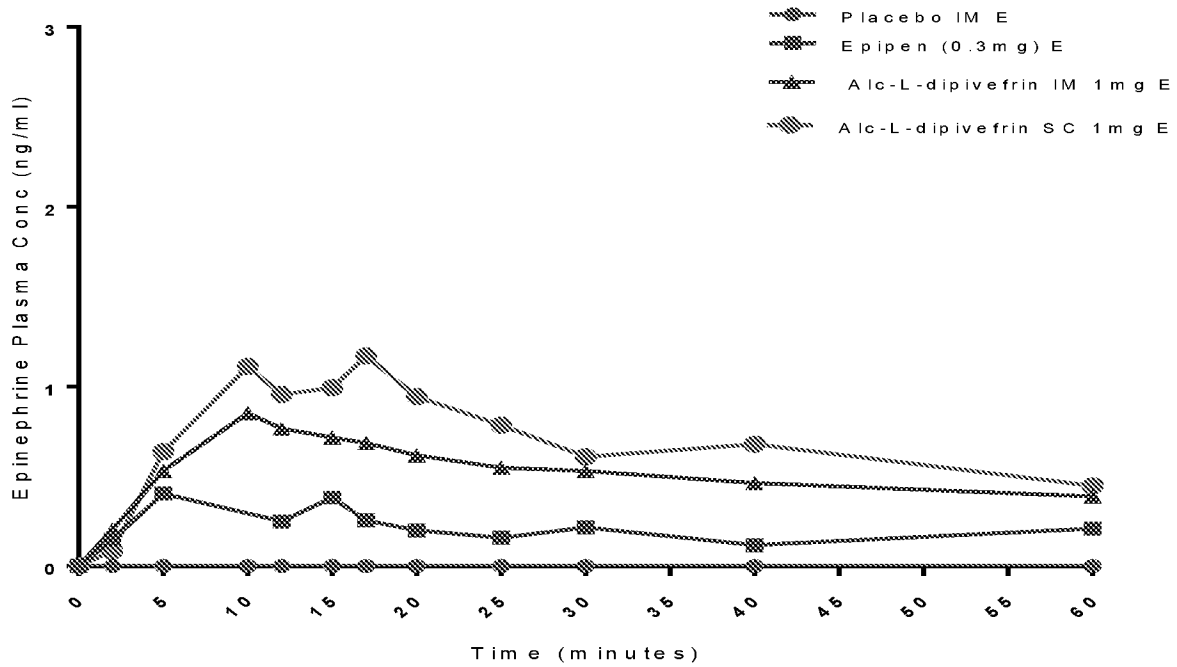


Fig. 9B

Comparison of IM & SC administration L-dipivefrin 2 mg-Average Epinephrine Plasma Concentration

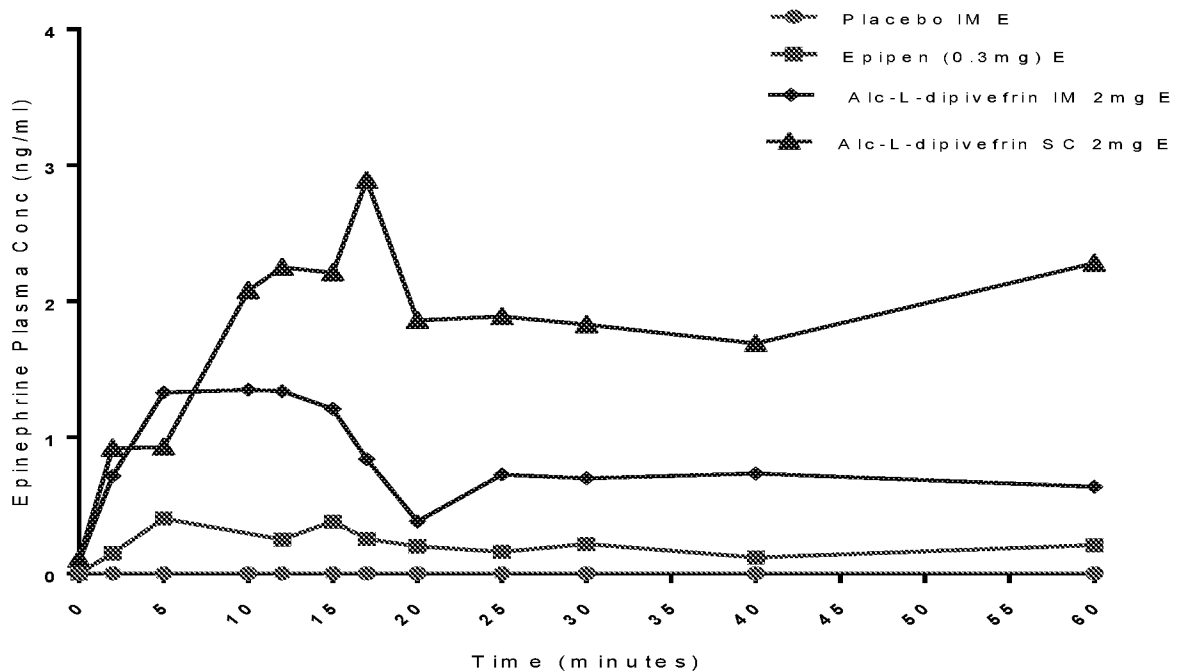


Fig. 9C

Average Dipivefrin Plasma Concentration vs Time Profiles

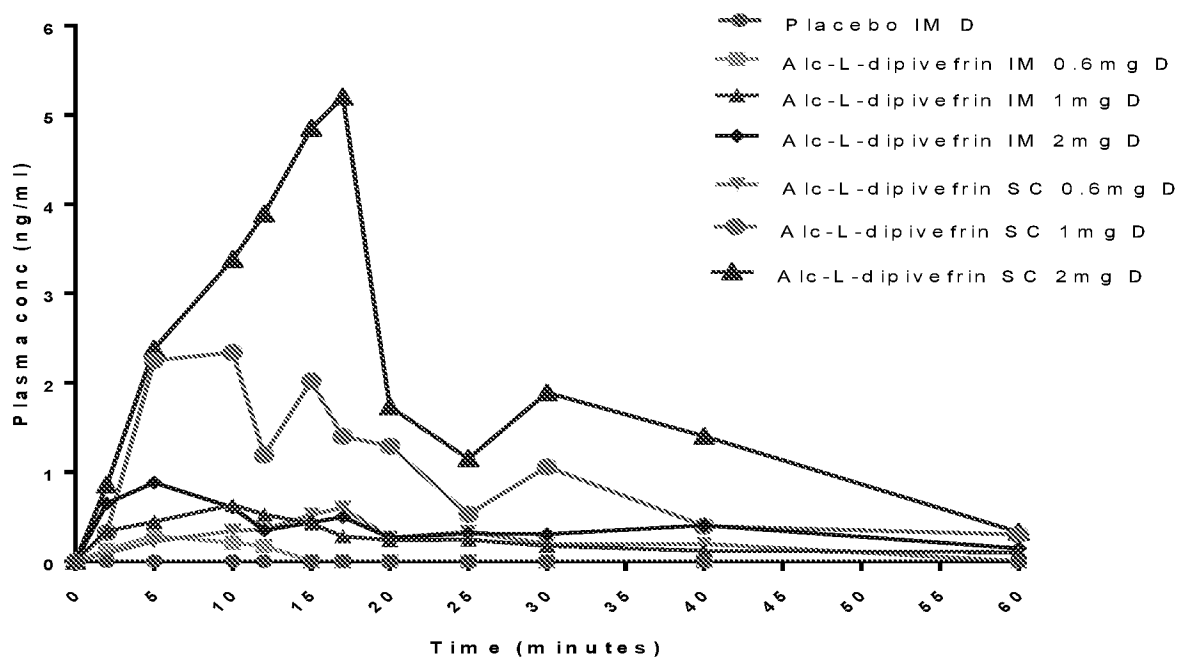


Fig. 10

Conversion of Dipivefrin to Epinephrine

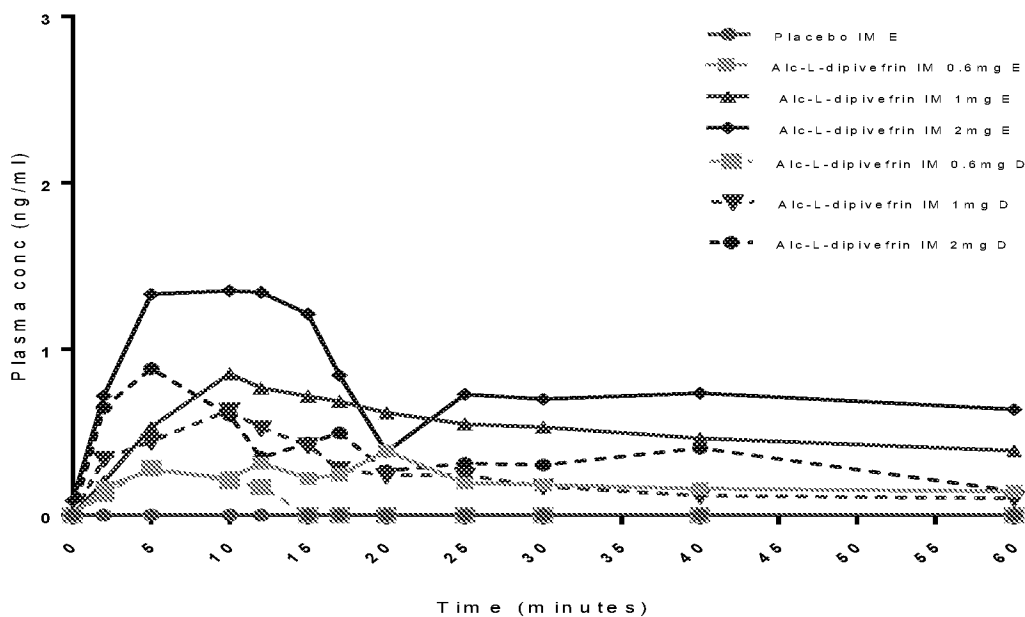


Fig. 11A

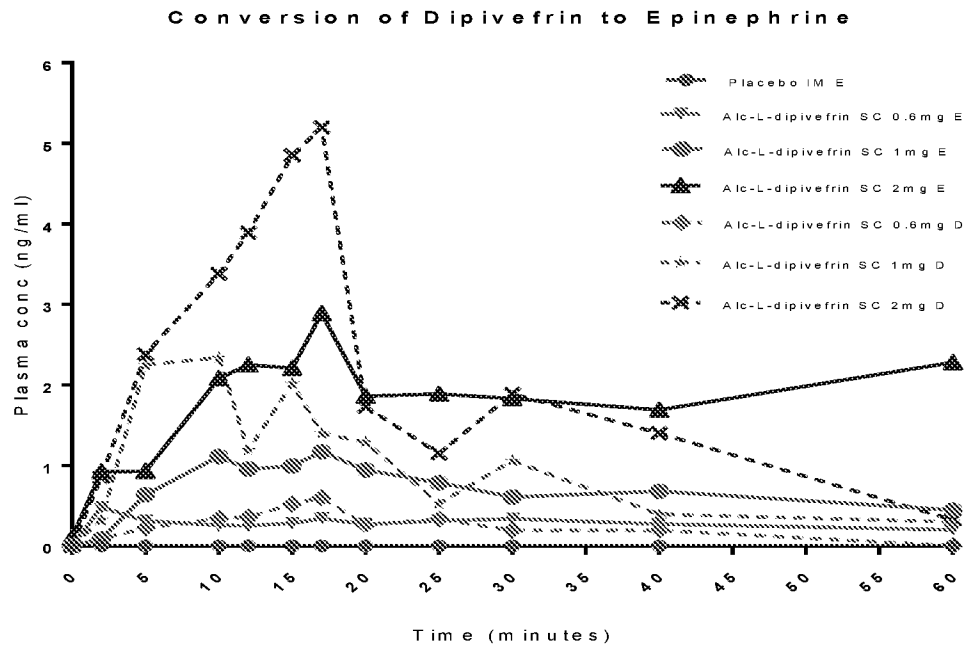


Fig. 11B

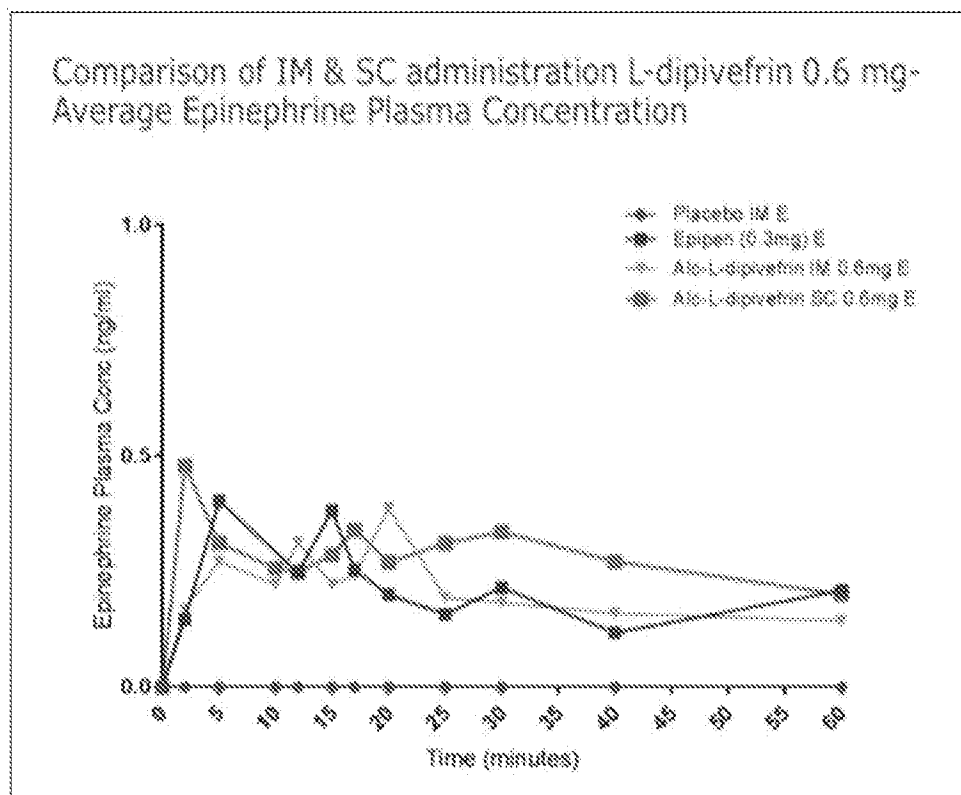


Fig. 12A

Dose Response (Epinephrine Plasma Levels)
as a Function of Route of Administration

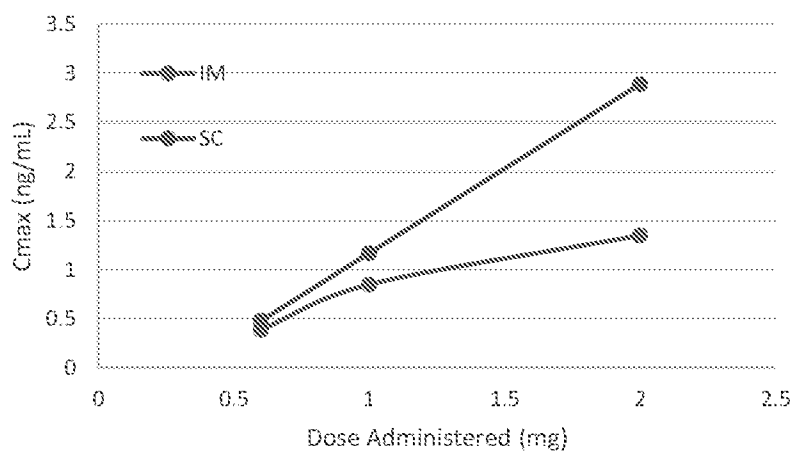


Fig. 12B

Dose Response (Epinephrine Plasma Levels)
as a Function of Route of Administration

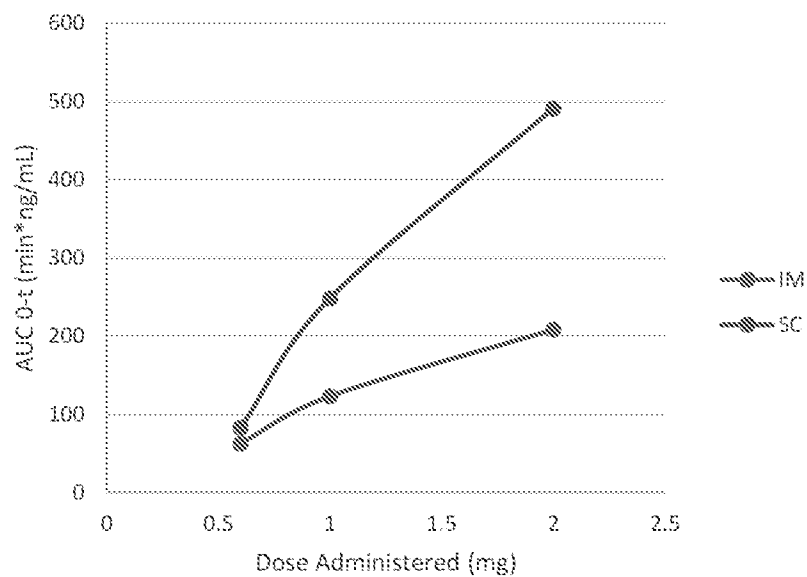


Fig. 12C

Epinephrine Concentration in Plasma

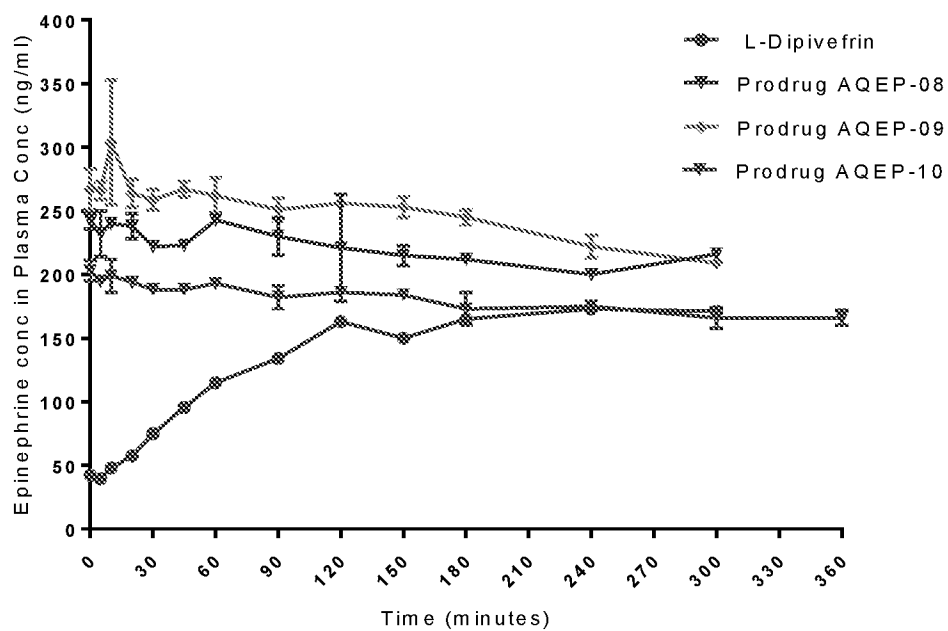


Fig. 13A

Epinephrine Concentration in Plasma

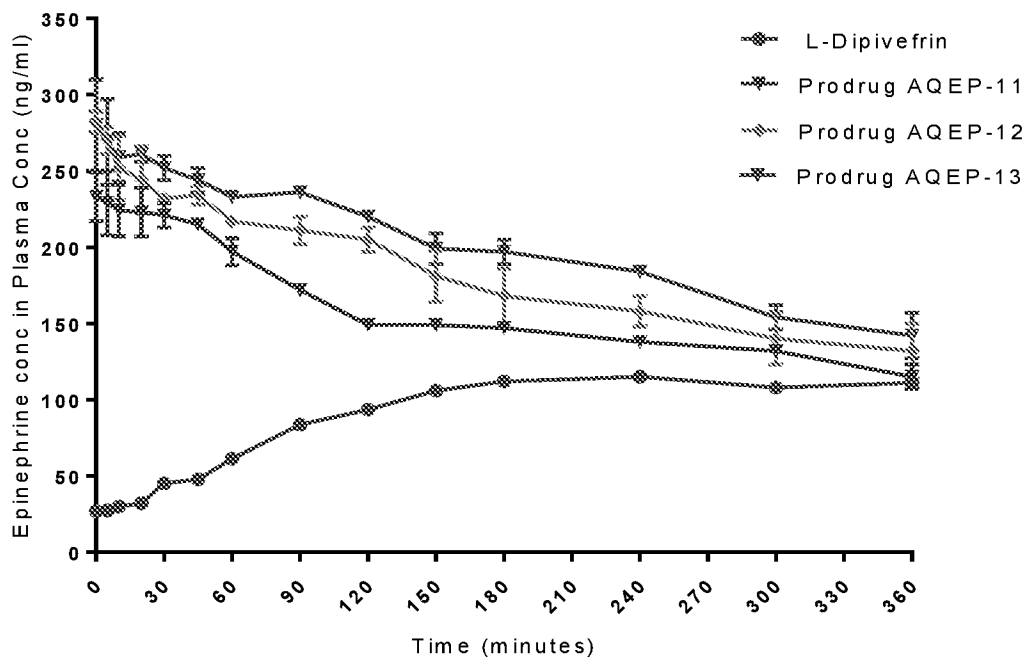


Fig. 13B

Epinephrine Concentration in Plasma

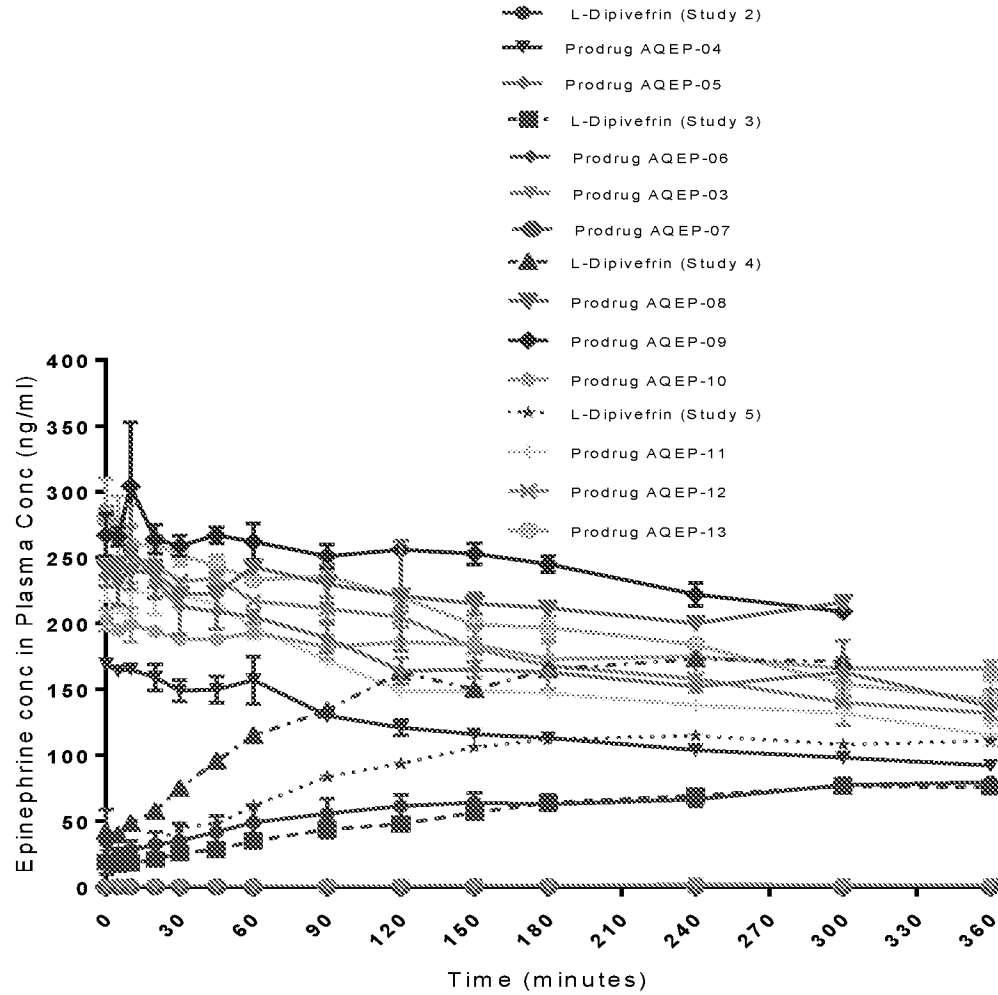


Fig. 13C

Ex Vivo Permeation Data of Prodrugs

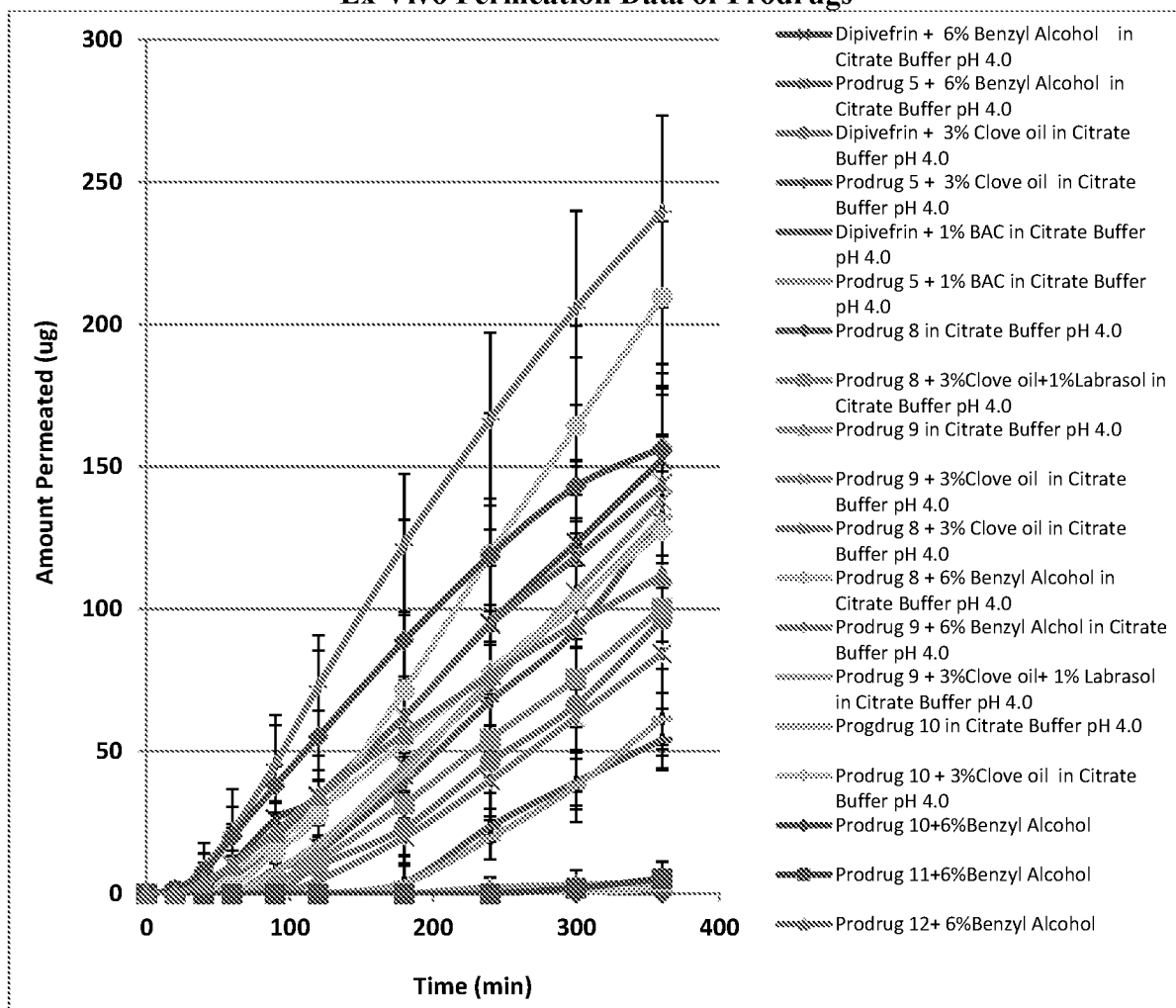
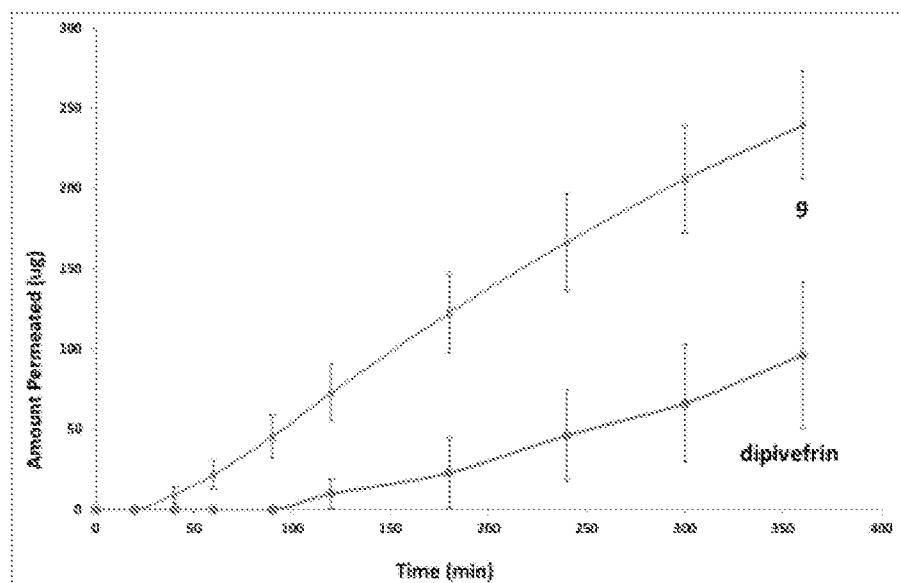


Fig. 14A

Ex vivo permeation data: AQEP-09 vs L-Dipivefrin



Prodrug AQEP-09 has faster onset and better absorption than Dipivefrin

Fig. 14B

In Vitro Human Whole Blood - Hydrolysis Data

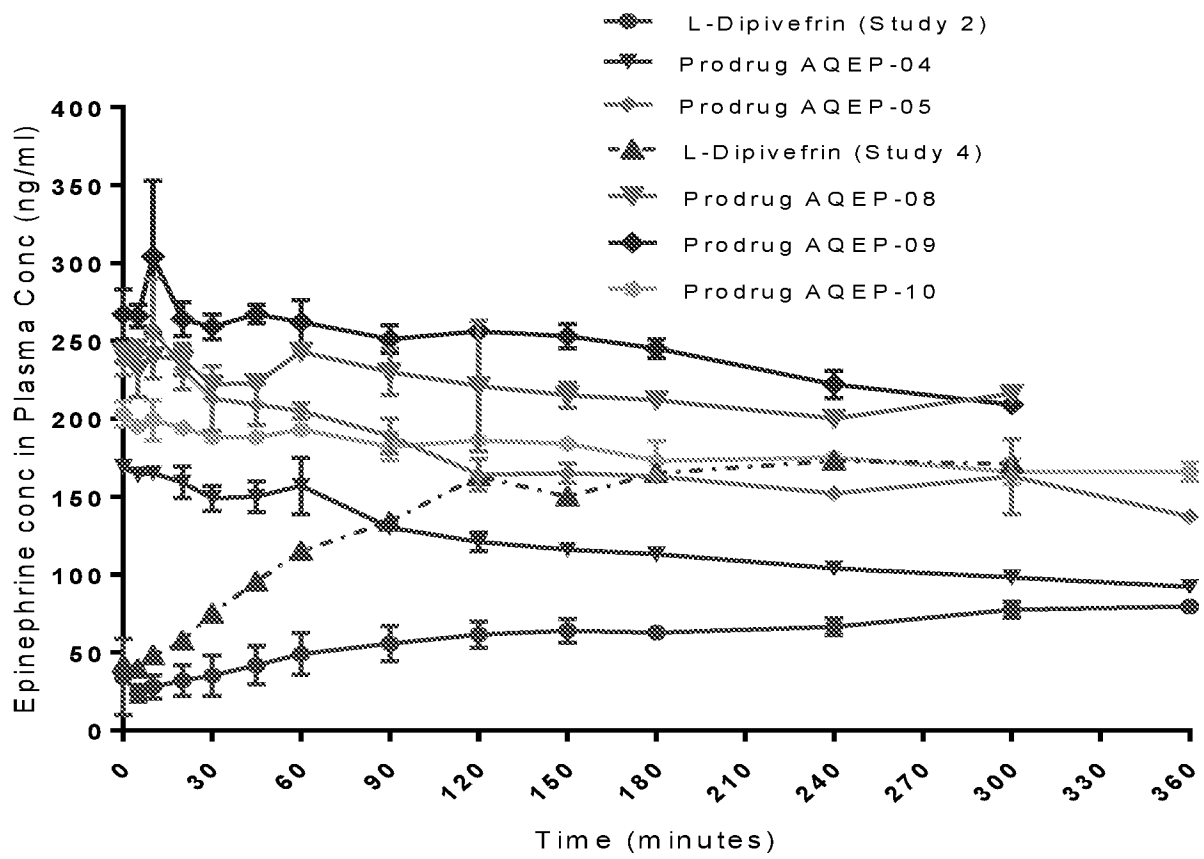


Fig. 15

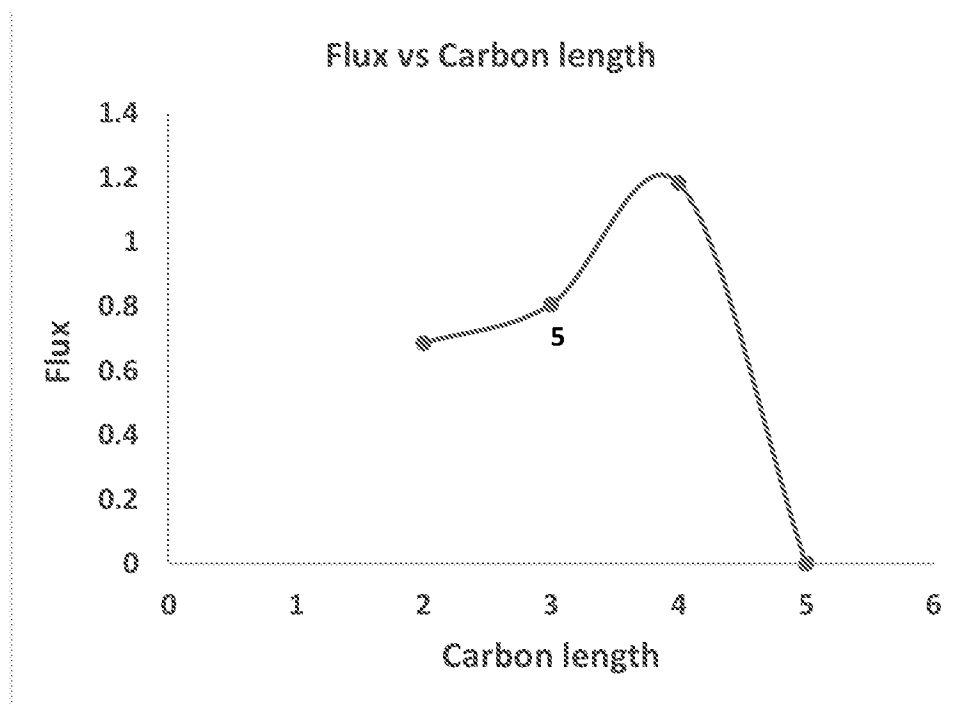


Fig. 16

PRODRUG COMPOSITIONS AND METHODS OF TREATMENT

TECHNICAL FIELD

This invention relates to pharmaceutical compositions and methods of treatment.

5

BACKGROUND

Active ingredients, such as drugs or pharmaceuticals, are delivered to patients in deliberate fashion using a one or more prodrugs. Active ingredients can also be delivered to patients in combination with at least one other active or drug in the composition as part of a drug delivery system. In certain instances, the prodrugs themselves may have biological activity as well as the ability to convert or transform into one or more active drugs.

10

SUMMARY

Prodrug design is an important part of drug discovery and can offer many advantages over parent drugs such as increased solubility, enhanced stability, improved bioavailability, reduced side effects, and better selectivity. The selection and design of the prodrug can be affected by the site of drug delivery, the tissue type, enzymatic conversion, steric hindrance, and other molecular considerations.

15

Delivery of drugs or pharmaceuticals transdermally or transmucosally can require that the prodrug, drug, active or pharmaceutical alone or in combination permeate or otherwise cross at least one biological membrane partially or completely in an effective and efficient manner.

20

In general, a method of treating a medical condition in a human subject can include administering a composition including a prodrug and a permeation enhancer from a matrix and the permeation enhancer promoting permeation of the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour.

25

In certain embodiments, the method of treating a medical condition can further include administering a pharmaceutically active ingredient with the prodrug.

In certain embodiments, the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 100:1 to 1:100 by weight. In certain embodiments, the enhancer to prodrug ratio is 50:1 to 1:50 by

30

weight. In certain embodiments, the permeation enhancer to prodrug ratio is 50:1 to 1:1 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 50:1 to 10:1 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 10:1 to 1:10 by weight

5 In certain embodiments, the prodrug comprises 0.01-90% of the matrix by % weight. In certain embodiments, the prodrug comprises 0.1-50% of the matrix by % weight. In certain embodiments, the permeation enhancer comprises 1-50% of the matrix by % weight. In certain embodiments, the permeation enhancer comprises 5-25% of the matrix by % weight.

10 In certain embodiments, the pharmaceutically active form of the prodrug has a Tmax of less than 240 minutes. In certain embodiments, the prodrug has a Tmax of less than 120 minutes. In certain embodiments, the prodrug has a Tmax of less than 60 minutes.

 In certain embodiments, the prodrug has a Cmax of 0.1 pg/ml-50,000 pg/ml.

 In some embodiments, the prodrug has particle size of no more than 200 microns.

15 In certain embodiments, the prodrug and permeation enhancer concurrently penetrate the mucosal tissue.

 In certain embodiments, the prodrug is an ester of a pharmaceutically active form of the prodrug.

 In certain embodiments, the prodrug includes an alkyl ester of a pharmaceutically active form of the prodrug.

20 In certain embodiments, the prodrug includes a butyl ester of a pharmaceutically active form of the prodrug.

 In certain embodiments, the prodrug includes an isopropyl ester pharmaceutically active form of the prodrug.

25 In certain embodiments, the prodrug includes an ethyl ester pharmaceutically active form of the prodrug.

 In certain embodiments, the prodrug includes an ester of epinephrine.

 In certain embodiments, the prodrug is converted to an active form of the prodrug compound. In certain embodiments, at least half of the administered prodrug is converted in less than 240 minutes.

30 In certain embodiments, at least half of the administered prodrug is converted in less than 120 minutes.

In certain embodiments, at least half of the administered prodrug is converted in less than 60 minutes.

In certain embodiments, at least half of the administered prodrug is converted in less than 30 minutes.

5 In certain embodiments, at least half of the administered prodrug is converted in less than 15 minutes.

In certain embodiments, at least half of the administered prodrug is converted in less than 10 minutes

10 In certain embodiments, at least half of the administered prodrug is converted in less than 1 minute.

In certain embodiments, the prodrug converts to produce a concentration of active compound of between 20 pg/ml to about 20 ng/ml in a period of less than 120 minutes.

In certain embodiments, the matrix is applied as chewable or gelatin based dosage form, capsule, inhaled dosage form, lyophilized solid dosage unit, mist, powder, spray, liquid, gum,
15 gel, cream, film or tablet.

In certain embodiments, the matrix is pharmaceutical film that has a residence time of less than 90 minutes in an oral cavity.

In certain embodiments, the matrix is pharmaceutical film as a residence time of less than 60 minutes in an oral cavity.

20 In certain embodiments, the matrix is pharmaceutical film as a residence time of less than 15 minutes in an oral cavity.

In certain embodiments, administering the prodrug stimulates one or more adrenergic receptors. In certain embodiments, administering the prodrug may not activate the alpha 1 adrenergic receptor relative to epinephrine. In certain embodiments, administering the prodrug
25 activates one or more adrenergic receptors in a ratio of 10:1 relative to epinephrine.

In certain embodiments, administering the prodrug minimizes a side effect of epigastric pain. The administering the prodrug can reduce or minimize a side effect of epigastric pain. In certain embodiments, administering the prodrug eliminates a side effect of epigastric pain.

30 In certain embodiments, the medical condition is in a spectrum of anaphylaxis. In certain embodiments, the medical condition is an allergic reaction. In certain embodiments, the medical

condition is a cardiac abnormality. In certain embodiments, the medical condition is a pulmonary abnormality.

In certain embodiments, the permeation enhancer includes a phenylpropanoid. In certain embodiments, the phenylpropanoid is a eugenol or eugenol acetate.

5 In certain embodiments, the phenylpropanoid is a cinnamic acid, cinnamic acid ester, cinnamic aldehyde or hydrocinnamic acid. In certain embodiments, the phenylpropanoid is a chavicol. In certain embodiments, the phenylpropanoid is a safrole.

In certain embodiments, the permeation enhancer includes an essential oil extract of a clove plant.

10 In certain embodiments, the permeation enhancer is synthetic. In certain embodiments, the permeation enhancer is biosynthetic. In certain embodiments, the permeation enhancer is natural.

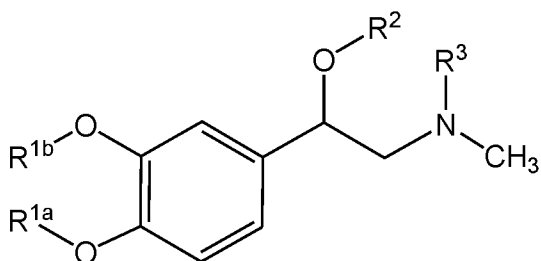
In certain embodiments, the permeation enhancer includes 15-95% eugenol. In certain embodiments, the permeation enhancer includes a terpenoid, terpene or a sesquiterpene. In 15 certain embodiments, the permeation enhancer includes a benzyl alcohol. In certain embodiments, the permeation enhancer includes farnesol. In certain embodiments, the permeation enhancer includes a self-emulsifying excipient. In certain embodiments, the permeation enhancer includes linoleic acid. In certain embodiments, the permeation enhancer includes a surfactant such as a cationic surfactant, for example.

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

In certain embodiments, the composition including a prodrug includes more than one prodrug with each prodrug being a derivative of a pharmaceutically active ingredient. In some of these embodiments, one of the prodrugs is dipivefrin.

In certain embodiments, the first prodrug is a first ester of epinephrine and the second 25 prodrug is a second ester of epinephrine, the first ester of epinephrine and the second ester of epinephrine being different.

In certain embodiments, the prodrug is a compound of formula (I), wherein



(I)

each of R^{1a} , R^{1b} , R^2 and R^3 , independently, can be H, C1-C16 acyl, alkyl aminocarbonyl, alkyloxycarbonyl, phenacyl, sulfate or phosphate, or R^{1a} and R^{1b} together, R^{1a} and R^2 together, R^{1a} and R^3 together, R^{1b} and R^2 together, R^{1b} and R^3 together, or R^2 and R^3 together form a cyclic structure including a dicarbonyl, disulfate or diphosphate moiety, provided that one of R^{1a} , R^{1b} , R^2 and R^3 is not H, or a pharmaceutically acceptable salt thereof.

In certain embodiments, R^2 and R^3 are H and each R^{1a} and R^{1b} , independently, can be ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl.

In general, a method of treating a medical condition can include administering a prodrug from a matrix, the prodrug being converted at rate of 20 pg/ml to about 20 ng/ml of active compound in less than 240 minutes.

The prodrug can be converted to 200 pg/ml to about 350 pg/ml of active compound in less than 120 minutes. In certain embodiments, prodrug is converted to 200 pg/ml to about 350 pg/ml of active compound in less than 100 minutes. The prodrug can also be converted to 200 pg/ml to about 350 pg/ml of active compound in less than 60 minutes. In certain embodiments, the prodrug is converted to 200 pg/ml to about 350 pg/ml of active compound in less than 45 minutes. In certain embodiments, the prodrug is converted to 200 pg/ml to about 350 ng/ml of active compound in less than 30 minutes.

In certain embodiments, the prodrug converts to create a sustained concentration of 200 pg/ml to about 350 pg/ml of active compound.

In certain embodiments, less than 100% of the prodrug is converted. In other embodiments, 100% of the prodrug is converted.

In general, a method of treating a medical condition comprising administering a prodrug, the prodrug being converted to produce a concentration of active from 20 pg/ml to about 20 ng/ml of active compound in less than 240 minutes and in which 100% of prodrug is converted.

In certain circumstances, a method of treating a medical condition comprising administering a prodrug from a matrix, the prodrug being converted to produce a concentration of active from 20 pg/ml to about 20 ng/ml of active compound in less than 240 minutes and in which less than 100% of prodrug is converted. The prodrug can be administered from a matrix.

5 In certain embodiments, the prodrug can produce therapeutic levels over 100 pg of epinephrine for a duration of at least 1 hour. In certain embodiments, the prodrug can produce therapeutic levels over 100 pg of epinephrine for a duration of at least 2 hours. In certain embodiments, the prodrug produces therapeutic levels over 100 pg of epinephrine for a duration of at least 3 hours. In certain embodiments, the prodrug produces therapeutic levels over 100 pg
10 of epinephrine for a duration of at least 4 hours.

 In certain embodiments, the permeation enhancer can be a phytoextract. In certain embodiments, the permeation enhancer can include a phenylpropanoid. In certain embodiments, the pharmaceutical composition can include a fungal extract. In certain embodiments, the pharmaceutical composition can include a saturated or unsaturated alcohol. In certain
15 embodiments, the alcohol can be an aromatic or aliphatic alcohol such as benzyl alcohol. In some cases, the flavonoid, phytoextract, phenylpropanoid, eugenol, or fungal extract can be used as a solubilizer. In certain embodiments, the phenylpropanoid can be eugenol, eugenol acetate, a cinnamic acid, a cinnamic acid ester, a cinnamic aldehyde, or a hydrocinnamic acid. In certain embodiments, the phenylpropanoid can be chavicol. In other embodiments, the phenylpropanoid
20 can be safrole. In certain embodiments, the phytoextract can be an essential oil extract of a clove plant, such as from a flower bud, leaf or a stem of a clove plant.

 In certain embodiments, the prodrug can be administered from a polymer matrix. The polymer matrix can include a polymer, which can include a water soluble polymer. The polymer can be a polyethylene oxide. The polymer can be a cellulosic polymer. The cellulosic polymer
25 can be hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethyl cellulose and/or sodium carboxymethylcellulose. The polymer can include polyethylene oxide and/or polyvinyl pyrrolidone. The polymeric matrix can include polyethylene oxide and/or a polysaccharide. The polymeric matrix can include polyethylene oxide, hydroxypropyl methylcellulose and/or a
30 polysaccharide. The polymeric matrix can include polyethylene oxide, a cellulosic polymer, polysaccharide and/or polyvinylpyrrolidone.

The polymeric matrix can include at least one polymer selected from the group of: pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, ethylene oxide or propylene oxide co-

5 polymers, collagen, albumin, poly-amino acids, polyphosphazenes, polysaccharides, chitin, chitosan, and derivatives thereof.

In certain embodiments, the pharmaceutical composition can further include a stabilizer. Stabilizers can include antioxidants, which can prevent unwanted oxidation of materials, sequestrants, which can form chelate complexes and inactivating traces of metal ions that would

10 otherwise act as catalysts, emulsifiers and surfactants, which can stabilize emulsions, ultraviolet stabilizers, which can protect materials from harmful effects of ultraviolet radiation, UV absorbers, chemicals absorbing ultraviolet radiation and preventing it from penetrating the composition, quenchers, which can dissipate the radiation energy as heat instead of letting it break chemical bonds, or scavengers which can eliminate free radicals.

15 A prodrug can be structured to ensure its variable or customizable metabolic stability or protection, e.g., from enzymatic cleavage until a desired target is reached to alleviate certain side effects and/or enhance efficacy. Enzymatic cleavage can result from endogenous enzymes for example. In certain situations, enzymes can be intentionally added to a body to enhance metabolism for example.

20 In yet another aspect, the pharmaceutical composition has a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent selected from: (a) an aggregation inhibitory agent; (b) a charge-modifying agent; (c) a pH control agent; (d) a degradative enzyme inhibitory agent; (e) a mucolytic or mucus clearing agent; (f) a ciliostatic agent; (g) a membrane

25 penetration-enhancing agent selected from: (i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) a nitric oxide donor compound; (vi) a long chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating

30 agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetyl amino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis;

(x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x); (h) a modulatory agent of epithelial junction physiology; (i) a vasodilator agent; (j) a selective transport-enhancing agent; and (k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is
5 effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for enhanced mucosal delivery, wherein the formulation of the compound with the transmucosal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject.

In general, a method of treating a medical condition can include administering an
10 effective amount of a pharmaceutical composition including a prodrug of an active pharmaceutical component. An active pharmaceutical component can include epinephrine. Epinephrine can be administered as a prodrug, such as dipivefrin or other prodrug. The prodrug can include a natural or synthetic prodrug. The prodrug can be selected and designed based on the active pharmaceutical compound. It can be designed to have certain permeation parameters
15 such that it can penetrate a transmucosal barrier, intercellular or intracellular space and a basement membrane such that it can reach the vascular system. The prodrug can also have sufficient hydrolysis parameters allowing it to be metabolized including by one or more enzymatic processes into one or more active compounds and absorbed in the tissue or biological fluid. This absorption can be in a range from a very rapid in uptake to very slow in uptake. In
20 some embodiments, the uptake is controlled so that pharmacokinetic performance or profiles can be custom designed for unique or different pharmacodynamic effects.

Thus, a method of treating a medical condition can include administering an effective amount of a pharmaceutical composition including a polymeric matrix, in which the pharmaceutically active component may include one or more of a prodrug, a permeation
25 enhancer, or a combination of these in a specific ratio. In certain embodiments, the medical condition can include cardiac dysfunction, pulmonary dysfunction, dermatitis, type I-IV hypersensitivity reactions, hypotension, cardiac arrest, heart failure, anaphylaxis, mydriasis, asystole, pulseless electrical activity, ventricular fibrillation, pulseless ventricular tachycardia, bradycardia, arrhythmia, supraventricular tachycardia or asthma exacerbation.

30 In certain embodiments, a pharmaceutical film can include a polymeric matrix, a pharmaceutically active component including epinephrine or a prodrug or at least one prodrug

alone or in combination with epinephrine contained in the polymeric matrix along with an adrenergic receptor interacter.

The active and/or the prodrug in the pharmaceutical film can have a Tmax of 1 seconds - 240 minutes, and a Cmax of 0.1 ng/ml-2 ng/ml. In certain embodiments, the Tmax is 40 minutes or less and wherein the Cmax is 0.1 ng/ml or greater. In certain embodiments, the Tmax is 35 minutes or less and wherein the Cmax is 0.15 ng/ml or greater. In certain embodiments, Tmax is 30 minutes or less and wherein the Cmax is 0.2 ng/ml or greater.

The Cmax can be 0.1 ng/ml- 2 ng/ml, 0.15 ng/ml-2.5 ng/ml, 0.2 ng/ml-1.0 ng/ml, 0.2 ng/ml - 1.2 ng/ml, and 0.2 ng/ml - 1.3 ng/ml. The Cmax can be greater than 0.1 ng/ml, greater than 0.15 ng/ml, greater than 0.2 ng/ml, greater than 0.4 ng/ml, greater than 0.5 ng/ml, greater than 1.0 ng/ml, greater than 1.2 ng/ml. The Cmax can be less than 3 ng/ml, less than 2 ng/ml and less than 1.5 ng/ml.

The Tmax can be 1 second-240 minutes, 10-60 minutes, 20-40 minutes, 12-15 minutes, and 5-10 minutes and 15 sec-5 min. The Tmax can be less than 120 minutes, 90 minutes, 60 minutes, 45 minutes, 35 minutes, 25 minutes, less than 20 minutes, 15 minutes, less than 12 minutes, and less than 10 minutes. It is understood that monophasic, biphasic and multiphasic pharmacokinetic curves can be produced with multiple and varying Tmax and Cmax and partial or complete AUC's (area under the curve or drug exposure) utilizing this invention.

Other aspects, embodiments, and features will be apparent from the following description, the drawings, and the claims.

BRIEF DESCRIPTION OF THE FIGURES

Referring to Fig. 1A and Fig. 1B, plasma concentration is shown for EpiPen vs. dipivefrin soluble film (DSF).

Referring to Fig. 2A and 2B, plasma concentration vs. time is shown for dipivefrin in varying doses.

Referring to Fig. 3A and 3B, epinephrine concentration in plasma is shown as converted from prodrugs dipivefrin and AQEP-10.

Referring to Fig. 4, epinephrine concentration in plasma is shown as converted from prodrugs dipivefrin and AQEP-04 and AQEP-05.

Referring to Fig. 5, epinephrine concentration in plasma is shown as converted from prodrugs dipivefrin and AQEP-03, AQEP-06 and AQEP-07.

Referring to Fig. 6A and Fig. 6B, epinephrine concentration in plasma is shown as converted from prodrugs dipivefrin and AQEP-01, AQEP-02, AQEP-03 and AQEP-04.

5 Referring to Fig. 7A and 7B, epinephrine concentration in plasma is shown as converted from prodrugs dipivefrin and AQEP-03 and AQEP-05.

Referring to Fig. 8A-8C, epinephrine concentration in plasma for prodrug conversion was measured in intramuscular (IM) and subcutaneous (SC) administrations of L-Dipivefrin to compare the pharmacokinetic profile of L-dipivefrin administered through intramuscular (IM) and subcutaneous (SC) routes to epinephrine (Epipen, 0.3 mg).

Referring to Fig. 9A, 9B and 9C, intramuscular (IM) and subcutaneous (SC) administrations of L-Dipivefrin was compared with the pharmacokinetic profile of L-dipivefrin.

Referring to Fig. 10, average dipivefrin plasma concentration over time is indicated as measured in IM and SC administration.

15 Referring to Fig. 11A conversion of dipivefrin to epinephrine was measured for 0.6 mg, 1 mg and 2 mg of dipivefrin using IM administration.

Referring to Fig. 11B, conversion of dipivefrin to epinephrine was measured for 0.6 mg, 1 mg and 2 mg of dipivefrin using SC administration.

Referring to Fig. 12A, the graph shows a comparison was performed for IM and SC administration of dipivefrin as compared to the Epipen.

Referring to Fig. 12B, the graph shows the dose response (epinephrine plasma levels) was obtained as a function of route of administration.

Referring to Fig. 12C, the graph shows dose response (epinephrine plasma levels) as a function of route of administration.

25 Referring to Fig. 13A, the graph shows prodrugs AQEP-08, AQEP-09 and AQEP-10 tested against L-dipivefrin for their resulting epinephrine concentration in human plasma (ng/ml) over time (min).

Referring to Fig. 13B, the graph indicates prodrugs AQEP-11, AQEP-12 and AQEP-13 tested against dipivefrin for resulting epinephrine concentration in human plasma (ng/ml) over time (min).

Referring to Fig. 13C, the graph indicates a comprehensive comparison of various prodrugs tested against dipivefrin for resulting epinephrine concentration in human plasma (ng/ml) over time (min).

Referring to Fig. 14A, the graph indicates a comprehensive comparison of various prodrugs tested against dipivefrin for resulting epinephrine concentration in human plasma (ng/ml) over time (min).

Referring to Fig. 14B, the graph shows the ex vivo permeation data for AQEP-09 compared to L-dipivefrin.

Referring to Fig. 15, the graph indicates a study comparing in vitro human whole blood hydrolysis data for those prodrugs having acceptable levels of permeation.

Referring to Fig. 16, the graph indicates the results from a study of flux vs. carbon chain length

DETAILED DESCRIPTION

Prodrugs can provide enhanced delivery of an active pharmaceutical ingredient such as epinephrine for example. Mucosal surfaces, such as the oral mucosa, are a convenient route for delivering drugs to the body due to the fact that they are highly vascularized and permeable, providing increased bioavailability and rapid onset of action because it does not pass through the digestive system and thereby avoids first pass metabolism. In particular, the buccal and sublingual tissues offer advantageous sites for drug delivery because they are highly permeable regions of the oral mucosa, allowing drugs diffusing from the oral mucosa to have direct access to systemic circulation. This also offers increased convenience and therefore increased compliance in patients. The permeation may be 100% for some mucosal surfaces but may also be absorbed fractionally from one or more mucosal sites such as buccal, gingival, sublingual, esophageal, gastric, intestinal tract, dermal, epidermal, nasal, aural, bronchial, and colon. For certain drugs, or pharmaceutically active components, a permeation enhancer can help to overcome the mucosal barrier and improve permeability. Permeation enhancers reversibly modulate the penetrability of the barrier layer in favor of drug absorption. Permeation enhancers facilitate transport of molecules through the tissue. Absorption profiles and their rates can be controlled and modulated by a variety of parameters, such as but not limited to film size, drug

loading, enhancer type/loading, polymer matrix release rate, mucosal residence time and by the use of at least one pharmaceutical active alone or in combination with one or more prodrugs.

A pharmaceutical composition can be designed to deliver a prodrug for a pharmaceutically active component in a deliberate and tailored way. U.S. Patent Applications 15/717,859 and 15/791,249, and PCT Application PCT/US2018/053042, published as WO 2019/067670 are each incorporated by reference herein.

Prodrug Design

Delivery of certain active compounds, such as epinephrine, is characterized by certain unique challenges. The compound is hydrophilic, endogenous, highly variable, requires rapid delivery, and promotes vasoconstriction. Thus, the concentration and timing of its delivery is often critical to manage and not easily accomplished. An effective approach to delivering epinephrine can be with a system that allows the compound to penetrate a transmucosal barrier. Transmucosal barriers include surface epithelial cells, intercellular space, and a basement membrane. The epithelial cells which can be overcome with a penetration enhancer or permeation enhancer. The intercellular space can be overcome with a cosolvent or fatty acid. Finally, the basement membrane delays, but does not prevent absorption of the compound, which can be delivered with a permeation enhancer and cosolvent or fatty acid, or a combination of these. While transmucosal delivery of epinephrine can be effective, often times, it may not be rapid enough, vasoconstriction can result in an undulating pharmacokinetic (PK) profile, and swallowed epinephrine that is not absorbed can result in epigastric pain (e.g., 7.5 mg - 30 mg).

A prodrug design can provide an alternative for the delivery of epinephrine, and indeed, for other active pharmaceutical ingredients. A prodrug can present improved hydrophobicity, better permeation, dose reduction, and enhanced speed of absorption. It can also provide alternative compositions with unique stability profiles. For example, while epinephrine is stabilized by sodium metabisulfite, the prodrug dipivefrin was found to be unstable in sodium metabisulfite. Other prodrugs could have similar stability and/or be designed based on the desired stability profile exhibited with certain additives. A prodrug that is not absorbed in the stomach can also avoid, minimize or eliminate the side effect of epigastric pain. Moreover, a prodrug can result in reduced adrenergic receptor binding, resulting in reduced variability of vasoconstriction and more stability. An expected disadvantage for the epinephrine prodrug approach is that it often requires conversion in the blood, can cause delay in epinephrine

exposure as a function of its conversion rate, and since the molecular weight is often higher than that of the active pharmaceutical ingredient, it can also require a higher drug loading (e.g. if the prodrug is twice the molecular weight of the active pharmaceutical ingredient, it can require twice the drug loading).

5 A prodrug can be metabolized, for example by hydrolysis. Metabolism can occur through enzymatic conversion, for example through hydrolytic enzymes, which convert a prodrug into an active compound. A prodrug can be converted at various times and in various ways in the body. A prodrug can be designed based on a targeted approach for in any suitable manner based on where and when conversion is desired. In some instances, prodrug conversion
10 can occur systemically (e.g. in circulation). In some situations, prodrug conversion occurs intracellularly (e.g., antiviral nucleoside analogs, lipid-lowering statins). In some situations, prodrug conversion can occur extracellularly, for examples in digestive fluids or other extracellular body fluids).

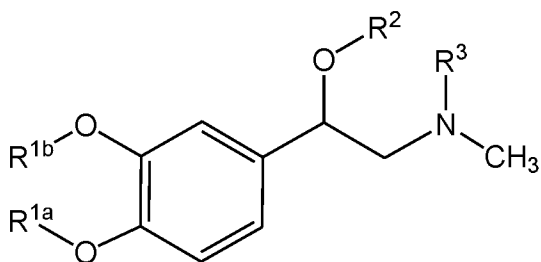
 A prodrug can be administered orally. It can be administered in sublingual or buccal
15 dosage forms, or a combination of the two. In certain embodiments, it can be administered as a chewable or gelatin based dosage form, inhalation dosage form, capsule, lyophilized solid dosage unit, mist, powder, spray, liquid, gum, gel, cream, film or tablet.

 In certain embodiments, at least half of the administered prodrug is converted in less than 240 minutes. In certain embodiments, at least half of the administered prodrug is converted in
20 less than 120 minutes. In other embodiments, at least half of the administered prodrug is converted in less than 60 minutes. In other embodiments, at least half of the administered prodrug is converted in less than 30 minutes. In other embodiments, at least half of the administered prodrug is converted in less than 15 minutes. In other embodiments, at least
25 half of the administered prodrug is converted in less than 5 minutes. In other embodiments, at least half of the administered prodrug is converted in less than 1 minute.

 In certain embodiments, a prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about 20 ng/ml in a period of less than 120 minutes. The prodrug can be designed to convert to produce a concentration of active compound of
30 between 20 pg/ml to about 20 ng/ml in a period of less than 60 minutes. A prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about

20 ng/ml in a period of less than 30 minutes. The prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about 20 ng/ml in a period of less than 15 minutes. The prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about 20 ng/ml in a period of less than 10 minutes. The prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about 20 ng/ml in a period of less than 5 minutes. The prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about 20 ng/ml in a period of less than 1 minute.

Other prodrugs for the delivery of an active pharmaceutical compound have been explored and are described herein. For example, the prodrug can be a compound of formula (I)



(I)

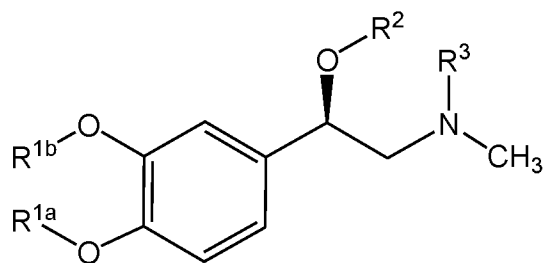
or a pharmaceutically acceptable salt thereof.

In formula I, each of R^{1a} , R^{1b} , R^2 and R^3 , independently, can be H, C1-C16 acyl, alkyl aminocarbonyl, alkyloxycarbonyl, phenacyl, sulfate or phosphate, or R^{1a} and R^{1b} together, R^{1a} and R^2 together, R^{1a} and R^3 together, R^{1b} and R^2 together, R^{1b} and R^3 together, or R^2 and R^3 together form a cyclic structure including a dicarbonyl, disulfate or diphosphate moiety, provided that one of R^{1a} , R^{1b} , R^2 and R^3 is not H, or a pharmaceutically acceptable salt thereof. In preferred circumstances, R^2 and R^3 are H and each R^{1a} and R^{1b} , independently, can be C1-C16 acyl, for example, ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl. In certain circumstances, each of R^{1a} and R^{1b} is the same and is not H and R^2 and R^3 are H.

The compound of formula I can be a pharmaceutically acceptable salt. The pharmaceutically acceptable salt can be an acid addition salt or a base addition salt. Acid addition salts can be prepared by reacting the purified compound in its free-based form with a suitable organic or inorganic acid and isolating the salt thus formed. Examples of pharmaceutically acceptable acid addition salts include, without limitations, salts of an amino

group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid, or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid. Base addition salts can be prepared by reacting the purified compound in its acid form with a suitable organic or inorganic base and isolating the salt thus formed. Such salts include, without limitations, alkali metal (e.g., sodium, lithium, and potassium), alkaline earth metal (e.g., magnesium and calcium), ammonium, alkylammonium, substituted alkylammonium and $N^+(C_{1-4}alkyl)_4$ salts. The alkyl can be a hydroxyalkyl. Other pharmaceutically acceptable salts of the compound can include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, glycolate, gluconate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate salts.

To deliver epinephrine, a class of prodrug compounds was tested having modifications made to the R^{1a} , R^{1b} , R^2 and R^3 groups of epinephrine as shown below. The R^{1a} and R^{1b} groups can include esters, amides, carbonates and carbamates, orthoesters or acetals. The groups can include for example, alkyl esters, chloroalkyl esters, amides, alkyl amides, chloroalkyl amides. The R^2 groups can include benzylic alcohol modification. The R^3 group can include amine modification or oxazolidines. An ideal prodrug would have one or more of the following attributes, is biologically acceptable, penetrates one or more mucosal membranes, is stable and converts in the body, tissue or blood. In some cases, the prodrug may not need any permeation enhancers at all but rather permeate sufficiently by itself. The conversion of the prodrug to active is not predictable based on chain length of the R^{1a} , R^{1b} , R^2 and R^3 groups. In particular, a tertiary group at the second atom of the R^{1a} , R^{1b} , R^2 or R^3 group. The permeation of the prodrug is also unpredictable based on the R^{1a} , R^{1b} , R^2 and R^3 groups.

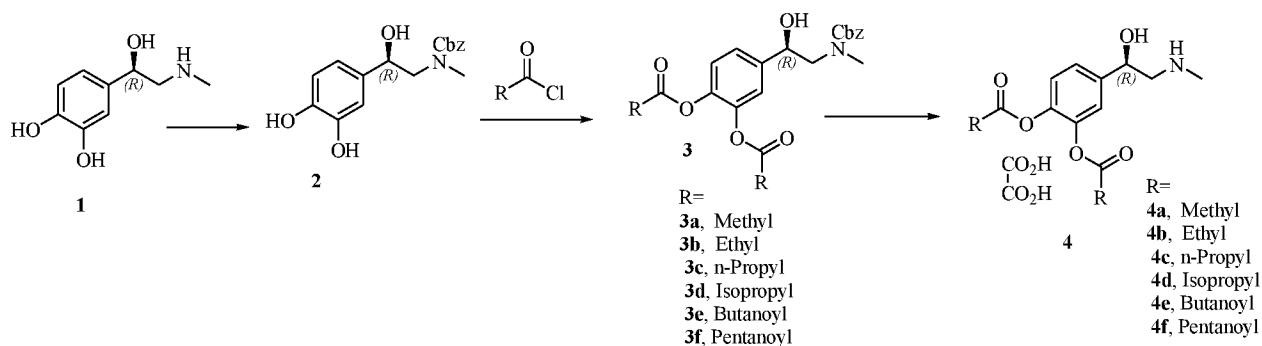


The prodrug selection process for an active pharmaceutical ingredient was conducted by first synthesizing prodrugs with various substituents, conducting ex vivo permeation studies, and following those with in vitro hydrolysis assay using a biological fluid (e.g., human whole blood).

5

Synthesis

General synthetic procedures were used to synthesize epinephrine prodrugs as shown below.



10

Preparation of 2:

To a mixture of (-)-epinephrine (5 g) in water (50 ml) and THF (25 ml), was added NaHCO_3 (4.6 g, 2 equiv) and stirred for 5 min at 0-5 °C, then added a solution of N-(Benzyloxycarbonyloxy)succinimide (6.82 g, 1 equiv) in THF (25 ml) slowly and stirred at RT for 12 h. Solvent was removed in rotary evaporator, the solid residue was extracted with ethyl acetate (100 mL), washed with 2N HCl (50 mL), followed by brine (100 mL), dried over anhydrous sodium sulfate and the solvent was removed to obtain compound 2 (8.5 g) as a thick brown syrup.

15

General procedure for preparation of esters 3a-3f.

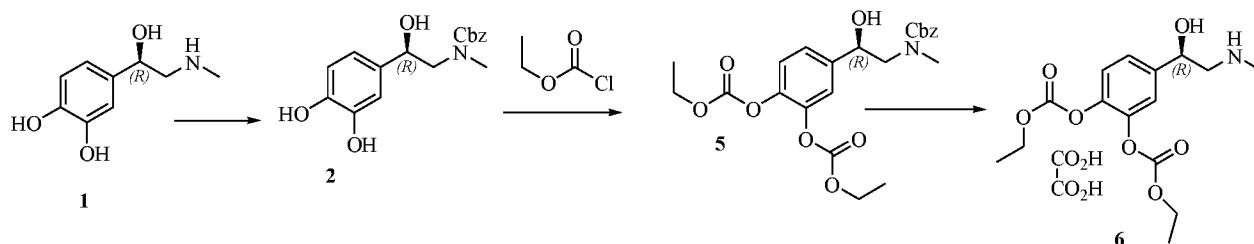
To a solution of compound 2 (1 equiv), triethylamine (3 equiv) in dichloromethane (30 volumes to compound 2) was added the corresponding acid chloride (1.8 equiv) dropwise at 0-5 °C. Then, the mixture was gradually warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with saturated NaHCO₃ solution (30 volumes to compound 2).

- 5 The organic phase was separated, dried over anhydrous sodium sulfate and concentrated to residue which was purified by column chromatography to isolate clean 3a-3f (~60% yield) as oils.

General procedure for preparation of 4a-4f.

- 10 A mixture of 3a-3f in methanol (~20 vol), oxalic acid (1 equiv), 10% Pd/C (50% wet, 20% wt to the starting material) was stirred under hydrogen atmosphere (using a balloon) for 12 h; TLC was used to ensure completion of the reaction. The catalyst was filtered through celite bed and the filtrate was concentrated to dryness. The solids were suspended in Methyl tert-butyl ether (5 vol), stirred for 30 min; filtered the solids and dried. 4a-4F were isolated as white solids and confirmed by NMR and Mass spec.

15 Synthesis of biscarbonate 6:



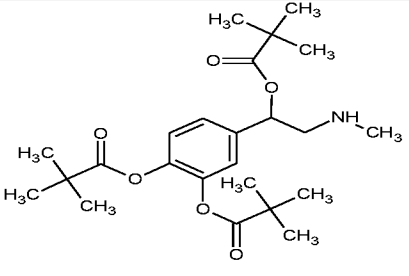
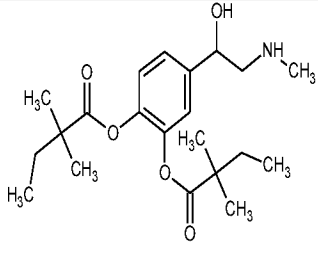
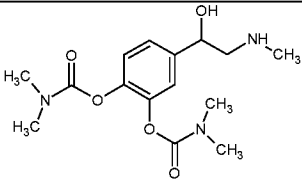
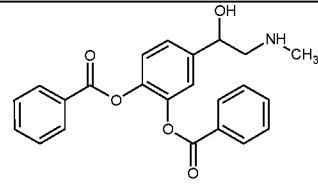
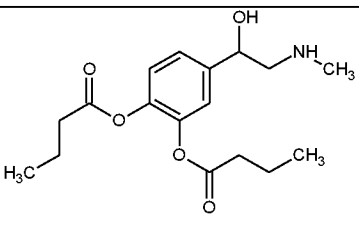
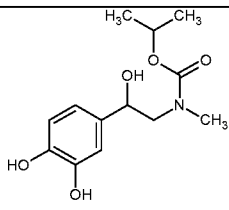
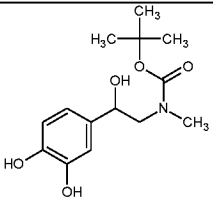
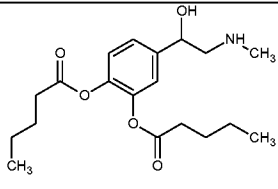
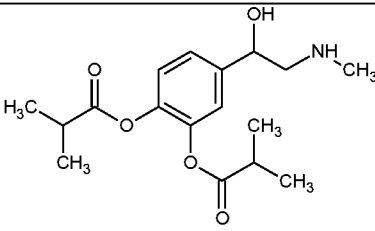
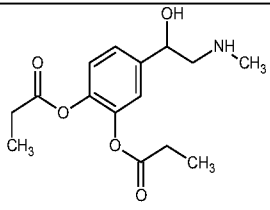
20 Compound 5:

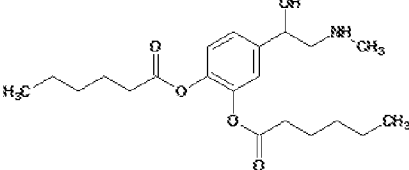
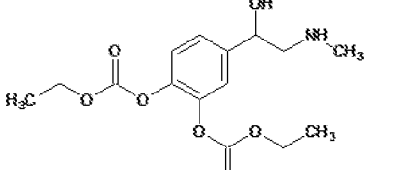
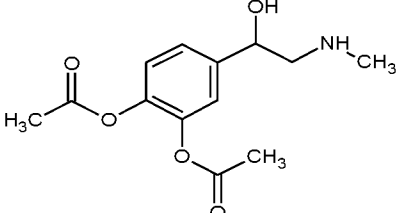
Same procedures as 3a-3f was followed.

Compound 6:

Same procedures as 4a-4f was followed.

Exemplary prodrugs are provided in the table below.

	
AQEP-01	AQEP-02
	
AQEP-03	AQEP-04
	
AQEP-05	AQEP-06
	
AQEP-07	AQEP-08
	
AQEP-09	AQEP-10

	
AQEP-11	AQEP-12
	
AQEP-13	

General Permeation Procedure – Ex vivo Permeation Study Protocol

A Franz diffusion cell is an apparatus used for ex vivo tissue permeation assay used in the formulation development to identify the most active permeation enhancer. The Franz diffusion cell apparatus consists of two chambers separated by a membrane. The permeation studies were conducted using porcine buccal mucosa obtained from a slaughterhouse. The tissues were dermatomed to typically 300-500 μm and mounted in vertical Franz diffusion cells maintained at 37 °C. The tissue membrane separates the donor compartment containing the drug mixed with the permeation enhancer solution and the receptor compartment containing the collection media which was selected to provide sink conditions throughout the experiment. The permeation rate was observed over several hours by analysing drug concentration in the receptor medium.

In one example, a permeation procedure is conducted as follows. A temperature bath is set to 37° C, and receiver media is placed in a water bath to adjust the temperature and begin degassing. A Franz diffusion cell is obtained and prepared. The Franz diffusion cell includes a donor compound, a donor chamber, a membrane, sampling port, receptor chamber, stir bar, and a heater/circulator. A stir bar is inserted into a Franz diffusion cell. Tissue is placed over the Franz diffusion cell, and it is ensured that the tissue covers the entire area with an overlap onto a glass joint. The top of a diffusion cell is placed over the tissue, and the top of the cell is clamped to the bottom. About 5 mL of receptor media is loaded into the receiver area to ensure that no air bubbles are trapped in the received portion of the cell. This ensures that all 5mL can fit into the

receiver area. Stirring is begun, and temperature is allowed to equilibrate for about 20 minutes. Meanwhile, High Performance Liquid Chromatography (HPLC) vials are labelled by cell number and time point. One must then check again for air bubbles as the solution will degas during heating.

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

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

Ex vivo Permeation Evaluation

An exemplary ex vivo permeation evaluation is as follows.

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

30

Permeation Enhancers

Solubility and permeability of the pharmaceutically active component in vivo, in particular, in the mouth of a subject, can vary tremendously. A particular class of permeation enhancer can improve the uptake and bioavailability of the pharmaceutically active component in vivo. In particular, when delivered to the mouth via a film, the permeation enhancer can improve the permeability of the pharmaceutically active component through the mucosa and into the blood stream of the subject. The permeation enhancer can improve absorption rate and amount of the pharmaceutically active component by more than 5%, more than 10%, more than 20%, more than 30%, more than 40%, more than 50%, more than 60%, more than 70%, more than 80%, more than 90%, more than 100%, more than 150%, about 200% or more, or less than 200%, less than 150%, less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%, or a combination of these ranges, depending on the other components in the composition.

In certain embodiments, a pharmaceutical composition has a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent selected from: (a) an aggregation inhibitory agent; (b) a charge-modifying agent; (c) a pH control agent; (d) a degradative enzyme inhibitory agent; (e) a mucolytic or mucus clearing agent; (f) a ciliostatic agent; (g) a membrane penetration-enhancing agent selected from: (i) a surfactant; (ii) a bile salt; (iii) a phospholipid additive, mixed micelle, liposome, or carrier; (iv) an alcohol; (v) an enamine; (vi) an NO donor compound; (vii) a long chain amphipathic molecule; (viii) a small hydrophobic penetration enhancer; (ix) sodium or a salicylic acid derivative; (x) a glycerol ester of acetoacetic acid; (xi) a cyclodextrin or beta-cyclodextrin derivative; (xii) a medium-chain fatty acid; (xiii) a chelating agent; (xiv) an amino acid or salt thereof; (xv) an N-acetylamino acid or salt thereof; (xvi) an enzyme degradative to a selected membrane component; (xvii) an inhibitor of fatty acid synthesis; (xviii) an inhibitor of cholesterol synthesis; and (xix) any combination of the membrane penetration enhancing agents recited in (i)-(xix); (h) a modulatory agent of epithelial junction physiology; (i) a vasodilator agent; (j) a selective transport-enhancing agent; and (k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for enhanced transmucosal delivery, wherein the formulation of the compound

with the transmucosal delivery-enhancing agents provides for increased bioavailability of the compound in blood plasma of a subject. Penetration enhancers have been described in J. Nicolazzo, et al., *J. of Controlled Disease*, 105 (2005) 1-15, which is incorporated by reference herein.

5 In certain embodiments, the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 100:1 to 1:100 by weight. In certain embodiments, the enhancer to prodrug ratio is 50:1 to 1:50 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 50:1 to 1:1 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 50:1 to 10:1 by weight. . In certain embodiments, the permeation enhancer to prodrug ratio is 10:1 to 1:10 by weight.

Oral Mucosa

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

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

30 The buccal mucosa delineates the inside lining of the cheek as well as the area between the gums and upper and lower lips and it has an average surface area of 100 cm². The surface of the buccal mucosa consists of a stratified squamous epithelium which is separated from the underlying connective tissue (lamina propria and submucosa) by an undulating basement

membrane (a continuous layer of extracellular material approximately 1–2 μm in thickness). This stratified squamous epithelium consists of differentiating layers of cells which change in size, shape, and content as they travel from the basal region to the superficial region, where the cells are shed. There are approximately 40–50 cell layers, resulting in a buccal mucosa which is 500–
5 600 μm thick.

Structurally the sublingual mucosa is comparable to the buccal mucosa but the thickness of this epithelium is 100–200 μm . This membrane is also non-keratinised and being relatively thinner has been demonstrated to be more permeable than buccal mucosa. Blood flow to the sublingual mucosal is slower compared with the buccal mucosa and is of the order of 1.0 ml/
10 $\text{min}^{-1}/\text{cm}^{-2}$.

The permeability of the buccal mucosa is greater than that of the skin, but less than that of the intestine. The differences in permeability are the result of structural differences between each of the tissues. The absence of organized lipid lamellae in the intercellular spaces of the buccal mucosa results in greater permeability of exogenous compounds, compared to keratinized
15 epithelia of the skin; while the increased thickness and lack of tight junctions results in the buccal mucosa being less permeable than intestinal tissue.

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

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

Paracellular and Transcellular Transport

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

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

A chemical penetration enhancer, or absorption promoter, is a substance added to a pharmaceutical formulation in order to increase the membrane permeation or absorption rate of the coadministered drug, without damaging the membrane and/or causing toxicity. There have been many studies investigating the effect of chemical penetration enhancers on the delivery of compounds across the skin, nasal mucosa, and intestine. In recent years, more attention has been given to the effect of these agents on the permeability of the buccal mucosa. Since permeability across the buccal mucosa is considered to be a passive diffusion process the steady state flux (J_{ss}) should increase with increasing donor chamber concentration (CD) according to Fick's first law of diffusion.

 In certain embodiments, the pharmaceutically active form of the prodrug has a T_{max} of less than 240 minutes. In certain embodiments, the prodrug has a T_{max} of less than 120 minutes. In certain embodiments, the prodrug has a T_{max} of less than 60 minutes.

In certain embodiments, the prodrug has a C_{max} of greater than 0.1 pg/ml. The prodrug can have a C_{max} of greater than 1 pg/ml. The prodrug can have a C_{max} of greater than 10 pg/ml. The prodrug can have a C_{max} of greater than 100 pg/ml. The prodrug can have a C_{max} of greater than 1000 pg/ml. The prodrug can have a C_{max} of greater than 10,000 pg/ml. The prodrug can have a C_{max} of greater than 20,000 pg/ml. The prodrug can have a C_{max} of greater than 30,000 pg/ml. The prodrug can have a C_{max} of greater than 40,000 pg/ml. The prodrug can have a C_{max} of less than 50,000 pg/ml.

The prodrug can be designed to be any particle size that enables it to be delivered effectively. In some embodiments, the prodrug has particle size of no more than 200 microns. In some embodiments, the prodrug has particle size of no more than 300 microns, the prodrug has particle size of no more than 400 microns. In some cases, the prodrug can be fully solubilized or partially solubilized, fully or partially suspended or fully or partially emulsified within a matrix.

The prodrug can be designed in a manner that permits effective metabolism or hydrolysis into an active compound. For example, in certain embodiments, the prodrug is an ester of a

pharmaceutically active form of the prodrug. In certain embodiments, the prodrug includes an alkyl ester of a pharmaceutically active form of the prodrug. In certain embodiments, the prodrug includes a butyl ester of a pharmaceutically active form of the prodrug. In certain embodiments, the prodrug includes an isopropyl ester of a pharmaceutically active form of the prodrug. In certain embodiments, the prodrug includes an ethyl ester of a pharmaceutically active form of the prodrug. In certain embodiments, the prodrug includes an amide of a pharmaceutically active form of the prodrug. In certain embodiments, the prodrug includes a carbonate of a pharmaceutically active form of the prodrug.

10 **Surfactants, Bile Salts and Other Permeation Enhancers**

Surfactants and bile salts have been shown to enhance the permeability of various compounds across the buccal mucosa, both in vitro and in vivo. The data obtained from these studies strongly suggest that the enhancement in permeability is due to an effect of the surfactants on the mucosal intercellular lipids. A permeation enhancer can be a synthetic compound. In certain embodiments, a permeation enhancer can be a biosynthetic compound. In certain embodiments, a permeation enhancer can be a natural compound. In other embodiments, a permeation enhancer can include a combination of compounds from one or more of these categories of compounds.

Fatty acids have been shown to enhance the permeation of a number of drugs through the skin, and this has been shown by differential scanning calorimetry and Fourier transform infrared spectroscopy to be related to an increase in the fluidity of intercellular lipids.

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

Oral transmucosal drug delivery (OTDD) is the administration of pharmaceutically active agents through the oral mucosa to achieve systemic effects. Permeation pathways and predictive models for OTDD are described, e.g. in M. Sattar, Oral transmucosal drug delivery – Current status and future prospects, *Int'l. Journal of Pharmaceutics*, 47(2014) 498-506, which is

incorporated by reference herein. OTDD continues to attract the attention of academic and industrial scientists. Despite limited characterization of the permeation pathways in the oral cavity compared with skin and nasal routes of delivery, recent advances in our understanding of the extent to which ionized molecules permeate the buccal epithelium, as well as the emergence of new analytical techniques to study the oral cavity, and the progressing development of in silico models predictive of buccal and sublingual permeation, prospects are encouraging.

In certain embodiments, the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 100:1 to 1:100 by weight. In certain embodiments, the enhancer to prodrug ratio is 50:1 to 1:50 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 50:1 to 1:1 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 50:1 to 10:1 by weight.

In certain embodiments, the prodrug comprises 0.01-90% of the matrix by % weight. In certain embodiments, the prodrug comprises 0.1-50% of the matrix by % weight. In certain embodiments, the permeation enhancer comprises 1-50% of the matrix by % weight. In certain embodiments, the permeation enhancer comprises 5-25% of the matrix by % weight.

In order to deliver broader classes of drugs across the buccal mucosa, reversible methods of reducing the barrier potential of this tissue should be employed. This requisite has fostered the study of penetration enhancers that will safely alter the permeability restrictions of the buccal mucosa. It has been shown that buccal penetration can be improved by using various classes of transmucosal and transdermal penetration enhancers such as bile salts, surfactants, fatty acids and their derivatives, chelators, cyclodextrins and chitosan. Among these chemicals used for the drug permeation enhancement, bile salts are the most common.

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

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

5 The permeation enhancer can be a phytoextract. A phytoextract can be an essential oil or composition including essential oils extracted by distillation of the plant material. In certain circumstances, the phytoextract can include synthetic analogues of the compounds extracted from the plant material (i.e., compounds made by organic synthesis). The phytoextract can include a phenylpropanoid, for example, phenyl alanine, eugenol, eugenol acetate, a cinnamic
10 acid, a cinnamic acid ester, a cinnamic aldehyde, a hydrocinnamic acid, chavicol, or safrole, or a combination thereof. The phytoextract can be an essential oil extract of a clove plant, for example, from the leaf, stem or flower bud of a clove plant. The clove plant can be *Syzygium aromaticum*. The phytoextract can include 20-95% eugenol, including 40-95% eugenol, including 60-95% eugenol, and for example, 80-95% eugenol. The extract can also include 5%
15 to 15% eugenol acetate. The extract can also include caryophyllene. The extract can also include up to 2.1% α -humulen. Other volatile compounds included in lower concentrations in clove essential oil can be β -pinene, limonene, farnesol, benzaldehyde, 2-heptanone and ethyl hexanoate. Other permeation enhancers may be added to the composition to improve absorption of the drug. Suitable permeation enhancers include natural or synthetic bile salts such as sodium
20 fusidate; glycocholate or deoxycholate and their salts; fatty acids and derivatives such as sodium laurate, oleic acid, oleyl alcohol, monoolein, and palmitoylcarnitine; chelators such as disodium EDTA, sodium citrate and sodium lauryl sulfate, azone, sodium cholate, sodium 5-methoxysalicylate, sorbitan laurate, glyceryl monolaurate, octoxynonyl-9, laureth-9, polysorbates, sterols, or glycerides, such as caprylocaproyl polyoxylglycerides, e.g., Labrasol.
25 The permeation enhancer can include phytoextract derivatives and/or monolignols. The permeation enhancer can also be a fungal extract.

Some natural products of plant origin have been known to have a vasodilatory effect. There are several mechanisms or modes by which plant-based products can evoke vasodilation. For review, see McNeill J.R. and Jurgens, T.M., Can. J. Physiol. Pharmacol. 84:803-821 (2006),
30 which is incorporated by reference herein. Specifically, vasorelaxant effects of eugenol have been reported in a number of animal studies. See, e.g., Lahlou, S., et al., J. Cardiovasc.

Pharmacol. 43:250-57 (2004), Damiani, C.E.N., et al., Vascular Pharmacol. 40:59-66 (2003), Nishijima, H., et al., Japanese J. Pharmacol. 79:327-334 (1998), and Hume W.R., J. Dent Res. 62(9):1013-15 (1983), each of which is incorporated by reference herein. Calcium channel blockade was suggested to be responsible for vascular relaxation induced by a plant essential oil, or its main constituent, eugenol. See, Interaminense L.R.L. et al., Fundamental & Clin. Pharmacol. 21: 497-506 (2007), which is incorporated by reference herein.

Fatty acids can be used as inactive ingredients in drug preparations or drug vehicles. Fatty acids can also be used as formulation ingredients due to their certain functional effects and their biocompatible nature. Fatty acid, both free and as part of complex lipids, are major metabolic fuel (storage and transport energy), essential components of all membranes and gene regulators. For review, see Rustan A.C. and Dreven, C.A., Fatty Acids: Structures and Properties, Encyclopedia of Life Sciences (2005), which is incorporated by reference herein. There are two families of essential fatty acids that are metabolized in the human body: ω -3 and ω -6 polyunsaturated fatty acids (PUFAs). If the first double bond is found between the third and the fourth carbon atom from the ω carbon, they are called ω -3 fatty acids. If the first double bond is between the sixth and seventh carbon atom, they are called ω -6 fatty acids. PUFAs are further metabolized in the body by the addition of carbon atoms and by desaturation (extraction of hydrogen). Linoleic acid, which is a ω -6 fatty acid, is metabolized to γ -linolenic acid, dihomo- γ -linolenic acid, arachidonic acid, adrenic acid, tetracosatetraenoic acid, tetracosapentaenoic acid, docosapentaenoic acid, α -linolenic acid, which is a ω -3 fatty acid is metabolized to octadecatetraenoic acid, eicosatetraenoic acid, eicosapentaenoic acid (EPA), docosapentaenoic acid, tetracosapentaenoic acid, tetracosahexaenoic acid and docosahexaenoic acid (DHA).

It has been reported that fatty acids, such as palmitic acid, oleic acid, linoleic acid and eicosapentaenoic acid, induced relaxation and hyperpolarization of porcine coronary artery smooth muscle cells via a mechanism involving activation of the Na^+K^+ -ATPase pump and the fatty acids with increasing degrees of *cis*-unsaturation had higher potencies. See, Pomposiello, S.I. et al., Hypertension 31:615-20 (1998), which is incorporated by reference herein. Interestingly, the pulmonary vascular response to arachidonic acid, a metabolite of linoleic acid, can be either vasoconstrictive or vasodilative, depending on the dose, animal species, the mode of arachidonic acid administration, and the tones of the pulmonary circulation. For example, arachidonic acid has been reported to cause cyclooxygenase-dependent and -independent

pulmonary vasodilation. See, Feddersen, C.O. et al., J. Appl. Physiol. 68(5):1799-808 (1990); and see, Spannake, E.W., et al., J. Appl. Physiol. 44:397-495 (1978) and Wicks, T.C. et al., Circ. Res. 38:167-71 (1976), each of which is incorporated by reference herein.

Many studies have reported effects of EPA and DHA on vascular reactivity after being administered as ingestible forms. Some studies found that EPA-DHA or EPA alone suppressed the vasoconstrictive effect of norepinephrine or increased vasodilatory responses to acetylcholine in the forearm microcirculation. See, Chin, J.P.F, et al., Hypertension 21:22-8 (1993), and Tagawa, H. et al., J Cardiovasc Pharmacol 33:633-40 (1999), each of which is incorporated by reference herein. Another study found that both EPA and DHA increased systemic arterial compliance and tended to reduce pulse pressure and total vascular resistance. See, Nestel, P. et al., Am J. Clin. Nutr. 76:326-30 (2002), which is incorporated by reference herein. Meanwhile, a study found that DHA, but not EPA, enhanced vasodilator mechanisms and attenuates constrictor responses in forearm microcirculation in hyperlipidemic overweight men. See, Mori, T.A., et al., Circulation 102:1264-69 (2000), which is incorporated by reference herein. Another study found vasodilator effects of DHA on the rhythmic contractions of isolated human coronary arteries *in vitro*. See Wu, K.-T. et al., Chinese J. Physiol. 50(4):164-70 (2007), which is incorporated by reference herein.

Adrenergic Receptors

The adrenergic receptors (or adrenoceptors) are a class of G protein-coupled receptors that are a target of catecholamines, especially norepinephrine (noradrenaline) and epinephrine (adrenaline). Epinephrine (adrenaline) interacts with both α - and β -adrenoceptors, causing vasoconstriction and vasodilation, respectively. Although α receptors are less sensitive to epinephrine, when activated, they override the vasodilation mediated by β -adrenoceptors because there are more peripheral α_1 receptors than β -adrenoceptors. The result is that high levels of circulating epinephrine cause vasoconstriction. At lower levels of circulating epinephrine, β -adrenoceptor stimulation dominates, producing vasodilation followed by decrease of peripheral vascular resistance. The α_1 -adrenoreceptor is known for smooth muscle contraction, mydriasis, vasoconstriction in the skin, mucosa and abdominal viscera and sphincter contraction of the gastrointestinal (GI) tract and urinary bladder. The α_1 -adrenergic receptors are member of the G_q protein-coupled receptor superfamily. Upon activation, a heterotrimeric G protein, G_q , activates phospholipase C (PLC). The mechanism of action involves interaction with calcium channels

and changing the calcium content in a cell. For review, see Smith R. S. et al., *Journal of Neurophysiology* 102(2): 1103-14 (2009), which is incorporated by reference herein. Many cells possess these receptors.

α 1-Adrenergic receptors can be a main receptor for fatty acids. For example, saw
 5 palmetto extract (SPE), widely used for the treatment of benign prostatic hyperplasia (BPH), has been reported to bind α 1-adrenergic, muscarinic and 1,4-dihydropyridine (1,4-DHP) calcium channel antagonist receptors. See, Abe M., et al., *Biol. Pharm. Bull.* 32(4) 646-650 (2009), and Suzuki M. et al., *Acta Pharmacologica Sinica* 30:271-81 (2009), each of which is incorporated by reference herein. SPE includes a variety of fatty acids including lauric acid, oleic acid,
 10 myristic acid, palmitic acid and linoleic acid. Lauric acid and oleic acid can bind noncompetitively to α 1-adrenergic, muscarinic and 1,4-DHP calcium channel antagonist receptors.

In certain embodiments, a permeation enhancer can be an adrenergic receptor interacter. An adrenergic receptor interacter refers to a compound or substance that modifies and/or
 15 otherwise alters the action of an adrenergic receptor. For example, an adrenergic receptor interacter can prevent stimulation of the receptor by increasing, or decreasing their ability to bind. Such interacters can be provided in either short-acting or long-acting forms. Certain short-acting interacters can work quickly, but their effects last only a few hours. Certain long-acting interacters can take longer to work, but their effects can last longer. The interacter can be
 20 selected and/or designed based on, e.g., on one or more of the desired delivery and dose, active pharmaceutical ingredient, permeation modifier, permeation enhancer, matrix, and the condition being treated. An adrenergic receptor interacter can be an adrenergic receptor blocker. The adrenergic receptor interacter can be a terpenoid, terpene (e.g. volatile unsaturated hydrocarbons found in the essential oils of plants, derived from units of isoprenes) or a C3-C22 alcohol or acid,
 25 preferably a C7-C18 alcohol or acid, or an aromatic or aliphatic alcohol. In certain embodiments, the adrenergic receptor interacter can include farnesol, linoleic acid, arachidonic acid, docosahexanoic acid, eicosapentanoic acid, and/or docosapentanoic acid. The acid can be a carboxylic acid, phosphoric acid, sulfuric acid, hydroxamic acid, or derivatives thereof. The derivative can be an ester, amide or carbonate. For example, the adrenergic receptor interacter
 30 can be a fatty acid or fatty alcohol.

The C3-C22 alcohol or acid can be an alcohol or acid having a straight C3-C22 hydrocarbon chain, for example a C3-C22 hydrocarbon chain optionally containing at least one double bond, at least one triple bond, or at least one double bond and one triple bond; said hydrocarbon chain being optionally substituted with C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, hydroxyl, halo, amino, nitro, cyano, C₃₋₅ cycloalkyl, 3-5 membered heterocycloalkyl, monocyclic aryl, 5-6 membered heteroaryl, C₁₋₄ alkylcarbonyloxy, C₁₋₄ alkyloxycarbonyl, C₁₋₄ alkylcarbonyl, or formyl; and further being optionally interrupted by -O-, -N(R^a)-, -N(R^a)-C(O)-O-, -O-C(O)-N(R^a)-, -N(R^a)-C(O)-N(R^b)-, or -O-C(O)-O-. Each of R^a and R^b, independently, is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, or haloalkyl.

Fatty acids with a higher degree of unsaturation are effective candidates to enhance the permeation of drugs. Unsaturated fatty acids showed higher enhancement than saturated fatty acids, and the enhancement increased with the number of double bonds. See, A. Mittal, et al. Status of Fatty Acids as Skin Penetration Enhancers – A Review, *Current Drug Delivery*, 2009, 6, pp. 274-279, which is incorporated by reference herein. Position of double bond also affects the enhancing activity of fatty acids. Differences in the physicochemical properties of fatty acid which originate from differences in the double bond position most likely determine the efficacy of these compounds as skin penetration enhancers. Skin distribution increases as the position of the double bond is shifted towards the hydrophilic end. It has also been reported that fatty acid which has a double bond at an even number position more rapidly effects the perturbation of the structure of both the stratum corneum and the dermis than a fatty acid which has double bond at an odd number position. Cis-unsaturation in the chain can tend to increase activity.

An adrenergic receptor interacter can be a terpene. Hypotensive activity of terpenes in essential oils has been reported. See, Menezes I.A. et al., *Z. Naturforsch.* 65c:652-66 (2010), which is incorporated by reference herein. In certain embodiments, the permeation enhancer can be a sesquiterpene. Sesquiterpenes are a class of terpenes that consist of three isoprene units and have the empirical formula C₁₅H₂₄. Like monoterpenes, sesquiterpenes may be acyclic or contain rings, including many unique combinations. Biochemical modifications such as oxidation or rearrangement produce the related sesquiterpenoids.

An adrenergic receptor interacter can be an unsaturated fatty acid such as linoleic acid. In certain embodiments, the permeation enhancer can be farnesol. Farnesol is a 15-carbon organic compound which is an acyclic sesquiterpene alcohol, which is a natural dephosphorylated form

of farnesyl pyrophosphate. Under standard conditions, it is a colorless liquid. It is hydrophobic, and thus insoluble in water, but miscible with oils. Farnesol can be extracted from oils of plants such as citronella, neroli, cyclamen, and tuberose. It is an intermediate step in the biological synthesis of cholesterol from mevalonic acid in vertebrates. It has a delicate floral or weak citrus-lime odor and is used in perfumes and flavors. It has been reported that farnesol selectively kills acute myeloid leukemia blasts and leukemic cell lines in preference to primary hemopoietic cells. See, Rioja A. et al., FEBS Lett 467 (2-3): 291-5 (2000), which is incorporated by reference herein. Vasoactive properties of farnesyl analogues have been reported. See, Rouillet, J.-B., et al., J. Clin. Invest., 1996, 97:2384-2390, which is incorporated by reference herein. Both Farnesol and N-acetyl-S-trans, trans-farnesyl-L-cysteine (AFC), a synthetic mimic of the carboxyl terminus of farnesylated proteins inhibited vasoconstriction in rat aortic rings. In certain embodiments, an interacter can be an aporphine alkaloid. For example, an interacter can be a dicentrine.

In general, an interacter can also be a vasodilator or a therapeutic vasodilator.

Vasodilators are drugs that open or widen blood vessels. They are typically used to treat hypertension, heart failure and angina, but can be used to treat other conditions as well, including glaucoma for example. Some vasodilators that act primarily on resistance vessels (arterial dilators) are used for hypertension, and heart failure, and angina; however, reflex cardiac stimulation makes some arterial dilators unsuitable for angina. Venous dilators are very effective for angina, and sometimes used for heart failure, but are not used as primary therapy for hypertension. Vasodilator drugs can be mixed (or balanced) vasodilators in that they dilate both arteries and veins and therefore can have wide application in hypertension, heart failure and angina. Some vasodilators, because of their mechanism of action, also have other important actions that can in some cases enhance their therapeutic utility or provide some additional therapeutic benefit. For example, some calcium channel blockers not only dilate blood vessels, but also depress cardiac mechanical and electrical function, which can enhance their antihypertensive actions and confer additional therapeutic benefit such as blocking arrhythmias.

Vasodilator drugs can be classified based on their site of action (arterial versus venous) or by mechanism of action. Some drugs primarily dilate resistance vessels (arterial dilators; e.g., hydralazine), while others primarily affect venous capacitance vessels (venous dilators; e.g., nitroglycerine). Many vasodilator drugs have mixed arterial and venous dilator properties (mixed

dilators; e.g., alpha-adrenoceptor antagonists, angiotensin converting enzyme inhibitors), such as phentolamine.

It is more common, however, to classify vasodilator drugs based on their primary mechanism of action. The figure to the right depicts important mechanistic classes of vasodilator drugs. These classes of drugs, as well as other classes that produce vasodilation, include: alpha-adrenoceptor antagonists (alpha-blockers); Angiotensin converting enzyme (ACE) inhibitors; Angiotensin receptor blockers (ARBs); beta₂-adrenoceptor agonists (β₂-agonists); calcium-channel blockers (CCBs); centrally acting sympatholytics; direct acting vasodilators; endothelin receptor antagonists; ganglionic blockers; nitrodilators; phosphodiesterase inhibitors; potassium-channel openers; or renin inhibitors.

In general, the active or inactive components or ingredients can be substances or compounds that create an increased blood flow or flushing of the tissue to enable a modification or difference (increase or decrease) in transmucosal uptake of the API(s), and/or have a positive or negative heat of solution which are used as aids to modify (increase or decrease) transmucosal uptake.

Sequence of Permeation Enhancer(s) and Active Pharmaceutical Ingredient(s)

The arrangement, order, or sequence of penetration enhancer(s) and active pharmaceutical ingredient(s)(API(s)) delivered to the desired mucosal surface can vary in order to deliver a desired pharmacokinetic profile. For example, one can apply the permeation enhancer(s) first by a film, by swab, spray, gel, rinse or by a first layer of a film then apply the API(s) by single film, by swab, or by a second layer of a film. The sequence can be reversed or modified, for example, by applying the API(s) first by film, by swab, or by a first layer of a film, and then applying the permeation enhancer(s) by a film, by swab, spray, gel, rinse or by a second layer of a film. In another embodiment, one may apply a permeation enhancer(s) by a film, and a drug by a different film. For example, the permeation enhancer(s) film positioned under a film containing the API(s), or the film containing the API(s) positioned under a film containing the permeation enhancer(s), depending on the desired pharmacokinetic profile.

The arrangement, order, or sequence of prodrug(s) delivered to the desired mucosal surface can vary in order to deliver a desired pharmacokinetic profile. For example, one can apply a prodrug or combination of prodrugs by a film, by swab, spray, gel, rinse or by a layer of a film. In another example, one can apply a first prodrug by a film, by swab, spray, gel, rinse or

by a layer of a film, followed by another application of a prodrug by a film, by swab, spray, gel, rinse or by a layer of a film. A subsequent prodrug can be a different prodrug from the first prodrug. In another example, the first prodrug and subsequent prodrug(s) can be the same compound. In another example, one can apply permeation enhancer(s) first by a film, by swab, spray, gel, rinse or by a first layer of a film then apply the prodrug(s) by single film, by swab, or by a second layer of a film. The sequence can be reversed or modified, for example, by applying the prodrug(s) first by film, by swab, or by a first layer of a film, and then applying the permeation enhancer(s) by a film, by swab, spray, gel, rinse or by a second layer of a film. In another embodiment, one may apply a permeation enhancer(s) by a film, and a drug by a different film. For example, the permeation enhancer(s) film positioned under a film containing the prodrug(s), or the film containing the prodrug(s) positioned under a film containing the permeation enhancer(s), depending on the desired pharmacokinetic profile.

For example, the penetration enhancer(s) can be used as a pretreatment alone or in combination with at least one API or prodrug to precondition the mucosa for further absorption of the API(s). The treatment can be followed by another treatment with neat penetration enhancer(s) to follow the at least one API mucosal application. The pretreatment can be applied as a separate treatment (film, gel, solution, swab etc.) or as a layer within a multilayered film construction of one or more layers. Similarly, the pretreatment may be contained within a distinct domain of a single film, designed to dissolve and release to the mucosa prior to release of the secondary domains with or without penetration enhancer(s) or API(s). The active ingredient may then be delivered from a second treatment, alone or in combination with additional penetration enhancer(s). There may also be a tertiary treatment or domain that delivers additional penetration enhancer(s) and/or at least one API(s) or prodrug(s), either at a different ratio relative to each other or relative to the overall loading of the other treatments. This allows a custom pharmacokinetic profile to be obtained. In this way, the product may have single or multiple domains, with penetration enhancer(s) and API(s) that can vary in mucosal application order, composition, concentration, or overall loading that leads to the desired absorption amounts and/or rates that achieve the intended pharmacokinetic profile and/or pharmacodynamic effect.

The film format can be oriented such that no distinct sides, or such that the film has at least one side of a multiple layer film where the edges are co-terminus (having or meeting at a shared border or limit).

The pharmaceutical composition can be a chewable or gelatin based dosage form, spray, gum, gel, cream, tablet, liquid or film. The composition can include textures, for example, at the surface, such as microneedles or micro-protrusions. Recently, the use of micron-scale needles in increasing skin permeability has been shown to significantly increase transdermal delivery, including and especially for macromolecules. Most drug delivery studies have emphasized solid microneedles, which have been shown to increase skin permeability to a broad range of molecules and nanoparticles in vitro. In vivo studies have demonstrated delivery of oligonucleotides, reduction of blood glucose level by insulin, and induction of immune responses from protein and DNA vaccines. For such studies, needle arrays have been used to pierce holes into skin to increase transport by diffusion or iontophoresis or as drug carriers that release drug into the skin from a microneedle surface coating. Hollow microneedles have also been developed and shown to microinject insulin to diabetic rats. To address practical applications of microneedles, the ratio of microneedle fracture force to skin insertion force (i.e. margin of safety) was found to be optimal for needles with small tip radius and large wall thickness. Microneedles inserted into the skin of human subjects were reported as painless. Together, these results suggest that microneedles represent a promising technology to deliver therapeutic compounds into the skin for a range of possible applications. Using the tools of the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and materials. Microneedles can be, for example, polymeric, microscopic needles that deliver encapsulated drugs in a minimally invasive manner, but other suitable materials can be used.

Microneedles can be used to enhance the delivery of drugs through the oral mucosa, particularly with the claimed compositions. The microneedles create micron sized pores in the oral mucosa which can enhance the delivery of drugs across the mucosa. Solid, hollow or dissolving microneedles can be fabricated out of suitable materials including, but not limited to, metal, polymer, glass and ceramics. The microfabrication process can include photolithography, silicon etching, laser cutting, metal electroplating, metal electro polishing and molding. Microneedles could be solid which is used to pretreat the tissue and are removed before applying the film. The drug loaded polymer film described in this application can be used as the matrix material of the microneedles itself. These films can have microneedles or micro protrusions fabricated on their surface which will dissolve after forming microchannels in the mucosa through which drugs can permeate.

The term “film” can include films and sheets, in any shape, including rectangular, square, or other desired shape. A film can be any desired thickness and size. In preferred embodiments, a film can have a thickness and size such that it can be administered to a user, for example, placed into the oral cavity of the user. A film can have a relatively thin thickness of from about 0.0025mm to about 0.250mm, or a film can have a somewhat thicker thickness of from about 0.250mm to about 1.0mm. For some films, the thickness may be even larger, i.e., greater than about 1.0mm or thinner, i.e., less than about 0.0025mm. A film can be a single layer or a film can be multi-layered, including laminated or multiple cast films. A permeation enhancer and pharmaceutically active component can be combined in a single layer, each contained in separate layers, or can each be otherwise contained in discrete regions of the same dosage form. In certain embodiments, the pharmaceutically active component contained in the polymeric matrix can be dispersed in the matrix. In certain embodiments, the permeation enhancer being contained in the polymeric matrix can be dispersed in the matrix.

Oral dissolving films can fall into three main classes: fast dissolving, moderate dissolving and slow dissolving. Oral dissolving films can also include a combination of any of the above categories. Fast dissolving films can dissolve in about 1 second to about 30 seconds in the mouth, including more than 1 second, more than 5 seconds, more than 10 seconds, more than 20 seconds, or less than 30 seconds. Moderate dissolving films can dissolve in about 1 to about 30 minutes in the mouth including more than 1 minute, more than 5 minutes, more than 10 minutes, more than 20 minutes or less than 30 minutes, and slow dissolving films can dissolve in more than 30 minutes in the mouth. As a general trend, fast dissolving films can include (or consist of) low molecular weight hydrophilic polymers (e.g., polymers having a molecular weight between about 1,000 to 9,000 daltons, or polymers having a molecular weight up to 200,000 daltons). In contrast, slow dissolving films generally include high molecular weight polymers (e.g., having a molecular weight in millions). Moderate dissolving films can tend to fall in between the fast and slow dissolving films.

It can be preferable to use films that are moderate dissolving films. Moderate dissolving films can dissolve rather quickly, but also have a good level of mucoadhesion. Moderate dissolving films can also be flexible, quickly wettable, and are typically non-irritating to the user. Such moderate dissolving films can provide a quick enough dissolution rate, most desirably between about 1 minute and about 20 minutes, while providing an acceptable mucoadhesion

level such that the film is not easily removable once it is placed in the oral cavity of the user. This can ensure delivery of a pharmaceutically active component to a user.

A pharmaceutical composition can include one or more pharmaceutically active components. The pharmaceutically active component can be a single pharmaceutical component or a combination of pharmaceutical components. The pharmaceutically active component can be an anti-inflammatory analgesic agent, a steroidal anti-inflammatory agent, an antihistamine, a local anesthetic, a bactericide, a disinfectant, a vasoconstrictor, a hemostatic, a chemotherapeutic drug, an antibiotic, a keratolytic, a cauterizing agent, an antiviral drug, an antirheumatic, an antihypertensive, a bronchodilator, an anticholinergic, an anti-anxiety drug, an antiemetic compound, a hormone, a peptide, a protein or a vaccine. The pharmaceutically active component can be a pharmaceutically acceptable salt of a drug, a prodrug, a derivative, a drug complex or analog of a drug.

The term “prodrug” refers to a biologically inactive compound that can be metabolized in the body to produce a biologically active drug or the “prodrug” can be a biologically active compound where in addition to its inherent biological activity can be metabolized to another or even preferred biologically active drug. In certain embodiments, the prodrug can have its own biological activity that can be similar to or different from the active drug. For example, the prodrug can be an ester of epinephrine, for example, dipivefrin which is hydrolysed into epinephrine. *See, e.g., J. Anderson, et al., Site of ocular hydrolysis of a prodrug, dipivefrin, and a comparison of its ocular metabolism with that of the parent compounds, epinephrine, Invest., Ophthalmol. Vis. Sci. July 1980.*

In some embodiments, more than one pharmaceutically active component may be included in the film. The pharmaceutically active components can be ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, amphetamines, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility

agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, 5 sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, 10 hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, diagnostic agents, imaging agents, dyes, or tracers, and combinations thereof. Suitable actives for use in the films herein include, but are not limited to, the following therapeutic classes: ace-inhibitor; 15 adrenergic agent; adrenocortical steroid; adrenocortical suppressant; aldosterone antagonist; alkaloid; amino acid; anabolic; analeptic; analgesic; anesthetic; anorectic; anti-acne agent; anti-adrenergic; anti-allergic; anti-amebic; anti-anemic; anti-anginal; anti-anxiety; anti-arthritis; anti-arrhythmia; anti-asthmatic; anti-atherosclerotic; anti-cholesterolemic; antibacterial; antibiotic; anticholinergic; anticoagulant; anticonvulsant; antidepressant; antidiabetic; antidiarrheal; antidiuretic; antidote; anti-emetic; anti- 20 epileptic; antifibrinolytic; antifungal; antihemorrhagic; antihistamine; antihyperlipidemia; antihypertensive; antihypotensive; anti-infective (both systemic and non-systemic); anti-inflammatory; anti-lipid; anti-manic; antimicrobial; antimigraine; antimitotic; antimycotic, antinauseant; antineoplastic; antineutropenic; anti-obesity; antiparasitic; anti-parkinson; antiproliferative; antipsychotic; anti-pyretic; antirheumatic; antiseborrheic; antisecretory; antispasmodic; anti-stroke; antithrombotic; anti-thyroid; anti- 25 tumor; anti-tussive; anti-ulcerative; anti-uricemic; antiviral; appetite suppressant; appetite stimulant; biological response modifier; blood glucose regulator; blood modifier; blood metabolism regulator; bone resorption inhibitor; bronchodilator; cardiovascular agent; central nervous system stimulant; cerebral dilator; contraceptive; coronary dilator; cholinergic; cough suppressant; decongestant; depressant; diagnostic aid; dietary supplement; diuretic; dopaminergic agent; enzymes; estrogen receptor agonist; 30 endometriosis management agent; expectorant; erectile dysfunction therapy; erythropoietic; ibrinolytic; fertility agent; fluorescent agent; free oxygen radical scavenger; gastric acid suppressant; gastrointestinal motility effector; genetic modifier; glucocorticoid; hair growth stimulant; hemostatic; histamine H2 receptor antagonists; homeopathic remedy; hormone; hypercalcemia management agent; hypocalcemia management agent; hypocholesterolemic; hypoglycemic; hypolipidemic; hypotensive; ion exchange resin;

imaging agent; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; keratolytic; laxative; LHRH agonist; mood regulator; motion sickness preparation; mucolytic; muscle relaxant; mydriatic; nasal decongestant; neuromuscular blocking agent; neuroprotective; NMDA antagonist; non-hormonal sterol derivative; osteoporosis therapy; oxytocic; 5 parasympatholytic; parasympathomimetic; plasminogen activator; platelet activating factor antagonist; platelet aggregation inhibitor; prostaglandin; psychotherapeutic; psychotropic; radioactive agent; respiratory agent; scabicide; sclerosing agent; sedative; sedative-hypnotic; selective adenosine A1 antagonist; serotonin antagonist; serotonin inhibitor; serotonin receptor antagonist; smoking cessation therapy; steroid; stimulant; sympatholytic; terine relaxant; thyroid hormone; thyroid inhibitor; 10 thyromimetic; tranquilizer; tremor therapy; amyotrophic lateral sclerosis agent; cerebral ischemia agent; Paget's disease agent; unstable angina agent; vasoconstrictor; vasodilator; weight management; wound healing agent; xanthine oxidase inhibitor; and combinations thereof.

Examples of actives suitable for use herein include antacids, H₂-antagonists, and analgesics. For example, antacid dosages can be prepared using the ingredients calcium carbonate alone or in 15 combination with magnesium hydroxide, and/or aluminum hydroxide. Moreover, antacids can be used in combination with H₂-antagonists.

Analgesics include opiates and opiate derivatives, such as oxycodone (commercially available as Oxycontin®); ibuprofen (commercially available as Motrin®, Advil®, Motrin Children's®, Motrin IB®, Advil Children's®, Motrin Infants'®, Motrin Junior®, Ibu-2®, Proprinal®, Ibu-200®, Midol Cramp 20 Formula®, Bufen®, Motrin Migraine Pain®, Addaprin® and Haltran®), aspirin (commercially available as Empirin®, Ecotrin®, Genuine Bayer®, and Halfprin®), acetaminophen (commercially available as Silapap Infant's®, Silapap Children's®, Tylenol®, Tylenol Children's®, Tylenol Extra Strength®, Tylenol Infants' Original®, Tylenol Infants'®, Tylenol Arthritis®, T-Painol®, Q-Pap®, Cetafen®, Dolono®, Tycolene®, APAP® and Aminofen®), and combinations thereof that may optionally include 25 caffeine. Other pain relieving agents may be used in the present invention, including meperidine hydrochloride (commercially available as Demerol®), capsaicin (commercially available as Qutenza®), morphine sulfate and naltrexone hydrochloride (commercially available as Embeda®), hydromorphone hydrochloride (commercially available as Dilaudid®), propoxyphene napsylate and acetaminophen (commercially available as Darvocet-N®), Fentanyl (commercially available as Duragesic®, Onsolis®, 30 and Fentora®), sodium hyaluronate (commercially available as Euflexxa®), adalimumab (commercially available as Humira®), sumatriptan succinate (commercially available as Imitrex®), fentanyl iontophoretic (commercially available as Ionsys®), orphenadrine citrate (commercially available as Norgesic®), magnesium salicylate tetrahydrate (commercially available as Novasal®), oxymorphone hydrochloride (commercially available as Opana ER®), methocarbamol (commercially available as

Robaxin®), carisoprodol (commercially available as Soma®), tramadol hydrochloride (commercially available as Ultracet® and Ultram®), morphine sulfate (commercially available as MS Contin®), metaxalone (commercially available as Skelaxin®), oxycodone hydrochloride (commercially available as OxyContin®), acetaminophen/oxycodone hydrochloride (commercially available as Percocet®),
 5 oxycodone/aspirin (commercially available as Percodan®), hydrocodone bitartrate/acetaminophen (commercially available as Vicodin®), hydrocodone bitartrate/ibuprofen (commercially available as Vicoprofen®), nepafenac (commercially available as Nevanac®), and pregabalin (commercially available as Lyrica®).

The films disclosed herein may further include agents such as NSAIDs, including etodolac
 10 (commercially available as Lodine®), ketorolac tromethamine (commercially available as Acular® or Acuvail®), naproxen sodium (commercially available as Anaprox®, Naprosyn®), flurbiprofen (commercially available as Ansaid®), diclofenac sodium/misoprostol (commercially available as Arthrotec®), celecoxib (commercially available as Celebrex®), sulindac (commercially available as Clinoril®), oxaprozin (commercially available as Daypro®), piroxicam (commercially available as
 15 Feldene®), indomethacin (commercially available as Indocin®), meloxicam (commercially available as Mobic®), mefenamic acid (commercially available as Ponstel®), tolmetin sodium (commercially available as Tolectin®), choline magnesium trisalicylate (commercially available as Trilisate®), diclofenac sodium (commercially available as Voltaren®), diclofenac potassium (commercially available as Cambia® or Zipsor®), and misoprostol (commercially available as Cytotec®). Opiate agonists and
 20 antagonists, such as buprenorphine and naloxone are further examples of drugs for use in the present invention.

Other drugs for other actives for use herein include anti-diarrheals such as loperamide (commercially available as Imodium AD®, Imotil®, Kaodene®, Imperim®, Diamode®, QC Anti-Diarrheal®, Health Care America Anti-Diarrheal®, Leader A-D®, and Imogen®), nitazoxanide
 25 (commercially available as Alinia®) and diphenoxylate hydrochloride/atropine sulfate (commercially available as Lomotil®), anti-histamines, anti-tussives, decongestants, vitamins, and breath fresheners. Common drugs used alone or in combination for colds, pain, fever, cough, congestion, runny nose and allergies, such as acetaminophen, ibuprofen, chlorpheniramine maleate, dextromethorphan, dextromethorphan HBr, phenylephrine HCl, pseudoephedrine HCl, diphenhydramine and combinations
 30 thereof, such as dextromethorphan HBr and phenylephrine HCl (available as Triaminic®) may be included in the film compositions of the present invention.

Other actives useful herein include, but are not limited to, alcohol dependence treatment, such as acamprosate calcium (commercially available as Campral®); Allergy treatment medications, such as promethazine hydrochloride (commercially available as Phenergan®), bepotastine besilate (commercially

available as Bepreve®), hydrocodone polistirex/chlorpheniramine polistirex (commercially available as Tussionex®), cetirizine hydrochloride (commercially available as Zyrtec®), cetirizine hydrochloride/pseudoephedrine hydrochloride (commercially available as Zyrtec-D®), promethazine hydrochloride/codeine phosphate (commercially available as Phenergan® with Codeine), pemirolast (commercially available as Alamast®), fexofenadine hydrochloride (commercially available as Allegra®), meclizine hydrochloride (commercially available as Antivert®), azelastine hydrochloride (commercially available as Astelin®), nizatidine (commercially available as Axid®), desloratadine (commercially available as Clarinex®), cromolyn sodium (commercially available as Crolom®), epinastine hydrochloride (commercially available as Elestat®), azelastine hydrochloride (commercially available as Optivar®), prednisolone sodium phosphate (commercially available as Orapred ODT®), olopatadine hydrochloride (commercially available as Patanol®), ketotifen fumarate (commercially available as Zaditor®), and montelukast sodium (commercially available as Singulair®); and anti-histamines such as diphenhydramine HCl (available as Benadryl®), loratadine (available as Claritin®), astemizole (available as Hismanal®), nabumetone (available as Relafen®), diphenhydramine HCL (available as TheraFlu®) and clemastine (available as Tavist®).

Films of the present disclosure may further include Alzheimer's treatment medications, such as tacrine hydrochloride (commercially available as Cognex®), galantamine (commercially available as Razadyne®), donepezil hydrochloride (commercially available as Aricept®), rivastigmine tartrate (commercially available as Exelon®), caprylidene (commercially available as Axona®), and memantine (commercially available as Namenda®); anemia medication, such as cyanocobalamin (commercially available as Nascobal®) and ferumoxytol (commercially available as Feraheme®); anesthetics, such as antipyrine with benzocaine (commercially available as Auralgan®, Aurodex® and Auroto®); angina medication, such as amlodipine besylate (commercially available as Norvasc®), nitroglycerin (commercially available as Nitro-Bid®, Nitro-Dur®, Nitrolingual®, Nitrostat®, Transderm-Nitro®), isosorbide mononitrate (commercially available as Imdur®), and isosorbide dinitrate (commercially available as Isordil®); anti-tussives such as guaifensin; anti-Alzheimer's agents, such as nicergoline; and Ca^H-antagonists such as nifedipine (commercially available as Procardia® and Adalat®).

Actives useful in the present disclosure may also include anti-asthmatics, such as albuterol sulfate (commercially available as Proventil®), ipratropium bromide (commercially available as Atrovent®), salmeterol xinafoate (commercially available as Serevent®), zafirlukast (commercially available as Accolate®), flunisolide (commercially available as AeroBid®), metaproterenol sulfate (commercially available as Alupent®), albuterol inhalation (commercially available as Ventolin®), terbutaline sulfate (commercially available as Brethine®), formoterol (commercially available as Foradil®), cromolyn sodium (commercially available as Intal®), levalbuterol hydrochloride (commercially available as

Xopenex®), zileuton (commercially available as Zyflo®), fluticasone propionate/salmeterol (commercially available as Advair®), albuterol sulfate/triamcinolone acetonide (commercially available as Azmacort®), dimethylxanthine (commercially available as Theophylline®), and beclomethasone (commercially available as Beclovent®, Beconase®, Qvar®, Vancenase®, Vanceril®); angioedema medication, such as C1 esterase Inhibitor (human) (commercially available as Berinert®) and ecallantide (commercially available as Kalbitor®); and antibacterial medications, such as trimethoprim/sulfamethoxazole (commercially available as Bactrim®), mupirocin (commercially available as Bactroban®), metronidazole (commercially available as Flagyl®), sulfisoxazole acetyl (commercially available as Gantrisin®), bismuth subsalicylate and metronidazole/tetracycline hydrochloride (commercially available as Helidac Therapy®), nitrofurantoin (commercially available as Macrochantin®), norfloxacin (commercially available as Noroxin®), erythromycin ethylsuccinate/Sulfisoxazole acetyl (commercially available as Pediazole®), and levofloxacin (commercially available as Levaquin®).

The films of the present disclosure may further include one or more antibiotics, including amoxicillin (commercially available as Amoxil®), ampicillin (commercially available as Omnipen®, Polycillin® and Principen®), amoxicillin/clavulanate potassium (commercially available as Augmentin®), moxifloxacin hydrochloride (commercially available as Avelox®), besifloxacin (commercially available as Besivance®), clarithromycin (commercially available as Biaxin®), ceftibuten (commercially available as Cedax®), cefuroxime axetil (commercially available as Ceftin®), cefprozil (commercially available as Cefzil®), ciprofloxacin hydrochloride (commercially available as Ciloxan® and Cipro®), clindamycin phosphate (commercially available as Cleocin T®), doxycycline hyclate (commercially available as Doryx®), dirithromycin (commercially available as Dynabac®), erythromycin (commercially available as E.E.S.®, E-Mycin®, Eryc®, Ery-Tab®, Erythrocin®, and PCE®), erythromycin topical (commercially available as A/T/S®, Erycette®, T-Stat®), gemifloxacin (commercially available as Factive®), ofloxacin (commercially known as Ocuflox®, Floxin®), telithromycin (commercially available as Ketek®), lomefloxacin hydrochloride (commercially available as Maxaquin®), minocycline hydrochloride (commercially available as Minocin®), fosfomycin tromethamine (commercially available as Monurol®), penicillin with potassium (commercially available as Penicillin VK®, Veetids®), trimethoprim (commercially available as Primisol®), ciprofloxacin hydrochloride (commercially available as Proquin XR®), rifampin, isoniazid and pyrazinamide (commercially available as Rifater®), cefditoren (commercially available as Spectracef®), cefixime (commercially available as Suprax®), tetracycline (commercially available as Achromycin V® and Sumycin®), tobramycin (commercially available as Tobrex®), rifaximin (commercially available as Xifaxan®), azithromycin (commercially available as Zithromax®), azithromycin suspension

(commercially available as Zmax®), linezolid (commercially available as Zyvox®), benzoyl peroxide and clindamycin (commercially available as BenzaClin®), erythromycin and benzoyl peroxide (commercially available as Benzamycin®), dexamethasone (commercially available as Ozurdex®), ciprofloxacin and dexamethasone (commercially available as Ciprodex®), polymyxin B sulfate/neomycin

- 5 sulfate/hydrocortisone (commercially available as Cortisporin®), colistin sulfate/neomycin sulfate/hydrocortisone acetate/thonzonium bromide (commercially available as Cortisporin-TC Otic®), cephalixin hydrochloride (commercially available as Keflex®), cefdinir (commercially available as Omnicef®), and gatifloxacin (commercially available as Zymar®).

- Other useful actives include cancer treatment medications, including cyclophosphamide
- 10 (commercially available as Cytosan®), methotrexate (commercially available as Rheumatrex® and Trexal®), tamoxifen citrate (commercially available as Nolvadex®), bevacizumab (commercially available as Avastin®), everolimus (commercially available as Afinitor®), pazopanib (commercially available as Votrient®), and anastrozole (commercially available as Arimidex®); leukemia treatment, such as ofatumumab (commercially available as Arzerra®); anti-thrombotic drugs, such as antithrombin
- 15 recombinant lyophilized powder (commercially available as Atryn®), prasugrel (commercially available as Efient®); anti-coagulants, such as aspirin with extended-release dipyridamole (commercially available as Aggrenox®), warfarin sodium (commercially available as Coumadin®), dipyridamole (commercially available as Persantine®), dalteparin (commercially available as Fragmin®), danaparoid (commercially available as Orgaran®), enoxaparin (commercially available as Lovenox®), heparin (commercially
- 20 available as Hep-Lock, Hep-Pak, Hep-Pak CVC, Heparin Lock Flush), tinzaparin (commercially available as Innohep®), and clopidogrel bisulfate (commercially available as Plavix®); antiemetics, such as granisetron hydrochloride (commercially available as Kytril®) and nabilone (commercially available as Cesamet®), trimethobenzamide hydrochloride (commercially available as Tigan®), and ondansetron hydrochloride (commercially available as Zofran®); anti-fungal treatment, such as ketoconazole
- 25 (commercially available as Nizoral®), posaconazole (commercially available as Noxafil®), ciclopirox (commercially available as Penlac®), griseofulvin (commercially available as Gris-PEG®), oxiconazole nitrate (commercially available as Oxistat®), fluconazole (commercially available as Diflucan®), sertaconazole nitrate (commercially available as Ertaczo®), terbinafine hydrochloride (commercially available as Lamisil®), ciclopirox (commercially available as Loprox®), nystatin/triamcinolone acetonide
- 30 (commercially available as Mycolog-II®), econazole nitrate (commercially available as Spectazole®), itraconazole (commercially available as Sporanox®), and terconazole (commercially available as Terazol®).

Actives may further include anti-inflammatory medications, such as hydroxychloroquine sulfate (commercially available as Plaquenil®), fluticasone propionate (commercially available as Cutivate®),

canakinumab (commercially available as Llaris®), amcinonide (commercially available as Cyclocort®), methylprednisolone (commercially available as Medrol®), budesonide (commercially available as Entocort EC®), anakinra (commercially available as Kineret®), diflorasone diacetate (commercially available as Psorcon®), and etanercept (commercially available as Enbrel®); antispasmodic medication, such as phenobarbital/hyoscyamine sulfate/atropine sulfate/scopolamine hydrobromide (commercially available as Donnatal®); antiviral treatment, such as oseltamivir phosphate (commercially available as Tamiflu®); anti-parasites medication, including tinidazole (commercially available as Tindamax®); appetite treatment mediations, such as megestrol acetate (commercially available as Megace ES®), phentermine hydrochloride (commercially available as Adipex-P®), and diethylpropion hydrochloride (commercially available as Tenuate®); arthritis medications, including leflunomide (commercially available as Arava®), certolizumab pegol (commercially available as Cimzia®), diclofenac sodium (commercially available as Pennsaid®), golimumab (commercially available as Simponi®), and tocilizumab (commercially available as Actemra®); bladder control medication, such as trospium chloride (commercially available as Sanctura®), desmopressin acetate (commercially available as DDAVP®), tolterodine tartrate (commercially available as Detrol®), oxybutynin chloride (commercially available as Ditropan® or Gelnique®), darifenacin (commercially available as Enablex®), and solifenacin succinate (commercially available as VESIcare®); blood vessel constrictors, such as methylergonovine maleate (commercially available as Methergine®); plasma uric managers, such as rasburicase (commercially available as Elitek®); iron deficiency anemia medications, such as ferumoxytol (commercially available as Feraheme®); lymphoma medications, such as pralatrexate (commercially available as Folutyn®), romidepsin (commercially available as Isodax®); malaria medication, such as artemether/lumefantrine (commercially available as Coartem®); hyponatremia medication, such as tolvatpan (commercially available as Samsca®); medication for treatment of von Willebrand disease (commercially available as Wilate®); anti-hypertension medications, such as treprostinil (commercially available as Tyvaso®), tadalafil (commercially available as Adcirca®); cholesterol lowering medication, including paricalcitol (commercially available as Altocor®), pitavastatin (commercially available as Livalo®), lovastatin, niacin (commercially available as Advicor®), colestipol hydrochloride (commercially available as Colestid®), rosuvastatin calcium (commercially available as Crestor®), fluvastatin sodium (commercially available as Lescol®), atorvastatin calcium (commercially available as Lipitor®), lovastatin (commercially available as Mevacor®), niacin (commercially available as Niaspan®), pravastatin sodium (commercially available as Pravachol®), pavastatin sodium with buffered aspirin (commercially available as Pravigard PAC®), cholestyramine (commercially available as Questran®), simvastatin and niacin (commercially available as Simcor®), atenolol, chlorthalidone (commercially available as Tenoretic®), atenolol (commercially available as Tenormin®), fenofibrate

(commercially available as Tricor®), fenofibrate (commercially available as Triglide®), ezetimibe/simvastatin (commercially available as Vytorin®), colessevelam (commercially available as WelChol®), bisoprolol fumarate (commercially available as Zebeta®), ezetimibe (commercially available as Zetia®), bisoprolol fumarate/hydrochlorothiazide (commercially available as Ziac®), and simvastatin (commercially available as Zocor®).

The actives included herein may also include chronic kidney disease medication, such as paricalcitol (commercially available as Zemplar®); contraceptive agents, including etonogestrel (commercially available as Implanon®), norethindrone acetate, ethinyl estradiol (commercially available as Loestrin 24 FE®), ethinyl estradiol, norelgestromin (commercially available as Ortho Evra®), levonorgestrel (commercially available as Plan B®), levonorgestrel and ethinyl estradiol (commercially available as Preven®), levonorgestrel, ethinyl estradiol (commercially available as Seasonique®), and medroxyprogesterone acetate (commercially available as Depo-Provera®); COPD medication, such as arformoterol tartrate (commercially available as Brovana®) and ipratropium bromide, albuterol sulfate (commercially available as Combivent®); cough suppressants, including benzonatate (commercially available as Tessalon®), guaifenesin, codeine phosphate (commercially available as Tussi-Organidin NR®), and acetaminophen, codeine phosphate (commercially available as Tylenol with Codeine®); medication for the treatment of diabetes, including pioglitazone hydrochloride, metformin hydrochloride (commercially available as ACTOplus met®), bromocriptine mesylate (commercially available as Cycloset®), liraglutide (commercially available as Victoza®), saxagliptin (commercially available as Onglyza®), pioglitazone hydrochloride (commercially available as Actos®), glimepiride (commercially available as Amaryl®), rosiglitazone maleate, metformin hydrochloride (commercially available as Avandamet®), rosiglitazone maleate (commercially available as Avandaryl®), rosiglitazone maleate (commercially available as Avandia®), exenatide (commercially available as Byetta®), exenatide (commercially available as Bydureon®), chlorpropamide (commercially available as Diabinese®), pioglitazone hydrochloride, glimepiride (commercially available as Duetact®), metformin hydrochloride (commercially available as Glucophage®), glipizide (commercially available as Glucotrol®), glyburide, metformin (commercially available as Glucovance® and Fortamet®), metformin hydrochloride (commercially available as Glumetza®), sitagliptin (commercially available as Januvia®), detemir (commercially available as Levemir®), glipizide, metformin hydrochloride (commercially available as Metaglip®), glyburide (commercially available as Micronase®), repaglinide (commercially available as Prandin®), acarbose (commercially available as Precose®), nateglinide (commercially available as Starlix®), pramlintide acetate (commercially available as Symlin®), canagliflozin (commercially available as Invokana®), linagliptin (commercially available as Tradjenta®), dapagliflozin (commercially available as Farxiga®), insulin glargine (commercially available as Lantus® or Toujeo®),

insulin aspart (commercially available as Novolog®), insulin lispro, empagliflozin (commercially available as Jardiance®), and tolazamide (commercially available as Tolinase®).

Other useful actives may include digestive agents, such as sulfasalazine (commercially available as Azulfidine®), rabeprazole sodium (commercially available as AcipHex®), lubiprostone (commercially available as Amitiza®), dicyclomine hydrochloride (commercially available as Bentyl®), sucralfate (commercially available as Carafate®), lactulose (commercially available as Chronulac®), docusate (commercially available as Colace®), balsalazide disodium (commercially available as Colazal®), losartan potassium (commercially available as Cozaar®), olsalazine sodium (commercially available as Dipentum®), chlordiazepoxide hydrochloride, clidinium bromide (commercially available as Librax®), esomeprazole magnesium (commercially available as Nexium®), famotidine (commercially available as Pepcid®), lansoprazole (commercially available as Prevacid®), lansoprazole and naproxen (commercially available as Prevacid NapraPAC®), amoxicillin/clarithromycin/lansoprazole (commercially available as Prevpac®), omeprazole (commercially available as Prilosec®), pantoprazole sodium (commercially available as Protonix®), metoclopramide hydrochloride (commercially available as Reglan® or Metozolv®), cimetidine (commercially available as Tagamet®), ranitidine hydrochloride (commercially available as Zantac®), and omeprazole, sodium bicarbonate (commercially available as Zegerid®); diuretics, including spironolactone, hydrochlorothiazide (commercially available as Aldactazide®), spironolactone (commercially available as Aldactone®), bumetanide (commercially available as Bumex®), torsemide (commercially available as Demadex®), chlorothiazide (commercially available as Diuril®), furosemide (commercially available as Lasix®), metolazone (commercially available as Zaroxolyn®), and hydrochlorothiazide, triamterene (commercially available as Dyazide®).

Actives useful herein may also include treatment for emphysema, such as tiotropium bromide (commercially available as Spiriva®); fibromyalgia medication, such as milnacipran hydrochloride (commercially available as Savella®); medication for the treatment of gout, such as colchicine (commercially available as Colcris®), and febuxostat (commercially available as Uloric®); enema treatments, including aminosalicic acid (commercially available as Mesalamine® and Rowasa®); epilepsy medications, including valproic acid (commercially available as Depakene®), felbamate (commercially available as Felbatol®), lamotrigine (commercially available as Lamictal®), primidone (commercially available as Mysoline®), oxcarbazepine (commercially available as Trileptal®), zonisamide (commercially available as Zonegran®), levetiracetam (commercially available as Keppra®), and phenytoin sodium (commercially available as Dilantin®).

Actives useful herein may further include eye medications and treatment, such as dipivefrin hydrochloride (commercially available as Propine®), valganciclovir (commercially available as Valcyte®), ganciclovir ophthalmic gel (commercially available as Zirgan®); bepotastine besilate

(commercially available as Bepreve®), besifloxacin (commercially available as Besivance®), bromfenac (commercially available as Xibrom®), fluorometholone (commercially available as FML®), pilocarpine hydrochloride (commercially available as Pilocar®), cyclosporine (commercially available as Restasis®), brimonidine tartrate (commercially available as Alphagan P®), dorzolamide hydrochloride/timolol maleate (commercially available as Cosopt®), bimatoprost (commercially available as Lumigan®), timolol maleate (available as Timoptic®), travoprost (commercially available as Travatan®), latanoprost (commercially available as Xalatan®), echothiophate iodide (commercially available as Phospholine Iodide®), and ranibizumab (commercially available as Lucentis®); fluid controllers, such as acetazolamide (commercially available as Diamox®); gallstone medications, including ursodiol (commercially available as Actigall®); medication for the treatment of gingivitis, including chlorhexidine gluconate (commercially available as Peridex®); headache medications, including butalbital/codeine phosphate/aspirin/caffeine (commercially available as Fiorinal® with Codeine), naratriptan hydrochloride (commercially available as Amerge®), almotriptan (commercially available as Axert®), ergotamine tartrate/caffeine (commercially available as Cafergot®), butalbital/acetaminophen/caffeine (commercially available as Fioricet®), butalbital/aspirin/caffeine (commercially available as Fiorinal®), frovatriptan succinate (commercially available as Frova®), rizatriptan benzoate (commercially available as Maxalt®), isometheptene mucate/dichloralphenazone/acetaminophen (commercially available as Midrin®), dihydroergotamine mesylate (commercially available as Migranal®), eletriptan hydrobromide (commercially available as Relpax®), and zolmitriptan (commercially available as Zomig®); influenza medication, such as haemophilus b conjugate vaccine; tetanus toxoid conjugate (commercially available as Hiberix®); and heart treatments, including quinidine sulfate, isosorbide dinitrate/hydralazine hydrochloride (commercially available as BiDil®), digoxin (commercially available as Lanoxin®), flecainide acetate (commercially available as Tambocor®), mexiletine hydrochloride (commercially available as Mexitil®), disopyramide phosphate (commercially available as Norpace®), procainamide hydrochloride (commercially available as Procanbid®), and propafenone (commercially available as Rythmol®).

Other useful actives include hepatitis treatments, including entecavir (commercially available as Baraclude®), hepatitis B immune globulin (commercially available as HepaGam B®), and copegus/rebetol/ribasphere/vilona/virazole (commercially available as Ribavirin®); herpes treatments, including valacyclovir hydrochloride (commercially available as Valtrex®), penciclovir (commercially available as Denavir®), acyclovir (commercially available as Zovirax®), and famciclovir (commercially available as Famvir®); treatment for high blood pressure, including enalaprilat (available as Vasotec®), captopril (available as Capoten®) and lisinopril (available as Zestril®), verapamil hydrochloride (available as Calan®), ramipril (commercially available as Altace®), olmesartan medoxomil

(commercially available as Benicar®), amlodipine/atorvastatin (commercially available as Caduet®), nicardipine hydrochloride (commercially available as Cardene®), diltiazem hydrochloride (commercially available as Cardizem®), quinapril hydrochloride (commercially available as Accupril®), quinapril hydrochloride/hydrochlorothiazide (commercially available as Accuretic®), perindopril erbumine (commercially available as Aceon®), candesartan cilexetil (commercially available as Atacand®), candesartan cilexetil/hydrochlorothiazide (commercially available as Atacand HCT®), irbesartan/hydrochlorothiazide (commercially available as Avalide®), irbesartan (commercially available as Avapro®), amlodipine besylate/olmesartan medoxomil (commercially available as Azor®), levobunolol hydrochloride (commercially available as Betagan®), betaxolol hydrochloride (commercially available as Betoptic®), nebivolol (commercially available as Bystolic®), captopril/hydrochlorothiazide (commercially available as Capozide®), doxazosin mesylate (commercially available as Cardura®), clonidine hydrochloride (commercially available as Catapres®), carvedilol (commercially available as Coreg®), nadolol (commercially available as Corgard®), nadolol/bendroflumethiazide (commercially available as Corzide®), valsartan (commercially available as Diovan®), isradipine (commercially available as DynaCirc®), Guanabenz acetate. (commercially available as Wytensin ®), Guanfacine hydrochloride (commercially available as Tenex ® or Intuniv®), losartan potassium/hydrochlorothiazide (commercially available as Hyzaar®), propranolol hydrochloride (commercially available as Indera®), propranolol hydrochloride/hydrochlorothiazide (commercially available as Inderide®), eplerenone (commercially available as Inspra®), ambrisentan (commercially available as Letairis®), enalapril maleate/felodipine (commercially available as Lexxel®), metoprolol tartrate (commercially available as Lopressor®), benazepril hydrochloride (commercially available as Lotensin®), benazepril hydrochloride/hydrochlorothiazide (commercially available as Lotensin HCT®), amlodipine/benazepril hydrochloride (commercially available as Lotrel®), indapamide (commercially available as Lozol®), trandolapril (commercially available as Mavik®), telmisartan (commercially available as Micardis®), telmisartan/hydrochlorothiazide (commercially available as Micardis HCT®), prazosin hydrochloride (commercially available as Minipress®), amiloride, hydrochlorothiazide (commercially available as Moduretic®), fosinopril sodium (commercially available as ZZXT Monopril®), fosinopril sodium/hydrochlorothiazide (commercially available as Monopril-HCT®), pindolol (commercially available as Viskin®), felodipine (commercially available as Plendil®), sildenafil citrate (commercially available as Revatio®), Nisoldipine (commercially available as Sular®), trandolapril/verapamil hydrochloride (commercially available as Tarka®), aliskiren (commercially available as Tekturna®), eprosartan mesylate (commercially available as Teveten®), eprosartan mesylate/hydrochlorothiazide (commercially available as Teveten HCT®), moexipril hydrochloride/hydrochlorothiazide (commercially available as Uniretic®), moexipril hydrochloride (commercially available as Univase®), enalapril

maleate/hydrochlorothiazide (commercially available as Vaseretic®), and lisinopril/hydrochlorothiazide (commercially available as Zestoretic®).

The films of the present disclosure may include actives useful in the medication for the treatment of HIV/AIDS, such as amprenavir (commercially available as Agenerase®), tipranavir (commercially available as Aptivus®), efavirenz/emtricitabine/tenofovir (commercially available as Atripla®), lamivudine/zidovudine (commercially available as Combivir®), indinavir sulfate (commercially available as Crixivan®), lamivudine (commercially available as Epivir®), saquinavir (commercially available as Fortovase®), zalcitabine (commercially available as Hivid®), lopinavir/ritonavir (commercially available as Kaletra®), fosamprenavir calcium (commercially available as Lexiva®), ritonavir (commercially available as Norvir®), zidovudine (commercially available as Retrovir®), atazanavir sulfate (commercially available as Reyataz®), efavirenz (commercially available as Sustiva®), abacavir/lamivudine/zidovudine (commercially available as Trizivir®), didanosine (commercially available as Videx®), nelfinavir mesylate (commercially available as Viracept®), nevirapine (commercially available as Viramune®), tenofovir disoproxil fumarate (commercially available as Viread®), stavudine (commercially available as Zerit®), and abacavir sulfate (commercially available as Ziagen®); homocysteine removers, including betaine anhydrous (commercially available as Cystadane®); medications, such as insulin (commercially available as Apidra®, Humalog®, Humulin®, Iletin®, Tresiba®, and Novolin®); and HPV treatment, such as Human papillomavirus vaccine (commercially available as Gardasil®) or human papillomavirus bivalent (commercially available as Cervarix®); immunosuppressants, including cyclosporine (commercially available as Gengraf®, Neoral®, Sandimmune®, and Apo-Cyclosporine®).

Actives useful in the present disclosure may further include prolactin inhibitors, such as bromocriptine mesylate (commercially available as Parlodel®); medications for aiding in stress tests, such as regadenoson (commercially available as Lexiscan®); baldness medication, including finasteride (commercially available as Propecia® and Proscar®); pancreatitis treatment, such as gemfibrozil (commercially available as Lopid®); hormone medications, such as norethindrone acetate/ethinyl estradiol (commercially available as femHRT®), goserelin acetate (commercially available as Zoladex®), progesterone gel (commercially available as Prochieve®), progesterone (commercially available as Prometrium®), calcitonin-salmon (commercially available as Miacalcin®), calcitriol (commercially available as Rocaltrol®), synthroid (commercially available as Levothroid®, Levoxyl®, Unithroid®), testosterone (commercially available as Testopel®, Androderm®, Testoderm®, and AndroGel®); menopause medication, such as estradiol/norethindrone acetate (commercially available as Activella®), drospirenone/estradiol (commercially available as Angeliq®), estradiol/levonorgestrel (commercially available as Climara Pro®), estradiol/norethindrone acetate (commercially available as CombiPatch®),

estradiol (commercially available as Estrasorb®, Vagifem® and EstroGel®), esterified estrogens and methyltestosterone (commercially available as Estratest®), estrogen (commercially available as Alora®, Climara®, Esclim®, Estraderm®, Vivelle®, Vivelle-Dot®), estropipate (commercially available as Ogen®), conjugated estrogens (commercially available as Premarin®), and medroxyprogesterone acetate (commercially available as Provera®); menstrual medications, including leuprolide acetate (commercially available as Lupron Depot), tranexamic acid (commercially available as Lysteda®), and norethindrone acetate (commercially available as Aygestin®); and muscle relaxants, including cyclobenzaprine hydrochloride (commercially available as Flexeril®), tizanidine (commercially available as Zanaflex®), and hyoscyamine sulfate (commercially available as Levsin®).

Actives useful herein may also include osteoporosis medications, including ibrandronate sodium (commercially available as Boniva®), risedronate (commercially available as Actonel®), raloxifene hydrochloride (commercially available as Evista®, Fortical®), and alendronate sodium (commercially available as Fosamax®); ovulation enhancers, including clomiphene citrate (commercially available as Serophene®, Clomid®, Serophene®); Paget's disease treatment, such as etidronate disodium (commercially available as Didronel®); pancreatic enzyme deficiency medications, such as pancrelipase (commercially available as Pancrease® or Zenpep®); medication for the treatment of Parkinson's disease, such as pramipexole dihydrochloride (commercially available as Mirapex®), ropinirole hydrochloride (commercially available as Requip®), carbidopa/levodopa (commercially available as Sinemet CR®), carbidopa/levodopa/entacapone (commercially available as Stalevo®), selegiline hydrochloride (commercially available as Zelapar®), rasagiline (commercially available as Azilect®), entacapone (commercially available as Comtan®), and selegiline hydrochloride (commercially available as Eldepryl®); multiple sclerosis medication, such as dalfampridine (commercially available as Ampyra®) and interferon beta-1 b (commercially available as Extavia®); prostate medication, including flutamide (commercially available as Eulexin®), nilutamide (commercially available as Nilandron®), dutasteride (commercially available as Avodart®), tamsulosin hydrochloride (commercially available as Flomax®), terazosin hydrochloride (commercially available as Hytrin®), and alfuzosin hydrochloride (commercially available as UroXatral®).

Films of the present disclosure may further include psychiatric medications, including alprazolam (available as Niravam®, Xanax®), clozapin (available as Clozaril®), haloperidol (available as Haldol®), fluoxetine hydrochloride (available as Prozac®), sertraline hydrochloride (available as Zoloft®), asenapine (commercially available as Saphris®), iloperidone (commercially available as Fanapt®), paroxetine hydrochloride (available as Paxil®), aripiprazole (commercially available as Abilify®), guanfacine (commercially available as Intuniv®), Amphetamines and methamphetamines (commercially available as Adderall® and Desoxyn®), clomipramine hydrochloride (commercially available as

Anafranil®), Buspirone hydrochloride (commercially available as BuSpar®), citalopram hydrobromide (commercially available as Celexa®), duloxetine hydrochloride (commercially available as Cymbalta®), methylphenidate (commercially available as Ritalin, Daytrana®), divalproex sodium (Valproic acid) (commercially available as Depakote®), dextroamphetamine sulfate (commercially available as
5 Dexedrine®), venlafaxine hydrochloride (commercially available as Effexor®), selegiline (commercially available as Emsam®), carbamazepine (commercially available as Equetro®), lithium carbonate (commercially available as Eskalith®), fluvoxamine maleate/dexmethylphenidate hydrochloride (commercially available as Focalin®), ziprasidone hydrochloride (commercially available as Geodon®), ergoloid mesylates (commercially available as Hydergine®), escitalopram oxalate (commercially
10 available as Lexapro®), chlordiazepoxide (commercially available as Librium®), molindone hydrochloride (commercially available as Moban®), phenelzine sulfate (commercially available as Nardil®), thiothixene (commercially available as Navane®), desipramine hydrochloride (commercially available as Norpramin®), benzodiazepines (such as those available as Oxazepam®), nortriptyline hydrochloride (commercially available as Pamelor®), tranlycypromine sulfate (commercially available as
15 Parnate®), prochlorperazine, mirtazapine (commercially available as Remeron®), risperidone (commercially available as Risperdal®), quetiapine fumarate (commercially available as Seroquel®), doxepin hydrochloride (commercially available as Sinequan®), atomoxetine hydrochloride (commercially available as Strattera®), trimipramine maleate (commercially available as Surmontil®), olanzapine/fluoxetine hydrochloride (commercially available as Symbyax®), imipramine hydrochloride
20 (commercially available as Tofranil®), protriptyline hydrochloride (commercially available as Vivactil®), bupropion hydrochloride (commercially available as Wellbutrin®, Wellbutrin SR®, and Wellbutrin XR®), and olanzapine (commercially available as Zyprexa®).

Actives useful herein may also include uric acid reduction treatment, including allopurinol (commercially available as Zyloprim®); seizure medications, including gabapentin (commercially
25 available as Neurontin®), ethotoin (commercially available as Peganone®), vigabatrin (commercially available as Sabril®), and topiramate (commercially available as Topamax®); treatment for shingles, such as zoster vaccine live (commercially available as Zostavax®); skin care medications, including calcipotriene (commercially available as Dovonex®), ustekinumab (commercially available as Stelara®), televancin (commercially available as Vibativ®), isotretinoin (commercially available as Accutane®),
30 hydrocortisone/iodoquinol (commercially available as Alcortin ®), sulfacetamide sodium/sulfur (commercially available as Avar®), azelaic acid (commercially available as Azelex®, Finacea®), benzoyl peroxide (commercially available as Desquam-E®), adapalene (commercially available as Differin®), fluorouracil (commercially available as Efudex®), pimecrolimus (commercially available as Elidel®), topical erythromycin (commercially available as A/T/S®, Erycette®, T-Stat®), hydrocortisone

(commercially available as Cetacort®, Hytone®, Nutracort®), metronidazole (commercially available as MetroGel®), doxycycline (commercially available as Oracea®), tretinoin (commercially available as Retin-A® and Renova®), mequinol/tretinoin (commercially available as Solag®), acitretin (commercially available as Soriatane®), calcipotriene hydrate/betamethasone dipropionate (commercially available as Taclonex®), tazarotene (commercially available as Tazorac®), fluocinonide (commercially available as Vanos®), desonide (commercially available as Verdeso®), miconazole nitrate/Zinc oxide (commercially available as Vusion®), ketoconazole (commercially available as Xolegel®), and efalizumab (commercially available as Raptiva®).

Other actives useful herein may include Sleep disorder medications, including zaleplon (available as Sonata®), eszopiclone (available as Lunesta®), zolpidem tartrate (commercially available as Ambien®, Ambien CR®, Edluar®), lorazepam (commercially available as Ativan®), flurazepam hydrochloride (commercially available as Dalmane®), triazolam (commercially available as Halcion®), clonazepam (commercially available as Klonopin®), barbituates, such as Phenobarbital®, Modafinil (commercially available as Provigil®), temazepam (commercially available as Restoril®), ramelteon (commercially available as Rozerem®), clorazepate dipotassium (commercially available as Tranxene®), diazepam (commercially available as Valium®), quazepam (commercially available as Doral®), and estazolam (commercially available as ProSom®); smoking cessation medications, such as varenicline (commercially available as Chantix®), nicotine, such as Nicotrol®, and bupropion hydrochloride (commercially available as Zyban®); and steroids, including alclometasone dipropionate (commercially available as Aclovate®), betamethasone dipropionate (commercially available as Diprolene®), mometasone furoate (commercially available as Elocon®), fluticasone (commercially available as Flonase®, Flovent®, Flovent Diskus®, Flovent Rotadisk®), fluocinonide (commercially available as Lidex®), mometasone furoate monohydrate (commercially available as Nasonex®), desoximetasone (commercially available as Topicort®), clotrimazole/betamethasone dipropionate (commercially available as Lotrisone®), prednisolone acetate (commercially available as Pred Forte®, Prednisone®, Budesonide Pulmicort®, Rhinocort Aqua®), prednisolone sodium phosphate (commercially available as Pediapred®), desonide (commercially available as Tridesilon®), and halobetasol propionate (commercially available as Ultravate®).

Films of the present invention may further include actives useful for thyroid disease treatment, such as hormones TC and TD (commercially available as Armour Thyroid®); potassium deficiency treatment, including potassium chloride (commercially available as Micro-K®); triglycerides regulators, including omega-3-acid ethyl esters (commercially available as Omacor®); urinary medication, such as phenazopyridine hydrochloride (commercially available as Pyridium®) and methenamine, methylene blue/phenyl salicylate/benzoic acid/atropine sulfate/hyoscyamine (commercially available as Urised®);

prenatal vitamins (commercially available as Advanced Natalcare®, Materna®, Natalins®, Prenate Advance®); weight control medication, including orlistat (commercially available as Xenical®) and sibutramine hydrochloride (commercially available as Meridia®).

5 The popular H₂-antagonists which are contemplated for use herein include cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Active antacid ingredients include, but are not limited to, the following: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsilylate, calcium carbonate, calcium phosphate, citrate ion (acid or salt),
 10 amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate, magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono-octabasic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.

The active agents employed in the present invention may include allergens or antigens, such as,
 15 but not limited to, plant pollens from grasses, trees, or ragweed; animal danders, which are tiny scales shed from the skin and hair of cats and other furred animals; insects, such as house dust mites, bees, and wasps; and drugs, such as penicillin.

Examples of specific actives include but are not limited to 16-alpha fluorocestradiol, 16-alpha-gitoxin, 16-epiestriol, 17 alpha dihydroequilenin, 17 alpha estradiol, 17 beta estradiol, 17 hydroxy
 20 progesterone, 17-alpha-hydroxyvitamin D₂, 1-dodecylpyrrolidinone, 20-epi-1,25 dihydroxyvitamin D₃, 22-oxacalcitriol, 2CVV, 2'-nor-cGMP, 3-isobutyl GABA, 5-ethynyluracil, 6-FUDCA, 7-methoxytacrine, Abamectin, abanoquil, abecarnil, abiraterone, Ablukast, Ablukast Sodium, Acadesine, acamprosate, Acarbose, Acebutolol, Acecainide Hydrochloride, Aceclidine, aceclofenae, Acedapsone, Aceglutamide Aluminum, Acemannan, Acetaminophen, Acetazolamide, Acetohexamide, Acetohydroxamic Acid,
 25 acetomepregenol, Acetophenazine Maleate, Acetosulfone Sodium, Acetylcholine Chloride, Acetylcysteine, acetyl-L-carnitine, acetylmetadone, Acifran, acipimox, acitemate, Acitretin, Acivicin, Aclarubicin, aclatonium, Acodazole Hydrochloride, aconiazide, Acrisorcin, Acrivastine, Acronine, Actisomide, Actodigin, Acyclovir, acylfulvene, adafenoxate, adapalene, Adapalene, adatanserin, Adatanserin Hydrochloride, adecypenol, adecypenol, Adefovir, adelmidrol, ademetonine, Adenosine,
 30 Adinazolam, Adipheine Hydrochloride, adiposin, Adozelesin, adrafinil, Adrenalone, airbutamine, alacepril, Alamecin, Alanine, Alaproclate, alaptide, Albendazole, albolabrin, Albuterol, Albutoin, Alclofenae, Alclometasone Dipropionate, Alcloxa, aldecalmycin, Aldesleukin, Aldioxa, Alendronate Sodium, alendronic acid, alentemol, Alentemol Hydrobromide, Aletamine Hydrochloride, Aleuronium Chloride, Alexidine, alfalcidol, Alfentanil Hydrochloride, alfuzosin, Algestone Acetonide, alglucerase,

Aliflurane, alinastine, Alipamide, Allantoin, Allobarbitol, Allopurinol, ALL-TK antagonists, Alogliptin, Alonimid, alosetron, Alosetron Hydrochloride, Alovudine, Alpertine, Alpha Amylase, alpha idosone, Alpidem, Alprazolam, Alprenolol Hydrochloride, Alprenoxime Hydrochloride, Alprostadil, Alrestatin Sodium, Altanserine Tartrate, Alteplase, Althiazide, Altretamine, altromycin B, Alverine Citrate, Alvircept

5 Sudotox, Amadinone Acetate, Amantadine Hydrochloride, ambamustine, Ambomycin, Ambruticin, Ambuphylline, Ambuside, Amcinafal, Amcinonide, Amdinocillin, Amdinocillin Pivoxil, Amedalin Hydrochloride, amelometasone, Ameltolide, Amesergide, Ametantrone Acetate, amezinium metilsulfate, amfebutamone, Amfenac Sodium, Amflutizole, Amicycline, Amidephrine Mesylate, amidox, Amifloxacin, amifostine, Amikacin, Amiloride Hydrochloride, Aminacrine Hydrochloride,

10 Aminobenzoate Potassium, Aminobenzoate Sodium, Aminocaproic Acid, Aminogluthethimide, Aminohippurate Sodium, aminolevulinic acid, Aminophylline, A minorex, Aminosalicylate sodium, Aminosalicylic acid, Amiodarone, Amiprilose Hydrochloride, Amiquinsin Hydrochloride, amisulpride, Amitraz, Amitriptyline Hydrochloride, Amlexanox, amlodipine, Amobarbital Sodium, Amodiaquine, Amodiaquine Hydrochloride, Amorolfine, Amoxapine, Amoxicillin, Amphecloral, Amphetamine Sulfate,

15 Amphomycin, Amphotericin B, Ampicillin, ampiroxicam, Ampyzine Sulfate, Amquinat, Amrinone, amrinone, amrubicin, Amsacrine, amylin, amythiamicin, Anagestone Acetate, anagrelide, Anakinra, ananain, anaritide, Anaritide Acetate, Anastrozole, Anazoline Sodium, Ancrod, andrographolide, Androstenedione, angiogenesis inhibitors, Angiotensin Amide, Anidoxime, Anileridine, Anilopam Hydrochloride, Aniracetam, Aniolac, Anisotropine Methylbromide, Anistreplase, Anitrazafen, anordrin,

20 antagonist D, antagonist G, antarelix, Antazoline Phosphate, Anthelmicycin, Anthralin, Anthramycin, antiandrogen, Acedapson, Felbamate, antiestrogen, antineoplaston, Antipyrine, antisense oligonucleotides, apadoline, apafant, Apalcillin Sodium, apaxifylline, Apazone, aphidicolin glycinate, Apixifylline, Apomorphine Hydrochloride, apraclonidine, Apraclonidine Hydrochloride, Apramycin, Aprindine, Aprindine Hydrochloride, aprosulate sodium, Aprotinin, Aptazapine Maleate, aptiganel,

25 apurinic acid, apurinic acid, aranidipine, Aranotin, Arbutamine Hydrochloride, Arbutamine Hydrochloride, Arclofenin, Ardeparin Sodium, argatroban, Arginine, Argipressin Tannate, Arildone, aripiprazol, arotinolol, Arpinocid, Arteflene, Artilide Fumarate, asimadoline, aspalatone, Asparaginase, Asparic Acid, Aspartocin, asperfuran, Aspirin, aspoxicillin, Asprelin, Astemizole, Astromicin Sulfate, asulacrine, atamestane, Atenolol, atevirdine, Atipamezole, Atiprosin Maleate, Atolide, Atorvastatin

30 Calcium, Atosiban, Atovaquone, atpenin B, Atracurium Besylate, atrimustine, atrinositol, Atropine, Auranofin, aureobasidin A, Aurothioglucose, Avilamycin, Avoparcin, Avridine, Axid, axinastatin 1, axinastatin 2, axinastatin 3, Azabon, Azacitidine, Azaclozine Hydrochloride, Azaconazole, azadirachtine, Azalanstat Dihydrochloride, Azaloxan Fumarate, Azanator Maleate, Azanidazole, Azaperone, Azaribine, Azaserine, azasetron, Azatadine Maleate, Azathioprine, Azathioprine Sodium,

azatoxin, azatyrosine, azelaic acid, azelastine, azelnidipine, Azepindole, Azetepa, azimilide,
 Azithromycin, Azlocillin, Azolimine, Azosemide, Azotomycin, Aztreonam, Azumolene Sodium,
 Bacampicillin Hydrochloride, baccatin III, Bacitracin, Baclofen, bacoside A, bacoside B, bactobolamine,
 balanol, balazipone, balhimycin, balofloxacin, balsalazide, Bambermycins, bambuterol, Bamethan
 5 Sulfate, Bamifylline Hydrochloride, Bamidazole, baohuoside 1, Barmastine, barnidipine, Basifungin,
 Batanopride Hydrochloride, batebulast, Batelapine Maleate, Batimastat, beauvericin, Becanthone
 Hydrochloride, becaplermin, becliconazole, Beclomethasone Dipropionate, befloxacitane, Beinserterazide,
 Belfosdil, Belladonna, Beloxamide, Bemesepron, Bemetradin, Bemoradan, Benapryzine Hydrochloride,
 Benazepril Hydrochloride, Benazeprilat, Bendacalol Mesylate, Bendazac, Bendroflumethiazide,
 10 benflumetol, benidipine, Benorterone, Benoxaprofen, Benoxaprofen, Benoxinate Hydrochloride,
 Benperidol, Bentazepam, Bentiromide, Benurestat, Benzbromarone, Benzethonium Chloride,
 Benzetimide Hydrochloride, Benzilium Bromide, Benzindopyrine Hydrochloride, benzisoxazole,
 Benzocaine, benzochlorins, Benzocetamine Hydrochloride, Benzodepa, benzoidazoxan, Benzonatate,
 Benzoyl Peroxide, Benzoylpas Calcium, benzoylstauroporine, Benzquinamide, Benzthiazide,
 15 benztropine, Benztropine Mesylate, Benzydamine Hydrochloride, Benzylpenicilloyl Polylysine, bepridil,
 Bepridil Hydrochloride, Beractant, Beraprost, Berefrine, berlafenone, bertosamil, Berythromycin,
 besipirdine, beta-alethine, betaclamycin B, Betamethasone, betamipron, betaxolol, Betaxolol
 Hydrochloride, Bethanechol Chloride, Bethanidine Sulfate, betulinic acid, bevantolol, Bevantolol
 Hydrochloride, Bezafibrate, bFGF inhibitor, Bialamicol Hydrochloride, Biapenem, Bicalutamide,
 20 Bicifadine Hydrochloride, Biclodil Hydrochloride, Bidisomide, bifemelane, Bifonazole, bimakalim,
 bimuthil, Bindarit, Biniramycin, binospirone, bioxalomycin alpha2, Bipenamol Hydrochloride, Biperiden,
 Biphenamine Hydrochloride, biriperone, bisantrene, bisaramil, bisaziridinylspermine, bis-benzimidazole
 A, bis-benzimidazole B, bisnafide, Bisobrin Lactate, Bisoprolol, Bispyrithione Magsulfex, bistramide D,
 bistramide K, bistratene A, Bithionolate Sodium, Bitolterol Mesylate, Bivalirudin, Bizelesin, Bleomycin
 25 Sulfate, Bolandiol Dipropionate, Bolasterone, Boldenone Undecylenate, boldine, Bolenol, Bolmantalate,
 bopindolol, Bosentan, Boxidine, brefeldin, breflate, Brequinar Sodium, Bretazenil, Bretylium Tosylate,
 Brifentanil Hydrochloride, brimonidine, Brinolase, Brocresine, Brocrinat, Brofoxine, Bromadoline
 Maleate, Bromazepam, Bromchlorenone, Bromelains, bromfenac, Brominidione, Bromocriptine,
 Bromodiphenhydramine Hydrochloride, Bromoxamide, Bromperidol, Bromperidol Decanoate,
 30 Brompheniramine Maleate, Broperamole, Bropirimine, Brotizolam, Bucainide Maleate, bucindolol,
 Buclizine Hydrochloride, Bucromarone, Budesonide, budipine, budotitane, Buformin, Bumetamide,
 Bunaprolast, bunazosin, Bunolol Hydrochloride, Bupicomide, Bupivacaine Hydrochloride,
 Buprenorphine Hydrochloride, Bupropion Hydrochloride, Buramate, Buserelin Acetate, Buspirone
 Hydrochloride, Busulfan, Butabarbital, Butacetin, Butaclamol Hydrochloride, Butalbital, Butamben,

Butamirate Citrate, Butaperazine, Butaprost, Butedronate Tetrasodium, butenafine, Buterizine, buthionine
 sulfoximine, Butikacin, Butilfenin, Butirosin Sulfate, Butixirate, butixocort propionate, Butoconazole
 Nitrate, Butonate, Butopamine, Butoprozine Hydrochloride, Butorphanol, Butoxamine Hydrochloride,
 5 Butriptyline Hydrochloride, Cactinomycin, Cadexomer Iodine, Caffeine, calanolide A, Calcifediol,
 Calcipotriene, calcipotriol, Calcitonin, Calcitriol, Calcium Undecylenate, calphostin C, Calusterone,
 Cambendazole, camonagrel, camptothecin derivatives, canagliflozin, canarypox IL-2, candesartan,
 Candicidin, candoxatril, candoxatrilat, Caniglibose, Canrenoate Potassium, Canrenone, capecitabine,
 Capobenate Sodium, Capobenic Acid, Capreomycin Sulfate, capromab, capsaicin, Captopril, Capuride,
 Caracemide, Carbachol, Carbadox, Carbamazepine, Carbamide Peroxide, Carbantel Lauryl Sulfate,
 10 Carbaspirin Calcium, Carbazeran, carbazomycin C, Carbenicillin Potassium, Carbenoxolone Sodium,
 Carbetimer, carbetocin, Carbidopa, Carbidopa-Levodopa, Carbinoxamine Maleate, Carbiphen
 Hydrochloride, Carbocloral, Carbocysteine, Carbol-Fuchsin, Carboplatin, Carboprost, carbovir,
 carboxamide-amino-triazo-le, carboxyamidotriazole, carboxymethylated beta-1,3-glucan, Carbuterol
 Hydrochloride, CaRest M3, Carfentanil Citrate, Carisoprodol, Carmantadine, Carmustine, CARN 700,
 15 Camidazole, Caroxazone, carperitide, Carphenazine Maleate, Carprofen, Carsatrin Succinate, Cartazolate,
 carteolol, Carteolol Hydrochloride, cartilage derived inhibitor, Carubicin Hydrochloride, Carumonam
 Sodium, carvedilol, carvotroline, Carvotroline Hydrochloride, carzelesin, casein kinase inhibitors (ICOS),
 castanospermine, caurumonam, cebaracetam, cecropin B, Cedefingol, Cefaclor, Cefadroxil, Cefamandole,
 Cefaparole, Cefatrizine, Cefazaflur Sodium, Cefazolin, Cefbuperazone, cefcapene pivoxil, cefdaloxime
 20 pentexil tosilate, Cefdinir, cefditoren pivoxil, Cefepime, cefetamet, Cefetecol, cefixime, cefluprenam,
 Cefinenoxime Hydrochloride, Cefinetazole, cefminlox, cefodizime, Cefonicid Sodium, Cefoperazone
 Sodium, Ceforamide, cefoselis, Cefotaxime Sodium, Cefotetan, cefotiam, Cefoxitin, cefozopran,
 cefpimizole, Cefpiramide, cefpirome, cefpodoxime proxetil, cefprozil, Cefroxadine, cefsulodin,
 Ceftazidime, cefteram, ceftibuten, Ceftizoxime Sodium, ceftriaxone, Cefuroxime, celastrol, celikalim,
 25 celiprolol, cepacidiine A, Cephacetrile Sodium, Cephalixin, Cephaloglycin, Cephaloridine, Cephalothin
 Sodium, Cephapirin Sodium, Cephradine, cericlamine, cerivastatin, Ceronapril, certoparin sodium,
 Ceruletide, Cetaben Sodium, Cetalkonium Chloride, Cetamolol Hydrochloride, cetiedil, cetirizine,
 Cetophenicol, Cetraxate Hydrochloride, cetrorelix, Cetylpyridinium Chloride, Chenodiol, Chlophedianol
 Hydrochloride, Chloral Betaine, Chlorambucil, Chloramphenicol, Chlordantoin, Chlordiazepoxide,
 30 Chlorhexidine Gluconate, chlorins, Chlormadinone Acetate, chloroorienticin A, Chloroprocaine
 Hydrochloride, Chloropropamide, Chloroquine, chloroquinoxaline sulfonamide, Chlorothiazide,
 Chlorotrianisene, Chloroxine, Chloroxilenol, Chlorphenesin Carbamate, Chlorpheniramine Maleate,
 Chlorpromazine, Chlorpropamide, Chlorprothixene, Chlortetracycline Bisulfate, Chlorthalidone,
 Chlorzoxazone, Cholestyramine Resin, Chromonar Hydrochloride, cibenzoline, cicaprost, Ciclafrine

Hydrochloride, Ciclazindol, ciclesonide, cicletanine, Ciclopirox, Cicloprofen, cicloprolol, Cidofovir, Cidoxepin Hydrochloride, Cifenline, Ciglitazone, Ciladopa Hydrochloride, cilansetron, Cilastatin Sodium, Cilazapril, cilnidipine, Cilobamine Mesylate, cilobradine, Cilofungin, cilostazol, Cimaterol, Cimetidine, cimetropium bromide, Cinalukast, Cinanserin Hydrochloride, Cinepazet Maleate,

5 Cinflumide, Cingestol, cinitapride, Cinnamedrine, Cinnarizine, cinolazepam, Cinoxacin, Cinperene, Cinromide, Cintazone, Cintriamide, Cioteronel, Cipamfylline, Ciprefadol Succinate, Ciprocinnonide, Ciprofibrate, Ciprofloxacin, ciprostone, Ciramadol, Cirolemycin, cisapride, cisatracurium besilate, Ciskonazole, Cisplatin, cis-porphyrin, cistinexine, citalopram, Citenamide, citicoline, citreamicin alpha, cladribine, Clamoxiquin Hydrochloride, Clarithromycin, clausenamide, Clavulanate Potassium,

10 Clazolam, Clazolimine, clebopride, Clemastine, Clentiazem Maleate, Clidinium Bromide, clinafloxacin, Clindamycin, Clioquinol, Clioamide, Clipofen, clobazam, Clobetasol Propionate, Clobetasone Butyrate, Clodronolone Acetate, Clodanolene, Clodazon Hydrochloride, clodronic acid, Clotazimine, Clotibrate, Clotilium Phosphate, Clotestone Acetate, Clomacran Phosphate, Clomegestone Acetate, Clomethetone, clomethiazole, clomifene analogues, Clominorex, Clomiphene, Clomipramine Hydrochloride,

15 Clonazepam, Clonidine, Clonitrate, Clonixeril, Clonixin, Clopamide, Clopenthixol, Cloperidone Hydrochloride, clonidogrel, Clopimozide, Clopipazan Mesylate, Clopirac, Cloprednol, Cloprostenol Sodium, Clorazepate Dipotassium, Clorethate, Clorexolone, Cloroperone Hydrochloride, Clorprenaline Hydrochloride, Clorsulon, Clortermine Hydrochloride, Closantel, Closiramine Acetate, Clothiapine, Clothixamide Maleate Cloticasone Propionate, Clotrimazole, Cloxacillin Benzathine, Cloxyquin,

20 Clozapine, Cocaine, Coccidioidin, Codeine, Codoxime, Colchicine, colestimide, Colestipol Hydrochloride, Colestolone, Colforsin, Colfosceril Palmitate, Colistimethate Sodium, Colistin Sulfate, collismycin A, collismycin B, Colterol Mesylate, combretastatin A4, combretastatin analogue, complestatin, conagenin, Conorphone Hydrochloride, contignasterol, contortrostatin, Cormethasone Acetate, Corticorelin Ovine Triflutate, Corticotropin, Cortisone Acetate, Cortivazol, Cortodoxone,

25 cosalane, costatolide, Cosyntropin, cotinine, Coumadin, Coumermycin, crambescidin 816, Crilvastatin, crisnatol, Cromitrile Sodium, Cromolyn Sodium, Crotamiton, cryptophycin 8, cucumariosid, Cuprimyxin, curacin A, curdlan sulfate, curiosin, Cyclacillin, Cyclazocine, cyclazosin, cyclic HPMPC, Cyclindole, Cycliramine Maleate, Cyclizine, Cyclobendazole, cyclobenzaprine, cyclobut A, cyclobut G, cyclocapron, Cycloguanil Pamoate, Cycloheximide, cyclopentantraquinones, Cyclopenthiiazide, Cyclopentolate

30 Hydrochloride, Cyclophenazine Hydrochloride, Cyclophosphamide, cycloplatam, Cyclopropane, Cycloserine, cyclosin, Cyclosporine, cyclothialidine, Cyclothiazide, cyclothiazomycin, Cyheptamide, cypemycin, Cypenamine Hydrochloride, Cyprazepam, Cyproheptadine Hydrochloride, Cyprolidol Hydrochloride, cyproterone, Cyproximide, Cysteamine, Cysteine Hydrochloride, Cystine, Cytarabine, Cytarabine Hydrochloride, cytarabine ocfosfate, cytochalasin B, cytolytic factor, cytostatin, Dacarbazine,

dacliximab, dactimicin, Dactinomycin, daidzein, Daledalin Tosylate, dalfopristin, Dalteparin Sodium,
 Daltroban, Dalvastatin, danaparoid, Danazol, Dantrolene, dapagliflozin, daphlnodorin A, dapiprazole,
 dapitant, Dapoxetine Hydrochloride, Dapsone, Daptomycin, Darglitazone Sodium, darifenacin, darlucin
 A, Darodipine, darsidomine, Daunorubicin Hydrochloride, Dazadrol Maleate, Dazepinil Hydrochloride,
 5 Dazmegrel, Dazopride Fumarate, Dazoxiben Hydrochloride, Debrisoquin Sulfate, Decitabine,
 deferiprone, deflazacort, Dehydrocholic Acid, dehydridemnin B, Dehydroepiandrosterone, delapril,
 Delapril Hydrochloride, Delavirdine Mesylate, delequamine, delfaprazine, Delmadinone Acetate,
 delmopinol, delphinidin, Demecarium Bromide, Demeclocycline, Demecycline, Demoxepam,
 Denofungin, deoxyypyridinoline, Depakote, deprodone, Deprotil, depsidomycin, deramciclane, dermatan
 10 sulfate, Desciclovir, Descinolone Acetonide, Desflurane, Desipramine Hydrochloride, desirudin,
 Deslanoside, deslorelin, desmopressin, desogestrel, Desonide, Desoximetasone, desoxoamiodarone,
 Desoxycorticosterone Acetate, detajmium bitartrate, Deterenol Hydrochloride, Detirelix Acetate,
 Devazepide, Dexamethasone, Dexamisole, Dexbrompheniramine Maleate, Dexchlorpheniramine
 Maleate, Dexclamol Hydrochloride, Dexetimide, Dexfenfluramine Hydrochloride, dexifosfamide,
 15 Deximafen, Dexivacaine, dexketoprofen, dexloxiglumide, Dexmedetomidine, Dexormaplatin,
 Dexoxadrol Hydrochloride, Dexpanthenol, Dexpemedolac, Dexpropranolol Hydrochloride, Dexrazoxane,
 dextotalol, dextrin 2-sulphate, Dextroamphetamine, Dextromethorphan, Dextrophan Hydrochloride,
 Dextrothyroxine Sodium, dexverapamil, Dezaguanine, dezinamide, dezocine, Diacetolol Hydrochloride,
 Diamocaine Cyclamate, Diapamide, Diatrizoate Meglumine, Diatrizoic Acid, Diaveridine, Diazepam,
 20 Diaziquone, Diazoxide, Dibenzepin Hydrochloride, Dibenzothiophene, Dibucaine, Dichliorvos,
 Dichloralphenazone, Dichlorphenamide, Dicirenone, Diclofenac Sodium, Dicloxacin, dicranin,
 Dicumarol, Dicyclomine Hydrochloride, Didanosine, didemnin B, didox, Dienestrol, dienogest,
 Diethylcarbamazine Citrate, diethylhomospermine, diethylnorspermine, Diethylpropion Hydrochloride,
 Diethylstilbestrol, Difenoximide Hydrochloride, Difenoxin, Diflorasone Diacetate, Difloxacin
 25 Hydrochloride, Difluanine Hydrochloride, Diflucortolone, Diflumidone Sodium, Diflunisal,
 Difluprednate, Diftalone, Digitalis, Digitoxin, Digoxin, Dihexyverine Hydrochloride, dihydrexidine,
 dihydro-5-azacytidine, Dihydrocodeine Bitartrate, Dihydroergotamine Mesylate, Dihydroestosterone,
 Dihydrostreptomycin Sulfate, Dihydrotachysterol, dihydrotaxol, 9-, Dilantin, Dilevalol Hydrochloride,
 Diltiazem Hydrochloride, Dimefadane, Dimeflin Hydrochloride, Dimenhydrinate, Dimercaprol,
 30 Dimethadione, Dimethindene Maleate, Dimethisterone, dimethyl prostaglandin A1, Dimethyl Sulfoxide,
 dimethylhomospermine, dimiracetam, Dimoxamine Hydrochloride, Dinoprost, Dinoprostone, Dioxadrol
 Hydrochloride, dioxamycin, Diphenhydramine Citrate, Diphenidol, Diphenoxylate Hydrochloride,
 diphenyl spiromustine, Dipivefin Hydrochloride, Dipivefrin, dipliencyprone, diprafenone,
 dipropylhomospermine, Dipyridamole, Dipyrithione, Dipyrone, dirithromycin, discodermolide,

Disobutamide, Disofenin, Disopyramide, Disoxaril, disulfiram, Ditekiren, Divalproex Sodium,
 Dizocilpine Maleate, Dobutamine, docarpamine, Docebenone, Docetaxel, Doconazole, docosanol,
 dofetilide, dolasetron, Ebastine, ebiratide, ebrotidine, ebselen, ecabapide, ecabet, ecadotril, ecdisteron,
 echicetin, echistatin, Echothiophate Iodide, Eclanamine Maleate, Eclazolast, ecomustine, Econazole,
 5 ecteinascidin 722, edaravone, Edatrexate, edelfosine, Edifolone Acetate, edobacomab, Edoxudine,
 edrecolomab, Edrophonium Chloride, edroxprogesterone Acetate, efegatran, eflornithine, efonidipine,
 egualcen, Elantrine, eleatonin, elemene, eletriptan, elgodipine, eliprodil, Elsamitrucin, eltenae, Elucaine,
 emalkalim, emedastine, Emetine Hydrochloride, emiglitate, Emilium Tosylate, emitefur, emoctakin,
 empagliflozin, Enadoline Hydrochloride, enalapril, Enalaprilat, Enalkiren, enazadrem, Encyprate,
 10 Endralazine Mesylate, Endrysone, Enflurane, englitazone, Enilconazole, Enisoprost, Enlimomab,
 Enloplatin, Enofelast, Enolicam Sodium, Enoxacin, enoxacin, enoxaparin sodium, Enoxaparin Sodium,
 Enoximone, Enpiroline Phosphate, Enprofylline, Enpromate, entacapone, enterostatin, Enviroxime,
 Enviroxime, Ephedrine, Epicillin, Epimestrol, Epinephrine, Epinephryl Borate, Epipropidine, Epirizole,
 epirubicin, Epitetracycline Hydrochloride, Epithiazide, Epoetin Alfa, Epoetin Beta, Epoprostenol,
 15 Epoprostenol Sodium, epoxymexrenone, epristeride, Eprosartan, eptastigmine, equilenin, Equilin,
 Erbulozole, erdosteine, Ergoloid Mesylates, Ergonovine Maleate, Ergotamine Tartrate, ersentilide,
 Ersofermin, erythritol, Erythrityl Tetranitrate, Erythromycin, Esmolol Hydrochloride, Esorubicin
 Hydrochloride, Esproquin Hydrochloride, Estazolam, Estradiol, Estramustine, estramustine analogue,
 Estrazinol Hydrobromide, Estriol, Estrofurate, estrogen agonists, estrogen antagonists, Estrogens,
 20 Conjugated Estrogens, Esterified Estrone, Estropipate, esuprone, Etafedrine Hydrochloride, Etanidazole,
 etanterol, Etarotene, Etazolate Hydrochloride, Eterobarb, ethacizin, Ethacrynate Sodium, Ethacrynic
 Acid, Ethambutol Hydrochloride, Ethamivan, Ethanolamine Oleate, Ethelhorvynol, Ether, Ethinyl
 estradiol, Ethiodized Oil, Ethionamide, Ethonam Nitrate, Ethopropazine Hydrochloride, Ethosuximide,
 Ethotoin, Ethoxazene Hydrochloride, Ethybenztropine, Ethyl Chloride, Ethyl Dibunate, Ethylestrenol,
 25 Ethyndiol, Ethynerone, Ethynodiol Diacetate, Etibendazole, Etidocaine, Etidronate Disodium, Etidronic
 Acid, Etifenin, Etintidine Hydrochloride, etizolam, Etodolac, Etofenamate, Etoformin Hydrochloride,
 Etomidate, Etonogestrel, Etoperidone Hydrochloride, Etoposide, Etoprine, Etoxadrol Hydrochloride,
 Etozolin, etrabamine, Etretnate, Etryptamine Acetate, Eucatropine Hydrochloride, Eugenol, Euprocine
 Hydrochloride, eveminomicin, Exametazime, examorelin, Exaprolol Hydrochloride, exemestane,
 30 fadrozole, faeriefungin, Famciclovir, Famotidine, Fampridine, fantofarone, Fantridone Hydrochloride,
 faropenem, fasidotril, fasudil, fazarabine, fedotozine, felbamate, Felbinac, Felodipine, Felypressin,
 Fenalamide, Fenamole, Fenbendazole, Fenbufen, Fencibutirol, Fenclofenac, Fenclonine, Fenclorac,
 Fendosal, Fenestrel, Fenethylline Hydrochloride, Fenfluramine Hydrochloride, Fengabine, Fenimide,
 Fenisorex, Fenmetozole Hydrochloride, Fenmetramide, Fenobam, Fenoctimine Sulfate, fenofibrate,

fenoldopam, Fenoprofen, Fenoterol, Fempipalone, Fenprinast Hydrochloride, Fenprostalene, Fenquizone,
 fenretinide, fenspiride, Fentanyl Citrate, Fentiazac, Fenticlor, fenticonazole, Fenyripol Hydrochloride,
 fepradinol, fepifosate sodium, ferristene, ferrixan, Ferrous Sulfate, Dried, Ferumoxides, ferumoxsil,
 Fetoxyate Hydrochloride, fexofenadine, Fezolamine Fumarate, Fiacitabine, Fialuridine, Fibrinogen 1
 5 125, filgrastim, Filipin, finasteride, Flavodilol Maleate, flavopiridol, Flavoxate Hydrochloride, Flazalone,
 flecainide, flerobuterol, Fleroxacin, flesinoxan, Flestolol Sulfate, Fletazepam, flezelastine, flobufen,
 Floctafenine, flomoxef, Flordipine, florfenicol, florifenine, flosatidil, Flosequinan, Floxacillin,
 Floxuridine, fluasterone, Fluazacort, Flubanilate Hydrochloride, Flubendazole, Flucindole, Flucloronide,
 Fluconazole, Flucytosine, Fludalanine, Fludarabine Phosphate, Fludazonium Chloride, Fludeoxyglucose
 10 F 18, Fludorex, Fludrocortisone Acetate, Flufenamic Acid, Flufenisal, Flumazenil, flumecinol,
 Flumequine, Flumeridone, Flumethasone, Flumetramide, Flumezapine, Fluminorex, Flumizole,
 Flumoxonide, flunarizine, Flunidazole, Flunisolid, Flunitrazepam, Flunixin, fluocalcitriol, Fluocinolone
 Acetonide, Fluocinonide, Fluocortin Butyl, Fluocortolone, Fluorescein, fluorodaunorubicin
 hydrochloride, Fluorodopa F 18, Fluorometholone, Fluorouracil, Fluotracen Hydrochloride, Fluoxetine,
 15 Fluoxymesterone, fluparoxan, Fluperamide, Fluperolone Acetate, Fluphenazine Decanoate, flupirtine,
 Fluprednisolone, Fluproquazone, Fluprostenol Sodium, Fluquazone, Fluradoline Hydrochloride,
 Flurandrenolide, Flurazepam Hydrochloride, Flurbiprofen, Fluretofen, flurithromycin, Flurocitabine,
 Flurofamide, Flurogestone Acetate, Flurothyl, Fluoxetine, Fluspirilene, Fluticasone
 Propionate, flutrimazole, Flutroline, fluvastatin, Fluvastatin Sodium, fluvoxamine, Fluzinamide, Folic
 20 Acid, Follicle regulatory protein, Folliculostatin, Fomepizole, Fonazine Mesylate, forasartan, forfenimex,
 forfenirmex, formestane, Formocortal, formoterol, Fosarilate, Fosazepam, Foscarnet Sodium, fosfomycin,
 Fosfonet Sodium, fosinopril, Fosinoprilat, fosphenyloin, Fosquidone, Fostedil, fostriecin, fotemustine,
 Fuchsin, Basic, Fumoxicillin, Fungimycin, Furaprofen, Furazolidone, Furazolium Chloride, Furegrelate
 Sodium, Furobifen, Furodazole, Furosemide, Fusidate Sodium, Fusidic Acid, gabapentin, Gadobenate
 25 Dimeglumine, gadobenid acid, gadobutrol, Gadodiamide, gadolinium texaphyrin, Gadopentetate
 Dimeglumine, gadoteric acid, Gadoteridol, Gadoversetamide, galantamine, galdanetron, Galdanetron
 Hydrochloride, Gallamine Triethiodide, gallium nitrate, gallopamil, galocitabine, Gamfexine, gamolenic
 acid, Ganciclovir, ganirelix, gelatinase inhibitors, Gemcadiol, Gemcitabine, Gemeprost, Gemfibrozil,
 Gentamicin Sulfate, Gentian Violet, gepirone, Gestaclone, Gestodene, Gestonorone Caproate, Gestrinone,
 30 Gevotroline Hydrochloride, girisopam, glaspimod, glaucocalyxin A, Glemanserin, Gliamilide,
 Glibornuride, Glicetanile Sodium, Gliflumide, Glimepiride, Glipizide, Gloximonom, Glucagon,
 glutapyrone, glutathione inhibitors, Glutethimide, Glyburide, glycopine, glycopril, Glycopyrrolate,
 Glyhexamide, Glymidine Sodium, Glyoctamide, Glyparamide, Gold Au 198, Gonadotrinins,
 Gonadorelin, Gonadotropins, Goserelin, Gramicidin, Granisetron, grepafloxacin, Griseofulvin, Guaiapate,

Guaithylline, Guanabenz, Guanabenz Acetate, Guanadrel Sulfate, Guancydine, Guanethidine Monosulfate, Guanfacine Hydrochloride, Guanisoquin Sulfate, Guanoclor Sulfate, Guanoctine Hydrochloride, Guanoxabenz, Guanoxan Sulfate, Guanoxyfen Sulfate, Gusperimus Trihydrochloride, Halazepam, Halcinonide, halichondrin B, Halobetasol Propionate, halofantrine, Halofantrine Hydrochloride, Halofenate, Halofuginone Hydrobromide, halomon, Halopemide, Haloperidol, halopredone, Haloprogesterone, Haloprogin, Halothane, Halquinols, Hamycin, Han memopausal gonadotropins, hatomamicin, hatomarubigin A, hatomarubigin B, hatomarubigin C, hatomarubigin D, Heparin Sodium, hepsulfam, heregulin, Hetacillin, Heteronium Bromide, Hexachlorophene: Hydrogen Peroxide, Hexafluorenum Bromide, hexamethylene bisacetamide, Hexedine, Hexobendine, Hexoprenaline Sulfate, Hexylresorcinol, Histamine Phosphate, Histidine, Histoplasmin, Histrelin, Homatropine Hydrobromide, Hoquizil Hydrochloride, Human chorionic gonadotropin, Hycanthone, Hydralazine Hydrochloride, Hydralazine Polistirex, Hydrochlorothiazide, Hydrocodone Bitartrate, Hydrocortisone, Hydroflumethiazide, Hydromorphone Hydrochloride, Hydroxyamphetamine Hydrobromide, Hydroxychloroquine Sulfate, Hydroxyphenamate, Hydroxyprogesterone Caproate, Hydroxyurca, Hydroxyzine Hydrochloride, Hymecromone, Hyoscyamine, hypericin, Ibafloxacin, ibandronic acid, ibogaine, Ibopamine, ibudilast, Ibufenac, Ibuprofen, Ibutilide Fumarate, Icatibant Acetate, Ichthammol, Icotidine, idarubicin, idoxifene, Idoxuridine, idramantone, Iemefloxacin, Iesopitron, Ifetroban, Ifosfamide, Ilepeimide, illimaquinone, ilmofofosine, ilomastat, Ilonidap, iloperidone, iloprost, Imafen Hydrochloride, Imazodan Hydrochloride, imidapril, imidazenil, imidazoacridones, Imidecyl Iodine, Imidocarb Hydrochloride, Imidoline Hydrochloride, Imidurea, Imiloxan Hydrochloride, Imipenem, Imipramine Hydrochloride, imiquimod, immunostimulant peptides, Impromidine Hydrochloride, Indacrinone, Indapamide, Indecainide Hydrochloride, Indeloxazine Hydrochloride, Indigotindisulfonate Sodium, indinavir, Indocyanine Green, Indolapril Hydrochloride, Indolidan, indometacin, Indomethacin Sodium, Indoprofen, indoramin, Indorenate Hydrochloride, Indoxole, Indriline Hydrochloride, inocoterone, inogatran, inolimomab, Inositol Niacinate, Insulin, interferons, interleukins, Intrazole, Intriptyline Hydrochloride, iobenguane, Iobenzamic Acid, iobitridol, Iocarmate Meglumine, Iocarmic Acid, Iocetamic Acid, Iodamide, Iodine, Iodipamide Meglumine, Iodixanol, iodoamiloride, Iodoantipyrine I 131, Iodocholesterol I 131, iododoxorubicin, Iodohippurate Sodium I 131, Iodopyracet I 125, Iodoquinol, Iodoxamate Meglumine, Iodoxamic Acid, Ioglicic Acid, Iofetamine Hydrochloride I 123, iofratol, Ioglucol, Ioglucomide, Ioglycamic Acid, Iogulamide, Iohexol, iomeprol, Iomethin I 125, Iopamidol, Iopanoic Acid, iopentol, Iophendylate, Ioprocemic Acid, iopromide, Iopronic Acid, Iopydol, Iopydone, iopyrol, Iosefamic Acid, Ioseric Acid, Iosulamide Meglumine, Iosumetic Acid, Iotasul, Iotetric Acid, Iothalamate Sodium, Iothalamic Acid, iotriside, Iotrolan, Iotroxic Acid, Iotyrosine I 131, Ioversol, Ioxagiate Sodium, Ioxaglate Meglumine, Ioxaglic Acid, ioxilan, Ioxotrizoic Acid, ipazilide,

ipenoxazone, ipidacrine, Ipodate Calcium, ipomeanol, 4-, Ipratropium Bromide, ipriflavone, Iprindole, Iprofenin, Ipronidazole, Iproplatin, Iproxamine Hydrochloride, ipsapirone, irbesartan, irinotecan, irloxacin, iroplact, irsogladine, Irtemazole, isalsteine, Isamoxole, isbogrel, Isepamicin, isobengazole, Isobutamben, Isocarboxazid, Isoconazole, Isoetharine, isofloxythepin, Isoflupredone Acetate, Isoflurane, Isoflurophate, isohomohalicondrin B, Isoleucine, Isomazole Hydrochloride, Isomylamine Hydrochloride, Isoniazid, Isopropamide Iodide, Isopropyl Alcohol, isopropyl unoprostone, Isoproterenol Hydrochloride, Isosorbide, Isosorbide Mononitrate, Isotiquimide, Isotretinoin, Isoxepac, Isoxicam, Isoxsuprine Hydrochloride, isradipine, itameline, itasetron, Itazigrel, itopride, Itraconazole, Ivermectin, jasplakinolide, Josamycin, kahalalide F, Kalafungin, Kanamycin Sulfate, Ketamine Hydrochloride, Ketanserin, Ketazocine, Ketazolam, Kethoxal, Ketipramine Fumarate, Ketoconazole, Ketoprofen, Ketorfanol, ketorolac, Ketotifen Fumarate, Kitasamycin, Labetalol Hydrochloride, Lacidipine, lacidipine, lactitol, lactivicin, lacosamide, laennec, lafutidine, lamellarin-N triacetate, lamifiban, Lamivudine, Lamotrigine, lanoconazole, Lanoxin, lanperisone, lanreotide, Lansoprazole, latanoprost, lateritin, laurocapram, Lauryl Isoquinolinium Bromide, Lavoltidine Succinate, lazabemide, Lecimibide, leinamycin, lemildipine, leminoprazole, lenercept, Leniquinsin, lenograstim, Lenperone, lentinan sulfate, leptin, leptolstatin, lercanidipine, Lergotril, lerisetron, Letimide Hydrochloride, letrazuril, letrozole, Leucine, leucomyzin, Leuprolide Acetate, leuprolide+estrogen+progesterone, leuprorelin, Levamfetamine Succinate, levamisole, Levdobutamine Lactobionate, Leveromakalim, levetiracetam, Leveycloserine, levobetaxolol, levobunolol, levobupivacaine, levocabastine, levocarnitine, Levodopa, levodropropizine, levofloxacin, Levofuraltadone, Levoleucovorin Calcium, Levomethadyl Acetate, Levomethadyl Acetate Hydrochloride, levomoprolol, Levonantradol Hydrochloride, Levonordefrin, Levonorgestrel, Levopropoxyphene Napsylate, Levopropylcillin Potassium, levormeloxifene, Levorphanol Tartrate, levosimendan, levosulpiride, Levothyroxine Sodium, Levoadrol Hydrochloride, Lexipafant, Lexithromycin, liarozole, Libenzapril, Lidamidine Hydrochloride, Lidocaine, Lidofenin, Lidoflazine, Lifarizine, Lifibrate, Lifibrol, Linarotene, Lincomycin, linear polyamine analogue, Linogiride, Linopirdine, linotroban, linsidomine, lintitript, lintopride, Liothyronine I 125, liothyronine sodium, Liotrix, lirexapride, lisinopril, lissoclinamide 7, Lixazinone Sulfate, lobaplatin, Lobenzarit Sodium, Lobucavir, Lodelaben, Iodoxamide, Lofemizole Hydrochloride, Lofentanil Oxalate, Lofepamine Hydrochloride, Lofexidine Hydrochloride, lombricine, Lomefloxacin, lomerizine, Lometraline Hydrochloride, lometrexol, Lomofungin, Lomoxicam, Lomustine, Lonapalene, lonazolac, lonidamine, Loperamide Hydrochloride, loracarbef, Lorajmine Hydrochloride, loratadine, Lorazepam, Lorbamate, Lorcaidine Hydrochloride, Loreclezole, Loreinadol, lorglumide, Lormetazepam, Lornoxicam, lornoxicam, Lortalamine, Lorzafone, losartan, losigamone, losoxantrone, Losulazine Hydrochloride, loteprednol, lovastatin, loviride, Loxapine, Loxoribine, lubeluzole, Lucanthone Hydrochloride, Lufironil,

Lurosetron Mesylate, lurtotecan, luteinizing hormone, lurasidone, lutetium, Lutrelin Acetate, luzindole,
 Lyapolate Sodium, Lycetamine, lydicamycin, Lydimycin, Lynestrenol, Lypressin, Lysine, lysofylline,
 lysostaphin, lytic peptides, Maduramicin, Mafenide, magainin 2 amide, Magnesium Salicylate,
 Magnesium Sulfate, magnolol, maitansine, Malethamer, mallotochromene, mallotojaponin, Malotilate,
 5 malotilate, mangafodipir, manidipine, maniwamycin A, Mannitol, mannostatin A, manumycin E,
 manumycin F, mapinastine, Maprotiline, marimastat, Martek 8708, Martek 92211, Masoprocol, maspin,
 massetolide, matrilysin inhibitors, Maytansine, Mazapertine Succinate, Mazindol, Mebendazole,
 Mebeverine Hydrochloride, Mebrofenin, Mebutamate, Mecamylamine Hydrochloride, Mechlorethamine
 Hydrochloride, Meclocycline, Meclofenamate Sodium, Mecloqualone, Meclorison Dibutyrate,
 10 Medazepam Hydrochloride, Medorinone, Medrogestone, Medroxalol, Medroxyprogesterone, Medrysone,
 Meelazine Hydrochloride, Mefenamic Acid, Mefenidil, Mefenorex Hydrochloride, Mefexamide,
 Mefloquine Hydrochloride, Mefruside, Megalomicin Potassium Phosphate, Megestrol Acetate,
 Meglumine, Meglutol, Melengestrol Acetate, Melitracen Hydrochloride, Melphalan, Memotine
 Hydrochloride, Menabitan Hydrochloride, Menoctone, menogaril, Menotropins, Meobentine Sulfate,
 15 Mepartricin, Mepenzolate Bromide, Meperidine Hydrochloride, Mephentermine Sulfate, Mephenyloin,
 Mephobarbital, Mepivacaine Hydrochloride, Meprobamate, Meptazinol Hydrochloride, Mequidox,
 Meralein Sodium, merbarone, Mercaptopurine, Mercufenol Chloride, Mercury, Ammoniated, Merisoprol
 Hg 197, Meropenem, Mesalamine, Meseclazone, Mesoridazine, Mesterolone, Mestranol, Mesuprine
 Hydrochloride, Metalol Hydrochloride, Metaproterenol Polistirex, Metaraminol Bitartrate, Metaxalone,
 20 Meteneprost, meterelin, Metformin, Methacholine Chloride, Methacycline, Methadone Hydrochloride,
 Methadyl Acetate, Methalthiazide, Methamphetamine Hydrochloride, Methaqualone, Methazolamide,
 Methdilazine, Methenamine, Methenolone Acetate, Methetoin, Methicillin Sodium, Methimazole,
 methioninase, Methionine, Methisazone, Methixene Hydrochloride, Methocarbamol, Methohexital
 Sodium, Methopholine, Methotrexate, Methotrimprazine, methoxatone, Methoxyflurane, Methsuximide,
 25 Methyclothiazide, Methyl Palmoxirate, Methylatropine Nitrate, Methylbenzethonium Chloride,
 Methylidopa, Methylidopate Hydrochloride, Methylene Blue, Methylergonovine Maleate,
 methylhistamine, R-alpha, methylinosine monophosphate, Methylphenidate Hydrochloride,
 Methylprednisolone, Methyltestosterone, Methynodiol Diacetate, Methysergide, Methysergide Maleate,
 Metiamide, Metiapine, Metioprim, metipamide, Metipranolol, Metizoline Hydrochloride, Metkephamid
 30 Acetate, metoclopramide, Metocurine Iodide, Metogest, Metolazone, Metopimazine, Metoprine,
 Metoprolol, Metoquizine, metrifonate, Metrizamide, Metrizoate Sodium, Metronidazole, Meturedopa,
 Metyrapone, Metyrosine, Mexiletine Hydrochloride, Mexrenoate Potassium, Mezlocillin, mfonelic Acid,
 Mianserin Hydrochloride, mibefradil, Mibefradil Dihydrochloride, Mibolerone, michellamine B,
 Miconazole, microcolin A, Midaflur, Midazolam Hydrochloride, midodrine, mifepristone, Mifobate,

miglitol, milacemide, milameline, mildronate, Milenperone, Milipertine, milnacipran, Milrinone,
 miltefosine, Mimbane Hydrochloride, minaprine, Minaxolone, Minocromil, Minocycline, Minoxidil,
 Mioflazine Hydrochloride, miokamycin, mipragoside, mirfentanil, mirimostim, Mirincamycin
 Hydrochloride, Mirisetron Maleate, Mirtazapine, mismatched double stranded RNA, Misonidazole,
 5 Misoprostol, Mitindomide, Mitocarcin, Mitocromin, Mitogillin, mitoguazone, mitolactol, Mitomalcin,
 Mitomycin, mitonafide, Mitosper, Mitotane, mitoxantrone, mivacurium chloride, mivazerol, mixanpril,
 Mixidine, mizolastine, mizoribine, Moclobemide, modafinil, Modaline Sulfate, Modecainide, moexipril,
 mofarotene, Mofegiline Hydrochloride, mofezolac, molgramostim, Molinazone, Molindone
 Hydrochloride, Molsidomine, mometasone, Monatepil Maleate, Monensin, Monoctanoin, Montelukast
 10 Sodium, montirelin, mopidamol, moracizine, Morantel Tartrate, Moricizine, Morniflumate, Morphine
 Sulfate, Morrhuate Sodium, mosapramine, mosapride, motilide, Motretinide, Moxalactam Disodium,
 Moxazocine, moxiraprine, Moxnidazole, moxonidine, Mumps Skin Test Antigen, mustard anticancer
 agent, Muzolimine, mycaperoxide B, Mycophenolic Acid, myriaporone, Nabazenil, Nabilone, Nabitan
 Hydrochloride, Naboctate Hydrochloride, Nabumetone, N-acetyldinaline, Nadide, nadifloxacin, Nadolol,
 15 nadroparin calcium, nafadotride, nafamostat, nafarelin, Nafcillin Sodium, Nafenopin, Nafimidone
 Hydrochloride, Naflocort, Nafomine Malate, Nafoxidine Hydrochloride, Nafronyl Oxalate, Naftifine
 Hydrochloride, naftopidil, naglivan, nagrestip, Nalbuphine Hydrochloride, Naldemedine, Nalidixate
 Sodium, Nalidixic Acid, nalmefene, Nalmexone Hydrochloride, naloxone+pentazocine, Naltrexone,
 Namoxyrate, Nandrolone Phenpropionate, Nantradol Hydrochloride, Napactadine Hydrochloride,
 20 napadisilate, Napamezole Hydrochloride, napaviin, Naphazoline Hydrochloride, naphterpin, Naproxen,
 Naproxol, napsagatran, Naranol Hydrochloride, Narasin, naratriptan, nartograstim, nasaruplase,
 Natamycin, nateplase, Naxagolide Hydrochloride, Nebivolol, Nebramycin, nedaplatin, Nedocromil,
 Nefazodone Hydrochloride, Neflumozide Hydrochloride, Nefopam Hydrochloride, Nelezaprine Maleate,
 Nemazoline Hydrochloride, nemorubicin, Neomycin Palmitate, Neostigmine Bromide, neridronic acid,
 25 Netilmicin Sulfate, neutral endopeptidase, Neutramycin, Nevirapine, Nexeridine Hydrochloride, Niacin,
 Nibroxane, Nicardipine Hydrochloride, Nicergoline, Niclosamide, Nicorandil, Nicotiny Alcohol,
 Nifedipine, Nifirmerone, Nifluridide, Nifuradene, Nifuraldezone, Nifuratel, Nifuratrone, Nifurdazil,
 Nifurimide, Nifurpirinol, Nifurquinazol, Nifurthiazole, nilutamide, Nilvadipine, Nimazone, Nimodipine,
 niperotidine, niravoline, Niridazole, nisamycin, Nisbuterol Mesylate, nisin, Nisobamate, Nisoldipine,
 30 Nisoxetine, Nisterime Acetate, Nitarstone, nitazoxamide, nitecapone, Nitrafudam Hydrochloride,
 Nitralamine Hydrochloride, Nitramisole Hydrochloride, Nitrazepam, Nitrendipine, Nitrocyline,
 Nitrodan, Nitrofurantoin, Nitrofurazone, Nitroglycerin, Nitromersol, Nitromide, Nitromifene Citrate,
 Nitrous Oxide, nitroxide antioxidant, nitrullyn, Nivazol, Nivimedone Sodium, Nizatidine, Noberastine,
 Nocodazole, Nogalamycin, Nolinium Bromide, Nomifensine Maleate, Noracymethadol Hydrochloride,

Norbolethone, Norepinephrine Bitartrate, Norethindrone, Norethynodrel, Norfloxacin, Norflurane, Norgestimate, Norgestomet, Norgestrel, Nortriptyline Hydrochloride, Noscapine, Novobiocin Sodium, N-substituted benzaimides, Nufenoxole, Nylestriol, Nystatin, O6-benzylguanine, Obidoxime Chloride, Ocaperidone, Ocfentanil Hydrochloride, Ocinaclone, Octanoic Acid, Octazamide, Octenidine Hydrochloride, Octodrine, Octreotide, Octriptyline Phosphate, Ofloxacin, Oformine, okicenone, Olanzapine, oligonucleotides, olopatadine, olprinone, olsalazine, Olsalazine Sodium, Olvanil, omeprazole, onapristone, ondansetron, Ontazolast, Oocyte maturation inhibitor, Opipramol Hydrochloride, oracin, Orconazole Nitrate, Orgotein, Orlisat, Ormaplatin, Ormetoprim, Ornidazole, Orpanoxin, Orphenadrine Citrate, osaterone, otenzepad, Oxacillin Sodium, Oxagrelate, oxaliplatin, Oxamarin Hydrochloride, oxamisole, Oxamniquine, oxandrolone, Oxantel Pamoate, Oxaprotiline Hydrochloride, Oxaprozin, Oxarbazole, Oxatomide, oxaunomycin, Oxazepam, oxcarbazepine, Oxendolone, Oxethazaine, Oxetorone Fumarate, Oxfendazole, Oxfenicine, Oxibendazole, oxiconazole, Oxidopamine, Oxidronic Acid, Oxifungin Hydrochloride, Oxilorphan, Oximonam, Oximonam Sodium, Oxiperomide, oxiracetam, Oxiramide, Oxisuran, Oxmetidine Hydrochloride, oxodipine, Oxogestone Phenpropionate, Oxolinic Acid, Oxprenolol Hydrochloride, Oxtriphylline, Oxybutynin Chloride, Oxychlorosene, Oxycodone, Oxymetazoline Hydrochloride, Oxymetholone, Oxymorphone Hydrochloride, Oxyperitine, Oxyphenbutazone, Oxypurinol, Oxytetracycline, Oxytocin, ozagrel, Ozolinone, Paclitaxel, palauamine, Paldimycin, palinavir, palmitoylrhizoxin, Palmoxirate Sodium, pamaqueside, Pamatolol Sulfate, pamicogrel, Pamidronate Disodium, pamidronic acid, Panadiplon, panamesine, panaxytriol, Pancopride, Pancuronium Bromide, panipenem, pannorin, panomifene, pantethine, pantoprazole, Papaverine Hydrochloride, parabactin, Parachlorophenol, Paraldehyde, Paramethasone Acetate, Paranyline Hydrochloride, Parapenzolate Bromide, Pararosanine Pamoate, Parbendazole, Parconazole Hydrochloride, Paregoric, Pareptide Sulfate, Pargyline Hydrochloride, parnaparin sodium, Paromomycin Sulfate, Paroxetine, parthenolide, Partricin, Paulomycin, pazelliptine, Pazinaclone, Pazoxide, pazufloxacin, pefloxacin, pegaspargase, Pegorgotein, Pelanserine Hydrochloride, peldesine, Peliomycin, Pelretin, Pelrinone Hydrochloride, Pemedolac, Pemetrid Nitrate, pemirolast, Pemoline, Penamocillin, Penbutolol Sulfate, Penciclovir, Penfluridol, Penicillin G Benzathine, Penicillin G Potassium, Penicillin G Procaine, Penicillin G Sodium, Penicillin V, Penicillin V Benzathine, Penicillin V Hydrabamine, Penicillin V Potassium, Pentabamate, Pentaerythritol Tetranitrate, pentafuside, pentamidine, pentamorphone, Pentamustine, Pentapiperium Methylsulfate, Pentazocine, Pentetic Acid, Pentiapine Maleate, pentigetide, Pentisomicin, Pentizidone Sodium, Pentobarbital, Pentomone, Pentopril, pentosan, pentostatin, Pentoxifylline, Pentrinitrol, pentrozone, Peplomycin Sulfate, Pepstatin, perflubron, perfofamide, Perfosfamide, pergolide, Perhexiline Maleate, perillyl alcohol, Perindopril, perindoprilat, Perlamine, Permethrin, perospirone, Perphenazine, Phenacemide, phenaridine, phenazinomycin,

Phenazopyridine Hydrochloride, Phenbutazone Sodium Glycerate, Phencarbamide, Phencyclidine Hydrochloride, Phendimetrazine Tartrate, Phenelzine Sulfate, Phenmetrazine Hydrochloride, Phenobarbital, Phenoxybenzamine Hydrochloride, Phenprocoumon, phenserine, phensuccinal, Phensuximide, Phentermine, Phentermine Hydrochloride, phentolamine mesilate, Phentoxifylline, Phenyl

5 Aminosalicylate, phenylacetate, Phenylalanine, phenylalanyl ketoconazole, Phenylbutazone, Phenylephrine Hydrochloride, Phenylpropanolamine Hydrochloride, Phenylpropanolamine Polistirex, Phenylramidol Hydrochloride, Phenylloin, phosphatase inhibitors, Physostigmine, picenadol, picibanil, Picotrin Diolamine, picroliv, picumeterol, pidotimod, Pifamine, Pilocarpine, pilsicainide, pimagidine, Pimetine Hydrochloride, pimilprost, Pimobendan, Pimozide, Pinacidil, Pinadoline, Pindolol, pinnenol,

10 pinocebrin, Pinoxepin Hydrochloride, pioglitazone, Pipamperone, Pipazethate, pipecuronium bromide, Piperacetazine, Piperacillin Sodium, Piperamide Maleate, piperazine, Pipobroman, Piposulfan, Pipotiazine Palmitate, Pipoxolan Hydrochloride, Piprozolin, Piquindone Hydrochloride, Piquizil Hydrochloride, Piracetam, Pirandamine Hydrochloride, pirarubicin, Pirazmonam Sodium, Pirazolac, Pirbenicillin Sodium, Pirbuterol Acetate, Pirenperone, Pirenzepine Hydrochloride, piretamide,

15 Pirfenidone, Piridicillin Sodium, Piridronate Sodium, Piriprost, piritrexim, Pirlimycin Hydrochloride, pirlindole, pirmagrel, Pirmenol Hydrochloride, Pimabine, Piroctone, Pirodavis, pirodomast, Pirogliride Tartrate, Pirolate, Pirolazamide, Piroxantrone Hydrochloride, Piroxicam, Piroximone, Pirprofen, Pirquinozol, Pirsidomine, Prenylamine, Pituitary, Posterior, Pivampicillin Hydrochloride, Pivopril, Pizotyline, placetin A, platinum compounds, platinum-triamine complex, Plicamycin, Plomestane,

20 Pobilukast Edamine, Podofilox, Poisonoak Extract, Poldine Methylsulfate, Poliglusam, Polignate Sodium, Polymyxin B Sulfate, Polythiazide, Ponalrestat, Porfimer Sodium, Porfiromycin, Potassium Chloride, Potassium Iodide, Potassium Permanganate, Povidone-Iodine, Practolol, Pralidoxime Chloride, Pramiracetam Hydrochloride, Pramoxine Hydrochloride, Pranolium Chloride, Pravadoline Maleate, Pravastatin (Pravachol), Prazepam, Prazosin, Prazosin Hydrochloride, Prednazate, Prednicarbate,

25 Prednimustine, Prednisolone, Prednisone, Prednival, Pregnenolone Succinate, Prenalterol Hydrochloride, Pridefine Hydrochloride, Prifelone, Prilocalne Hydrochloride, Prilosec, Primaquine Phosphate, Primidolol, Primidone, Prinivil, Prinomide Tromethamine, Prinoxodan, Prizidilol Hydrochloride, Proadifen Hydrochloride, Probenecid, Probicromil Calcium, Probucol, Procainamide Hydrochloride, Procaine Hydrochloride, Procarbazine Hydrochloride, Procaterol Hydrochloride, Prochlorperazine,

30 Procinonide, Proclonol, Procyclidine Hydrochloride, Prodilidine Hydrochloride, Prodolic Acid, Profadol Hydrochloride, Progabide, Progesterone, Proglumide, Proinsulin Human, Proline, Prolintane Hydrochloride, Promazine Hydrochloride, Promethazine Hydrochloride, Propafenone Hydrochloride, propagermanium, Propanidid, Propantheline Bromide, Proparacaine Hydrochloride, Propatyl Nitrate, propentofylline, Propenzolate Hydrochloride, Propikacin, Propiomazine, Propionic Acid,

propionylcarnitine, L-, propiram, propiram+paracetamol, propiverine, Propofol, Propoxycaine Hydrochloride, Propoxyphene Hydrochloride, Propranolol Hydrochloride, Propulsid, propyl bis-acridone, Propylhexedrine, Propylidone, Propylthiouracil, Proquazone, Prorenoate Potassium, Proroxan Hydrochloride, Proscillaridin, Prostalene, prostratin, Protamine Sulfate, protegrin, Protirelin,

5 protosulfloxacin, Protriptyline Hydrochloride, Proxazole, Proxazole Citrate, Proxicromil, Proxorphan Tartrate, prulifloxacin, Pseudoephedrine Hydrochloride, Puromycin, purpurins, Pyrabrom, Pyrantel Pamoate, Pyrazinamide, Pyrazofurin, pyrazoloacridine, Pyridostigmine Bromide, Pyriline Maleate, Pyrimethamine, Pyrinoline, Pyrithione Sodium, Pyrithione Zinc, Pyrovalerone Hydrochloride, Pyroxamine Maleate, Pyrrocaine, Pyrroliphen Hydrochloride, Pyrrolnitrin, Pyrvinium Pamoate,

10 Quadazocine Mesylate, Quazepam, Quazinson, Quazodine, Quazolast, quetiapine, quiflapon, quinagolide, Quinaldine Blue, quinapril, Quinaprilat, Quinazolin Hydrochloride, Quinbolone, Quinctolate, Quindecamine Acetate, Quindonium Bromide, Quinelorane Hydrochloride, Quinestrol, Quinfamide, Quingestanol Acetate, Quingestron, Quinidine Gluconate, Quinilorane Hydrochloride, Quinine Sulfate, Quinpirole Hydrochloride, Quinterenol Sulfate, Quinuclidium Bromide, Quinupristin, Quipazine Maleate,

15 Rabepazole Sodium, Racephenicol, Racepinephrine, raf antagonists, Rafoxamide, Ralitoline, raloxifene, raltitrexed, ramatroban, Ramipril, Ramoplanin, ramosetron, ranelic acid, Ranimycin, Ranitidine, ranolazine, Rauwolfia Serpentina, recainam, Recainam Hydrochloride, Reclazepam, regavirumab, Regramostim, Relaxin, Relomycin, Remacemide Hydrochloride, Remifentanil Hydrochloride, Remiprostol, Remoxipride, Repirinast, Repromicin, Reproterol Hydrochloride, Reserpine, resinferatoxin,

20 Resorcinol, retelliptine demethylated, reticulon, reviparin sodium, revizinone, rhenium Re 186 etidronate, rhizoxin, Ribaminol, Ribavirin, Riboprine, ribozymes, ricasetron, Ridogrel, Rifabutin, Rifametan, Rifamexil, Rifamide, Rifampin, Rifapentine, Rifaximin, RII retinamide, rilopirox, Riluzole, rimantadine, Rimcazole Hydrochloride, Rimexolone, Rimiterol Hydrobromide, rimoprogin, riodipine, Rioprostil, Ripazepam, ripisartan, Risedronate Sodium, risedronic acid, Risocaine, Risotilide Hydrochloride,

25 rispenzepine, Risperdal, Risperidone, Ritanserine, ritipenem, Ritodrine, Ritolukast, ritonavir, rizatriptan benzoate, Rocastine Hydrochloride, Rocuronium Bromide, Rodocaine, Roflurane, Rogletimide, rohitukine, rokitamycin, Roletamicide, Rolgamidine, Rolicyprine, Rolipram, Rolitetraacycline, Rolodine, Romazarit, romurtide, Ronidazole, ropinirole, Ropitoin Hydrochloride, ropivacaine, Ropizine, roquinimex, Rosaramicin, rosiglitazone, Rosoxacin, Rotoxamine, roxaitidine, Roxarsone, roxindole,

30 roxithromycin, rubiginone B1, ruboxyl, rufloxacin, rupatidine, Rutamycin, ruzadolane, Sabeluzole, safingol, safironil, saintopin, salbutamol, R-Salcolex, Salethamide Maleate, Salicyl Alcohol, Salicylamide, Salicylate Meglumine, Salicylic Acid, Salmeterol, Salnacediin, Salsalate, sameridine, sampatrilat, Sancycline, sanfetrinem, Sanguinarium Chloride, Saperconazole, saprisartan, sapropterin, saquinavir, Sarafloxacin Hydrochloride, Saralasin Acetate, SarCNU, sarcophytol A, sargramostim,

Sarmoxicillin, Sarpicillin, sarpogrelate, saruplase, saterinone, satigrel, satumomab pendetide, Schick Test Control, Scopafungin, Scopolamine Hydrobromide, Scrazaipine Hydrochloride, Sdi 1 mimetics, Secalciferol, Secobarbital, Seelzone, Seglitide Acetate, selegiline, Selegiline Hydrochloride, Selenium Sulfide, Selenomethionine Se 75, Selfotel, sematilide, semduramicin, semotiadil, semustine, sense
 5 oligonucleotides, Sepazonium Chloride, Seperidol Hydrochloride, Seprilose, Seproxetine Hydrochloride, Seractide Acetate, Sergolexole Maleate, Serine, Sermetacin, Sermorelin Acetate, sertaconazole, sertindole, sertraline, setiptiline, Setoperone, sevirumab, sevoflurane, sezolamide, Sibopirdine, Sibutramine Hydrochloride, signal transduction inhibitors, Silandrone, silipide, silteplase, Silver Nitrate, simendan, Simtrazene, Simvastatin, Sincalide, Sinefungin, sinitrodil, sinnabidol, sipatrigine, sirolimus,
 10 Sisomicin, Sitogluside, sizofiran, sobuzoxane, Sodium Amylosulfate, Sodium Iodide I 123, Sodium Nitroprusside, Sodium Oxybate, sodium phenylacetate, Sodium Salicylate, solverol, Solypertine Tartrate, Somalapor, Somantadine Hydrochloride, somatomedin B, somatomedin C, somatrem, somatropin, Somenopor, Somidobove, sonermin, Sorbinil, Sorivudine, sotalol, Soterenol Hydrochloride, Sparfloxacin, Sparfosate Sodium, sparfosic acid, Sparsomycin, Sparteine Sulfate, Spectinomycin Hydrochloride,
 15 spicamycin D, Spiperone, Spiradoline Mesylate, Spiramycin, Spirapril Hydrochloride, Spiraprilat, Spirogermanium Hydrochloride, Spiromustine, Spironolactone, Spiroplatin, Spiroxasone, splenopentin, spongistatin 1, Sprodiamide, squalamine, Stallimycin Hydrochloride, Stannous Pyrophosphate, Stannous Sulfur Colloid, Stanozolol, Statolon, staurosporine, stavudine, Steffimycin, Stenbolone Acetate, stepronin, Stilbazium Iodide, Stilonium Iodide, stipiamide, Stiripentol, stobadine, Streptomycin Sulfate,
 20 Streptonicozid, Streptonigrin, Streptozocin, stromelysin inhibitors, Strontium Chloride Sr 89, succibun, Succimer, Succinylcholine Chloride, Sucralfate, Sucrosofate Potassium, Sudoxicam, Sufentanil, Sufotidine, Sulazepam, Sulbactam Pivoxil, Sulconazole Nitrate, Sulfabenz, Sulfabenzamide, Sulfacetamide, Sulfacytine, Sulfadiazine, Sulfadoxine, Sulfalene, Sulfamerazine, Sulfameter, Sulfamethazine, Sulfamethizole, Sulfamethoxazole, Sulfamonomethoxine, Sulfamoxole, Sulfanilate Zinc,
 25 Sulfanitran, sulfasalazine, Sulfasomizole, Sulfazamet, Sulfinalol Hydrochloride, sulfinosine, Sulfinpyrazone, Sulfisoxazole, Sulfomyxin, Sulfonterol Hydrochloride, sulfoxamine, Sulinldac, Sulmarin, Sulnidazole, Suloctidil, Sulofenur, sulopenem, Suloxifen Oxalate, Sulpiride, Sulprostone, sultamicillin, Sulthiame, sultopride, sulukast, Sumarotene, sumatriptan, Suncillin Sodium, Suproclone, Suprofen, suradista, suramin, Surfomer, Suricainide Maleate, Suritozole, Suronacrine Maleate, Suxemerid Sulfate,
 30 swainsonine, symakalim, Symclosene, Symetine Hydrochloride, synthetic glycosaminoglycans, Taciamine Hydrochloride, Tacrine Hydrochloride, Tacrolimus, Talampicillin Hydrochloride, Taleranol, Talisomycin, tallimustine, Talmetacin, Talniflumate, Talopram Hydrochloride, Talosalate, Tametraline Hydrochloride, Tamoxifen, Tampramine Fumarate, Tamsulosin Hydrochloride, Tandamine Hydrochloride, tandospirone, tapgen, taprostene, Tasosartan, tauromustine, Taxane, Taxoid, Tazadolene

Succinate, tazanolast, tazarotene, Tazifylline Hydrochloride, Tazobactam, Tazofelone, Tazolol Hydrochloride, Tebufelone, Tebuquine, Technetium Tc 99 m Bicisate, Teclozan, Tecogalan Sodium, Teeceleukin, Teflurane, Tegafur, Tegretol, Teicoplanin, telenzepine, tellurapyrylium, telmesteine, telmisartan, telomerase inhibitors, Teloxantrone Hydrochloride, Teludipine Hydrochloride, Temafloxacin Hydrochloride, Tematropium Methyl sulfate, Temazepam, Temelastine, temocapril, Temocillin, temoporfin, temozolomide, Tenidap, Teniposide, tenosal, tenoxicam, tepirindole, Tepoxalin, Teprotide, terazosin, Terbinafine, Terbutaline Sulfate, Terconazole, terfenadine, terflavoxate, terguride, Teriparatide Acetate, terlakiren, terlipressin, terodiline, Teroxalene Hydrochloride, Teroxirone, tertatolol, Tesicam, Tesimide, Testolactone, Testosterone, Tetracaine, tetrachlorodecaoxide, Tetracycline, Tetrahydrozoline Hydrochloride, Tetramisole Hydrochloride, Tetrazolast Meglumine, tetrazomine, Tetrofosmin, Tetroquinone, Tetroxoprim, Tetrydamine, thaliblastine, Thalidomide, Theofibrate, Theophylline, Thiabendazole, Thiamiprine, Thiamphenicol, Thiamylal, Thiazesim Hydrochloride, Thiazinamium Chloride, Thiethylperazine, Thimerfonate Sodium, Thimerosal, thiocoraline, thiofedrine, Thioguanine, thiomarinol, Thiopental Sodium, thioperamide, Thioridazine, Thiotepa, Thiothixene, Thiphenamil Hydrochloride, Thiphencillin Potassium, Thiram, Thozalinone, Threonine, Thrombin, thrombopoietin, thrombopoietin mimetic, thymalfasin, thymopoietin receptor agonist, thymotrinan, Thyromedan Hydrochloride, Thyroxine 1 125, Thyroxine 1 131, Tiacrilast, Tiacrilast Sodium, tiagabine, Tiamenidine, tianeptine, tiapafant, Tiapamil Hydrochloride, Tiaramide Hydrochloride, Tiazofurin, Tibenelast Sodium, Tibolone, Tibric Acid, Ticabesone Propionate, Ticarbodine, Ticarcillin Cresyl Sodium, Ticlatone, ticlopidine, Ticrynafen, tienoxolol, Tifurac Sodium, Tigemonam Dicholine, Tigestol, Tiletamine Hydrochloride, Tilidine Hydrochloride, tilisolol, tilnoprofen arbamel, Tilorone Hydrochloride, Tiludronate Disodium, tiludronic acid, Timefurone, Timobesone Acetate, Timolol, tin ethyl etiopurpurin, Tinabinal, Timidazole, Tinzaparin Sodium, Tioconazole, Tiodazosin, Tiodonium Chloride, Tioperidone Hydrochloride, Tiopinac, Tiospirone Hydrochloride, Tiotidine, tiotropium bromide, Tioxidazole, Tipentosin Hydrochloride, Tipredane, Tiprenolol Hydrochloride, Tiprinast Meglumine, Tipropidil Hydrochloride, Tiqueside, Tiquinamide Hydrochloride, tirandalydigin, Tirapazamine, tirilazad, tirofiban, tiopramide, titanocene dichloride, Tixanox, Tixocortol Pivalate, Tizanidine Hydrochloride, Tobramycin, Tocainide, Tocamphyl, Tofenacin Hydrochloride, Tolamolol, Tolazamide, Tolazoline Hydrochloride, Tolbutamide, Tolcapone, Tolciclate, Tolfamide, Tolgabide, lamotrigine, Tolimidone, Tolindate, Tolmetin, Tolnaftate, Tolpovidone 1 131, Tolpyrramide, Tolrestat, Tomelukast, Tomoxetine Hydrochloride, Tonazocine Mesylate, Topiramate, topotecan, Topotecan Hydrochloride, topsentin, Topterone, Toquizine, torasemide, toremifene, Torsemide, Tosifen, Tosufloxacin, totipotent stem cell factor, Tracazolate, trafermin, Tralonide, Tramadol Hydrochloride, Tramazoline Hydrochloride, trandolapril, Tranexamic Acid, Tranilast, Transcainide, translation inhibitors, traxanox, Trazodone

Hydrochloride, Trazodone-HCL, Trebenzomine Hydrochloride, Trefentanil Hydrochloride, Treloxinate, Trepipam Maleate, Trestolone Acetate, tretinoin, Triacetin, triacetyluridine, Triafungin, Triamcinolone, Triampyzine Sulfate, Triamterene, Triazolam, Tribenoside, tricaprilin, Tricetamide, Trichlormethiazide, trichohyalin, tricitriline, Tricitrates, Triclofenol piperazine, Triclofos Sodium, Triclonide, trientine,

5 Trifenagrel, triflavin, Triflocin, Triflubazam, Triflumidate, Trifluoperazine Hydrochloride, Trifluoperidol, Triflupromazine, Triflupromazine Hydrochloride, Trifluridine, Trihexyphenidyl Hydrochloride, Trilostane, Trimazosin Hydrochloride, trimegestone, Trimeprazine Tartrate, Trimethadione, Trimethaphan Camsylate, Trimethobenzamide Hydrochloride, Trimethoprim, Trimetozine, Trimetrexate, Trimipramine, Trimoprostil, Trimoxamine Hydrochloride, Triolein 1 125, Triolein 1 131, Trioxifene

10 Mesylate, Tripamide, Tripelennamine Hydrochloride, Triprolidine Hydrochloride, Triptorelin, Trisulfapyrimidines, Troclosen Potassium, troglitazone, Trolamine, Troleandomycin, trombodipine, trometamol, Tropanserine Hydrochloride, Tropicamide, tropine ester, tropisetron, trospectomycin, trovafloxacin, trovirdine, Tryptophan, Tuberculin, Tubocurarine Chloride, Tubulazole Hydrochloride, tucarcisol, tulobuterol, turosteride, Tybamate, tylogenin, Tyropanoate Sodium, Tyrosine, Tyrothricin,

15 tyrphostins, ubenimex, Uldazepam, Undecylenic Acid, Uracil Mustard, urapidil, Urea, Uredepa, uridine triphosphate, Urofollitropin, Urokinase, Ursodiol, valaciclovir, Valine, Valnoctamide, Valproate Sodium, Valproic Acid, valsartan, vamicamide, vanadeine, Vancomycin, vaninolol, Vapiprost Hydrochloride, Vapreotide, variolin B, Vasopressin, Vecuronium Bromide, velaresol, Velnacrine Maleate, venlafaxine, Veradoline Hydrochloride, veramine, Verapamil Hydrochloride, verdins, Verilopam Hydrochloride,

20 Verlukast, Verofylline, veroxan, verteporfin, Vesnarinone, vexibinol, Vidarabine, vigabatrin, Viloxazine Hydrochloride, Vinblastine Sulfate, vinburnine citrate, Vincosol, vinconate, Vincristine Sulfate, Vindesine, Vindesine Sulfate, Vinepidine Sulfate, Vinglycinic Sulfate, Vinleurosine Sulfate, vinorelbine, vinpocetine, vintoperol, vinxaltine, Vinzolidine Sulfate, Viprostol, Virginiamycin, Viridofulvin, Viroxime, vitaxin, Volazocine, voriconazole, vorozole, voxergolide, Warfarin Sodium, Xamoterol,

25 Xanomeline, Xanoxate Sodium, Xanthinol Niacinate, xemilofiban, Xenalipin, Xenbucin, Xilobam, ximoprofen, Xipamide, Xorphanol Mesylate, Xylamidine Tosylate, Xylazine Hydrochloride, Xylometazoline Hydrochloride, Xylose, yangambin, zabicipril, zacopride, zafirlukast, Zalcitabine, zaleplon, zalospirone, Zaltidine Hydrochloride, zaltoprofen, zanamivir, zankiren, zanoterone, Zantac, Zarirlukast, zatebradine, zatosetron, Zatosetron Maleate, zenarestat, Zenazocine Mesylate, Zeniplatin,

30 Zeranor, Zidometacin, Zidovudine, zifrosilone, Zilantel, zilascorb, zileuton, Zimeldine Hydrochloride, Zinc Undecylenate, Zindotrine, Zinoconazole Hydrochloride, Zinostatin, Zinterol Hydrochloride, Zinviroxime, ziprasidone, Zobolt, Zofenopril Calcium, Zofenoprilat, Zolamine Hydrochloride, Zolazepam Hydrochloride, zoledronic acid, Zolertine Hydrochloride, zolmitriptan, zolpidem, Zomepirac Sodium,

Zometapine, Zoniclezole Hydrochloride, Zonisamide, zopiclone, Zopolrestat, Zorbamyciin, Zorubicin Hydrochloride, zotepine, Zucapsaicin.

Another pharmaceutical active acceptable for use herein is lumateperone, as disclosed in U.S. Patent Nos. 9745300, 9708322, 7183282, 7071186, 6552017, 8648077, 8598119, 9751883, 9371324, 9315504, 9428506, 8993572, 8309722, 6713471, 8779139, 9168258, RE039680E1, 9616061, 9586960, and in U.S. Patent Publication Nos. 2017114037, 2017183350, 2015072964, 2004034015, 2017189398, 2016310502, 2015080404, the aforementioned contents of which are incorporated by reference herein in their entirety.

Further examples of antidiabetic actives include but not limited to JTT-501 (PNU-182716) (Reglitazar), AR-H039242, MCC-555 (Netoglitazone), AR-H049020 Tesaglitazar), CS-011 (CI-1037), GW-409544x, KRP-297, RG-12525, BM-15.2054, CLX-0940, CLX-0921, DRF-2189, GW-1929, GW-9820, LR-90, LY-510929, NIP-221, NIP-223, JTP-20993, LY 29311 Na, FK 614, BMS 298585, R 483, TAK 559, DRF 2725 (Ragaglitazar), L-686398, L-168049, L-805645, L-054852, Demethyl asteriquinone B1 (L-783281), L-363586, KRP-297, P32/98, CRE-16336 and EML-16257.

Erectile dysfunction therapies useful herein include, but are not limited to, agents for facilitating blood flow to the penis, and for effecting autonomic nervous activities, such as increasing parasympathetic (cholinergic) and decreasing sympathetic (adrenergic) activities. Useful actives for treatment of erectile dysfunction include, for example, but are not limited to, alprostadil, tadalafil, vardenafil, apomorphine, yohimbine hydrochloride, sildenafil citrate, and any combination thereof. In an embodiment, the active is tadalafil.

Actives or medications for the treatment of headaches and/or migraines may also be used herein. Examples of specific actives include, but are not limited to, triptans, such as eletriptan, naratriptan, rizatriptan (rizatriptan benzoate), sumatriptan, and zolmitriptan. In an embodiment, the active is rizatriptan, optionally in combination with an NSAID

In certain embodiments, the pharmaceutically active component can be epinephrine, a prodrug, analog, derivative or salt of epinephrine.

Epinephrine/Dipivefrin Dosage Profiles

In one example, a composition including a prodrug, such as a prodrug for epinephrine, can have a biodelivery profile similar to that of epinephrine administered by injection, for example, using an EpiPen.

Epinephrine or its prodrug can be present in an amount of from about 0.01 mg to about 100 mg per dosage, for example, at a 0.1 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg,

70 mg, 80 mg, 90 mg or 100 mg dosage, including greater than 0.1 mg, more than 5 mg, more than 20 mg, more than 30 mg, more than 40 mg, more than 50 mg, more than 60 mg, more than 70 mg, more than 80 mg, more than 90 mg, or less than 100 mg, less than 90 mg, less than 80 mg, less than 70 mg, less than 60 mg, less than 50 mg, less than 40 mg, less than 30 mg, less than 20 mg, less than 10 mg, or less than 5 mg, or any combination thereof.

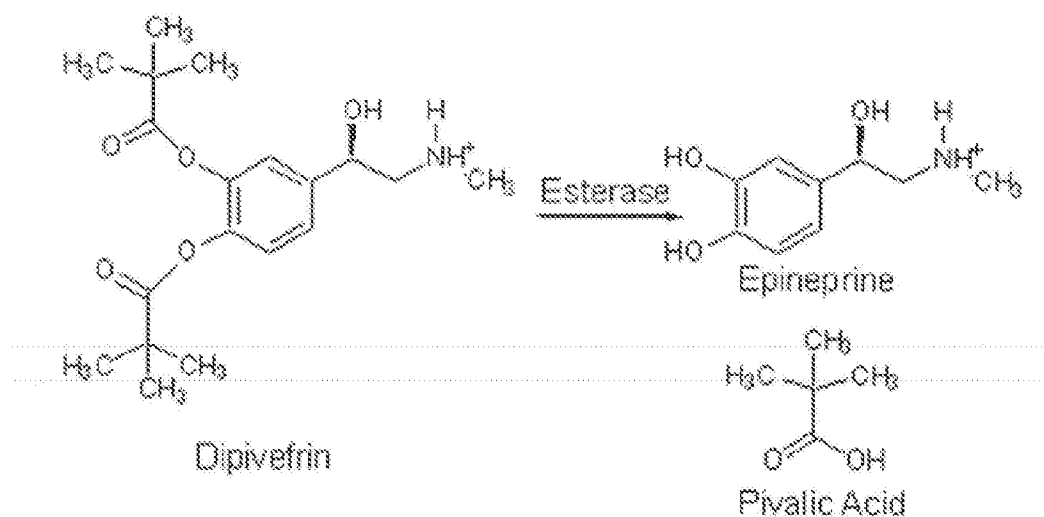
Dipivefrin can be present in an amount of from about 0.5 mg to about 100 mg per dosage, for example, at a 0.5mg, 1 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg or 100 mg dosage including greater than 1 mg, more than 5 mg, more than 20 mg, more than 30 mg, more than 40 mg, more than 50 mg, more than 60 mg, more than 70 mg, more than 80 mg, more than 90 mg, or less than 100 mg, less than 90 mg, less than 80 mg, less than 70 mg, less than 60 mg, less than 50 mg, less than 40 mg, less than 30 mg, less than 20 mg, less than 10 mg, or less than 5 mg, or any combination thereof.

Prodrug Composition

In another example, a composition (e.g., including epinephrine) can have a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent selected from: (a) an aggregation inhibitory agent; (b) a charge-modifying agent; (c) a pH control agent; (d) a degradative enzyme inhibitory agent; (e) a mucolytic or mucus clearing agent; (f) a ciliostatic agent; (g) a membrane penetration-enhancing agent selected from: (i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long chain amphipathic molecule; (vii) a hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x); (h) a modulatory agent of epithelial junction physiology; (i) a vasodilator agent; (j) a selective transport-enhancing agent; or (k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for enhanced mucosal delivery, wherein the

formulation of the compound with the transmucosal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject. The formulation can include approximately the same active pharmaceutical ingredient (API): enhancer ratio as in the other examples for epinephrine.

- 5 Administering epinephrine as a prodrug such as dipivefrin confers certain advantages. For one, dipivefrin is lipophilic and therefore has a higher permeation through a mucosa. It also has a longer plasma half-life due to higher protein binding. It is capable of sustained blood levels, and has a reduced interaction with α -receptors, therefore minimizing or eliminating unwanted or harmful vasoconstriction.



10

Dipivefrin can be delivered in sublingual film in a similar manner as with epinephrine.

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

20

Polymeric Matrix

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

The pharmaceutical composition film can include dendritic polymers which can include highly branched macromolecules with various structural architectures. The dendritic polymers can include dendrimers, dendronised polymers (dendrigrafted polymers), linear dendritic hybrids, multi-arm star polymers, or hyperbranched polymers.

Hyperbranched polymers are highly branched polymers with imperfections in their structure. However, they can be synthesized in a single step reaction which can be an advantage over other dendritic structures and are therefore suitable for bulk volume applications. The properties of these polymers apart from their globular structure are the abundant functional groups, intramolecular cavities, low viscosity and high solubility. Dendritic polymers have been used in several drug delivery applications. See, e.g., Dendrimers as Drug Carriers: Applications in Different Routes of Drug Administration. J Pharm Sci, VOL. 97, 2008, 123-143, which is incorporated by reference herein.

The dendritic polymers can have internal cavities which can encapsulate drugs. The steric hindrance caused by the highly dense polymer chains might prevent the crystallization of the drugs. Thus, branched polymers can provide additional advantages in formulating crystallizable drugs in a polymer matrix.

Examples of suitable dendritic polymers include poly(ether) based dendrons, dendrimers and hyperbranched polymers, poly(ester) based dendrons, dendrimers and hyperbranched polymers, poly(thioether) based dendrons, dendrimers and hyperbranched polymers, poly(amino acid) based dendrons dendrimers and hyperbranched polymers, poly(arylalkylene ether) based dendrons, dendrimers and hyperbranched polymers, poly(alkyleneimine) based dendrons, dendrimers and hyperbranched polymers, poly(amidoamine) based dendrons, dendrimers or hyperbranched polymers.

Other examples of hyperbranched polymers include poly(amines)s, polycarbonates, poly(ether ketone)s, polyurethanes, polycarbosilanes, polysiloxanes, poly(ester amine)s, poly(sulfone amine)s, poly(urea urethane)s and polyether polyols such as polyglycerols.

A film can be produced by a combination of at least one polymer and a solvent,
5 optionally including other components. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, or any combination thereof. In some embodiments, the solvent may be a non-polar organic solvent, such as methylene chloride. The film may be prepared by utilizing a selected casting or deposition method and a controlled drying process. For example, the film may be prepared through a controlled drying processes, which
10 include application of heat and/or radiation energy to the wet film matrix to form a visco-elastic structure, thereby controlling the uniformity of content of the film. The controlled drying processes can include air alone, heat alone or heat and air together contacting the top of the film or bottom of the film or the substrate supporting the cast or deposited or extruded film or contacting more than one surface at the same time or at different times during the drying process.
15 Some of such processes are described in more detail in U.S. Patent No. 8,765,167 and U.S. Patent No. 8,652,378, which are incorporated by reference herein. Alternatively, the films may be extruded as described in U.S. Patent Publication No. 2005/0037055 A1, which is incorporated by reference herein.

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

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

Other polymers useful for incorporation into the films include biodegradable polymers,
10 copolymers, block polymers or combinations thereof. It is understood that the term "biodegradable" is intended to include materials that chemically degrade, as opposed to materials that physically break apart (i.e., bioerodable materials). The polymers incorporated in the films can also include a combination of biodegradable or bioerodable materials. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA),
15 poly(lactic acid) (PLA), polydioxanes, polyoxalates, poly(alpha-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy)propane acid and sebacic acid, sebacic acid copolymers,
20 copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid)), copolymers of alpha-amino acids, copolymers of alpha-amino acids and caproic acid, copolymers of alpha-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates or mixtures thereof. The polymer matrix can include one, two, three,
25 four or more components.

Although a variety of different polymers may be used, it is desired to select polymers that provide mucoadhesive properties to the film, as well as a desired dissolution and/or
disintegration rate. In particular, the time period for which it is desired to maintain the film in
contact with the mucosal tissue depends on the type of pharmaceutically active component
30 contained in the composition. Some pharmaceutically active components may only require a few minutes for delivery through the mucosal tissue, whereas other pharmaceutically active

components may require up to several hours or even longer. Accordingly, in some embodiments, one or more water-soluble polymers, as described above, may be used to form the film. In other embodiments, however, it may be desirable to use combinations of water-soluble polymers and polymers that are water-swellaable, water-insoluble and/or biodegradable, as provided above. The inclusion of one or more polymers that are water-swellaable, water-insoluble and/or biodegradable may provide films with slower dissolution or disintegration rates than films formed from water-soluble polymers alone. As such, the film may adhere to the mucosal tissue for longer periods of time, such as up to several hours, which may be desirable for delivery of certain pharmaceutically active components.

10 Film Properties

Desirably, an individual film dosage of the pharmaceutical film can have a suitable thickness, and small size, which is between about 0.0625-3 inch by about 0.0625-3 inch. The film size can also be greater than 0.0625 inch, greater than 0.5 inch, greater than 1 inch, greater than 2 inches, about 3 inches, and greater than 3 inches, less than 3 inches, less than 2 inches, less than 1 inch, less than 0.5 inch, less than 0.0625 inch in at least one aspect, or greater than 0.0625 inch, greater than 0.5 inch, greater than 1 inch, greater than 2 inches, or greater than 3 inches, about 3 inches, less than 3 inches, less than 2 inches, less than 1 inch, less than 0.5 inch, less than 0.0625 inch in another aspect. The aspect ratio, including thickness, length, and width can be optimized by a person of ordinary skill in the art based on the chemical and physical properties of the polymeric matrix, the active pharmaceutical ingredient, dosage, enhancer, and other additives involved as well as the dimensions of the desired dispensing unit. The film dosage should have good adhesion when placed in the buccal cavity or in the sublingual region of the user. Further, the film dosage should disperse and dissolve, most desirably dispersing within about 1 minute and dissolving within about 3 minutes. In some embodiments, the film dosage may be capable of dispersing and dissolving between about 1 to about 30 minutes, for example, about 1 to about 20 minutes, or more than 1 minute, more than 5 minutes, more than 7 minutes, more than 10 minutes, more than 12 minutes, more than 15 minutes, more than 20 minutes, more than 30 minutes, about 30 minutes, or less than 30 minutes, less than 20 minutes, less than 15 minutes, less than 12 minutes, less than 10 minutes, less than 7 minutes, less than 5 minutes, or less than 1 minute. Sublingual dispersion times may be shorter than buccal dispersion times.

For instance, in some embodiments, the films may include polyethylene oxide alone or in combination with a second polymer component. The second polymer may be another water-soluble polymer, a water-swellaable polymer, a water-insoluble polymer, a biodegradable polymer or any combination thereof. Suitable water-soluble polymers include, without
5 limitation, any of those provided above. In some embodiments, the water-soluble polymer may include hydrophilic cellulosic polymers, such as hydroxypropyl cellulose and/or hydroxypropylmethyl cellulose. In some embodiments, one or more water-swellaable, water-insoluble and/or biodegradable polymers also may be included in the polyethylene oxide-based film. Any of the water-swellaable, water-insoluble or biodegradable polymers provided above
10 may be employed. The second polymer component may be employed in amounts of about 0% to about 80% by weight in the polymer component, more specifically about 30% to about 70% by weight, and even more specifically about 40% to about 60% by weight, including greater than 5%, greater than 10%, greater than 15%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, and greater than 70%, about 70%, less than 70%, less than
15 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10% or less than 5% by weight.

Steric Hindrance

Steric hindrance is the slowing of chemical reactions due to steric bulk. It is usually manifested in intermolecular reactions such as enzymatic reactions. Steric hindrance is often
20 exploited to control selectivity, such as slowing unwanted side-reactions. In pharmacology, steric effects determine how and at what rate a drug will interact with its target bio-molecules. The design of a prodrug needs to account for steric hindrance resulting from the prodrug substituents and its interactions with respective enzymes, including hydrolases, esterases and amidases for example. In certain embodiments, one or more of these enzymes can be endogenous. In other
25 embodiments, one or more of these enzymes can be exogenous. Stereospecific nucleophilic attack on substituted carbon atoms is a simple and versatile way to construct stereocenter next to heteroatoms with overall inversion of stereochemistry. A tertiary group adjacent to the ester unexpectedly impedes hydrolysis more when compared to non-tertiary groups.

Additives

Additives may be included in the films. Examples of classes of additives include preservatives, antimicrobials, excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers, anti-tacking agents, anti-static agents and mixtures thereof. These additives may be added with the pharmaceutically active component(s). As used herein, the term “stabilizer” means an excipient capable of preventing aggregation or other physical degradation, as well as chemical degradation, of the active pharmaceutical ingredient, another excipient, or the combination thereof.

Stabilizers may also be classified as antioxidants, sequestrants, pH modifiers, emulsifiers and/or surfactants, or UV stabilizers.

Antioxidants (i.e., pharmaceutically compatible compound(s) or composition(s) that decelerates, inhibits, interrupts and/or stops oxidation processes) include, in particular, the following substances: tocopherols and the esters thereof, sesamol of sesame oil, coniferyl benzoate of benzoin resin, nordihydroguaietic resin and nordihydroguaiaretic acid (NDGA), gallates (among others, methyl, ethyl, propyl, amyl, butyl, lauryl gallates), butylated hydroxyanisole (BHA/BHT, also butyl-p-cresol); ascorbic acid and salts and esters thereof (for example, ascorbyl palmitate), erythorbic acid (isoascorbic acid) and salts and esters thereof, monothioglycerol, sodium formaldehyde sulfoxylate, sodium metabisulfite, sodium bisulfite, sodium sulfite, potassium metabisulfite, butylated hydroxyanisole, butylated hydroxytoluene (BHT), propionic acid. Typical antioxidants are tocopherol such as, for example, α -tocopherol and the esters thereof, butylated hydroxytoluene and butylated hydroxyanisole. The terms "tocopherol" also includes esters of tocopherol. A known tocopherol is α -tocopherol. The term “ α -tocopherol” includes esters of α -tocopherol (for example, α -tocopherol acetate).

Sequestrants (i.e., any compounds which can engage in host-guest complex formation with another compound, such as the active ingredient or another excipient; also referred to as a sequestering agent) include calcium chloride, calcium disodium ethylene diamine tetra-acetate, glucono delta-lactone, sodium gluconate, potassium gluconate, sodium tripolyphosphate, sodium hexametaphosphate, and combinations thereof. Sequestrants also include cyclic oligosaccharides,

such as cyclodextrins, cyclomannins (5 or more α -D-mannopyranose units linked at the 1,4 positions by α linkages), cyclogalactins (5 or more β -D-galactopyranose units linked at the 1,4 positions by β linkages), cycloaltrins (5 or more α -D-altropyranose units linked at the 1,4 positions by α linkages), and combinations thereof.

5 pH modifiers or stabilizers include acids (e.g., tartaric acid, citric acid, lactic acid, fumaric acid, phosphoric acid, ascorbic acid, acetic acid, succinic acid, adipic acid and maleic acid), acidic amino acids (e.g., glutamic acid, aspartic acid, etc.), inorganic salts (alkali metal salt, alkaline earth metal salt, ammonium salt, etc.) of such acidic substances, a salt of such acidic substance with an organic base (e.g., basic amino acid such as lysine, arginine and the like, meglumine and the like),
 10 and a solvate (e.g., hydrate) thereof. Other examples of pH modifiers include silicified microcrystalline cellulose, magnesium aluminometasilicate, calcium salts of phosphoric acid (e.g., calcium hydrogen phosphate anhydrous or hydrate, calcium, sodium or potassium carbonate or hydrogencarbonate and calcium lactate or mixtures thereof), sodium and/or calcium salts of carboxymethyl cellulose, cross-linked carboxymethylcellulose (e.g., croscarmellose sodium
 15 and/or calcium), polacrilin potassium, sodium and or/calcium alginate, docusate sodium, magnesium calcium, aluminium or zinc stearate, magnesium palmitate and magnesium oleate, sodium stearyl fumarate, and combinations thereof.

Examples of emulsifiers and/or surfactants include poloxamers or pluronics, polyethylene glycols, polyethylene glycol monostearate, polysorbates, sodium lauryl sulfate, polyethoxylated
 20 and hydrogenated castor oil, alkyl polyoside, a grafted water soluble protein on a hydrophobic backbone, lecithin, glyceryl monostearate, glyceryl monostearate/polyoxyethylene stearate, ketostearyl alcohol/sodium lauryl sulfate, carbomer, phospholipids, (C₁₀-C₂₀)-alkyl and alkylene carboxylates, alkyl ether carboxylates, fatty alcohol sulfates, fatty alcohol ether sulfates, alkylamide sulfates and sulfonates, fatty acid alkylamide polyglycol ether sulfates,
 25 alkanesulfonates and hydroxyalkanesulfonates, olefinsulfonates, acyl esters of isethionates, α -sulfo fatty acid esters, alkylbenzenesulfonates, alkylphenol glycol ether sulfonates, sulfosuccinates, sulfosuccinic monoesters and diesters, fatty alcohol ether phosphates, protein/fatty acid condensation products, alkyl monoglyceride sulfates and sulfonates, alkylglyceride ether sulfonates, fatty acid methyltaurides, fatty acid sarcosinates, sulforicinoleates,
 30 and acylglutamates, quaternary ammonium salts (e.g., di-(C₁₀-C₂₄)-alkyl-dimethylammonium chloride or bromide), (C₁₀-C₂₄)-alkyl-dimethylethylammonium chloride or bromide, (C₁₀-C₂₄)-

alkyl-trimethylammonium chloride or bromide (e.g., cetyltrimethylammonium chloride or bromide), (C₁₀-C₂₄)-alkyl-dimethylbenzylammonium chloride or bromide (e.g., (C₁₂-C₁₈)-alkyl-dimethylbenzylammonium chloride), N-(C₁₀-C₁₈)-alkyl-pyridinium chloride or bromide (e.g., N-(C₁₂-C₁₆)-alkyl-pyridinium chloride or bromide), N-(C₁₀-C₁₈)-alkyl-isoquinolinium
 5 chloride, bromide or monoalkyl sulfate, N-(C₁₂-C₁₈)-alkyl-polyoxyaminoformylmethylpyridinium chloride, N-(C₁₂-C₁₈)-alkyl-N-methylmorpholinium chloride, bromide or monoalkyl sulfate, N-(C₁₂-C₁₈)-alkyl-N-ethylmorpholinium chloride, bromide or monoalkyl sulfate, (C₁₆-C₁₈)-alkyl-pentaoxethylammonium chloride, diisobutylphenoxyethoxyethyl dimethylbenzylammonium chloride, salts of N,N-di-
 10 ethylaminoethylstearylamine and -oleylamine with hydrochloric acid, acetic acid, lactic acid, citric acid, phosphoric acid, N-acylaminoethyl-N,N-diethyl-N-methylammonium chloride, bromide or monoalkyl sulfate, and N-acylaminoethyl-N,N-diethyl-N-benzylammonium chloride, bromide or monoalkyl sulfate (in the foregoing, "acyl" standing for, e.g., stearyl or oleyl), and combinations thereof.

15 Examples of UV stabilizers include UV absorbers (e.g., benzophenones), UV quenchers (i.e., any compound that dissipates UV energy as heat, rather than allowing the energy to have a degradation effect), scavengers (i.e., any compound that eliminates free radicals resulting from exposure to UV radiation), and combinations thereof.

In other embodiments, stabilizers include ascorbyl palmitate, ascorbic acid, alpha
 20 tocopherol, butylated hydroxytoluene, butylated hydroxyanisole, cysteine HCl, citric acid, ethylenediamine tetra acetic acid (EDTA), methionine, sodium citrate, sodium ascorbate, sodium thiosulfate, sodium metabisulfite, sodium bisulfite, propyl gallate, glutathione, thioglycerol, singlet oxygen quenchers, hydroxyl radical scavengers, hydroperoxide removing agents, reducing agents, metal chelators, detergents, chaotropes, and combinations thereof. "Singlet oxygen
 25 quenchers" include, but are not limited to, alkyl imidazoles (e.g., histidine, L-carnosine, histamine, imidazole 4-acetic acid), indoles (e.g., tryptophan and derivatives thereof, such as N-acetyl-5-methoxytryptamine, N-acetylserotonin, 6-methoxy-1,2,3,4-tetrahydro-beta-carboline), sulfur-containing amino acids (e.g., methionine, ethionine, djenkolic acid, lanthionine, N-formyl methionine, felinine, S-allyl cysteine, S-aminoethyl-L-cysteine), phenolic compounds (e.g.,
 30 tyrosine and derivatives thereof), aromatic acids (e.g., ascorbate, salicylic acid, and derivatives thereof), azide (e.g., sodium azide), tocopherol and related vitamin E derivatives, and carotene and

related vitamin A derivatives. “Hydroxyl radical scavengers” include, but are not limited to azide, dimethyl sulfoxide, histidine, mannitol, sucrose, glucose, salicylate, and L-cysteine. “Hydroperoxide removing agents” include, but are not limited to catalase, pyruvate, glutathione, and glutathione peroxidases. “Reducing agents” include, but are not limited to, cysteine and mercaptoethylene. “Metal chelators” include, but are not limited to, EDTA, EGTA, o-phenanthroline, and citrate. “Detergents” include, but are not limited to, SDS and sodium lauroyl sarcosyl. “Chaotropes” include, but are not limited to guanidinium hydrochloride, isothiocyanate, urea, and formamide. As discussed herein, stabilizers can be present in 0.0001%-50% by weight, including greater than 0.0001%, greater than 0.001%, greater than 0.01%, greater than 0.1%, greater than 1%, greater than 5%, greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, less than 1%, less than 0.1%, less than 0.01%, less than 0.001%, or less than 0.0001% by weight.

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

methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; or other similar polymers.

Stabilizers can include nanoparticulate stabilizers, such as a dispersant layer around a nanoparticulate surface. *See, e.g.*, Langmuir 2007, (23)3, 1081-1090, December 20, 2006,

5 <https://doi.org/10.1021/la062042s>. Stabilizers can include stabilizer ligands, e.g., monomers

bearing functional groups that can get chemisorbed on nanoparticles to form polymerizable

monolayers. *See, e.g.*, Jadhav et al <https://doi.org/10.1002/ppsc.201400074>. Stabilizers can

include surface stabilizers. *See, e.g.*, U.S. Pat. No. 6428814 and Japanese Pat. JP 4598399B2.

Surface stabilizers can include tyloxapol (U.S. Pat. No. 5,429,824), polyalkylene block

10 copolymers (U.S. Pat. No. 5,565,188), sulfated non-ionic block copolymers (U.S. Pat. No.

5,569,448), high molecular weight, linear, poly(ethylene oxide) polymers (U.S. Pat. No.

5,580,579), butylene oxide-ethylene oxide block copolymers (U.S. Pat. No. 5,587,143),

hydroxypropyl cellulose (U.S. Pat. No. 5,591,456), and sugar based surface stabilizers (U.S. Pat.

No. 5,622,938). Stabilizers can include peptide stabilizers. *See, e.g.*, WO2006097748A2.

15 Stabilizers can include for example, L-cysteine hydrochloride, glycine hydrochloride, malic acid,

sodium metabisulfite, citric acid, tartaric acid, and L-cystine dihydrochloride. *See, e.g.*, U.S.

Pat. 6,153,223. Stabilizers can include natural compounds. Stabilizers can include synthetic

compounds. Stabilizers can include a blend of one of more compounds or categories of

compounds described above. Stabilizers can be function to protect the metabolism of a prodrug

20 until a desired time or until it reaches a specific target, tissue or environment.

The additional components can range up to about 80%, desirably about 0.005% to 50% and more desirably within the range of 1% to 20% based on the weight of all composition

components, including greater than 1%, greater than 5%, greater than 10%, greater than 20%,

greater than 30%, greater than 40%, greater than 50%, greater than 60%, greater than 70%, about

25 80%, greater than 80%, less than 80%, less than 70%, less than 60%, less than 50%, less than

40%, less than 30%, less than 20%, less than 10%, less than 5%, about 3%, or less than 1%.

Other additives can include anti-tacking, flow agents and opacifiers, such as the oxides of

magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.005%

to about 5% by weight and desirably about 0.02% to about 2% based on the weight of all film

30 components, including greater than 0.02%, greater than 0.2%, greater than 0.5%, greater than

1%, greater than 1.5%, greater than 2%, greater than 4%, about 5%, greater than 5%, less than 4%, less than 2%, less than 1%, less than 0.5%, less than 0.2%, or less than 0.02%.

In certain embodiments, the composition can include plasticizers, which can include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-
5 propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sugar alcohols sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, phytoextracts, fatty acid esters, fatty acids, oils and the like, added in concentrations ranging from about 0.1% to about 40%, and desirably ranging from about 0.5% to about 20% based on the weight of the
10 composition including greater than 0.5%, greater than 1%, greater than 1.5%, greater than 2%, greater than 4%, greater than 5%, greater than 10%, greater than 15%, about 20%, greater than 20%, less than 20%, less than 15%, less than 10%, less than 5%, less than 4%, less than 2%, less than 1%, or less than 0.5%. There may further be added compounds to improve the texture properties of the film material such as animal or vegetable fats, desirably in their hydrogenated
15 form. The composition can also include compounds to improve the textural properties of the product. Other ingredients can include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, natural gums, pregelatinized starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, or
20 polyvinylalcohols.

Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or
25 instable pharmaceutically active components may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly, the formation of the inclusion complex permits very insoluble and/or unstable pharmaceutically active components to be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered
30 well within the scope of the present invention.

Suitable coloring agents include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide. Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides of iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, including greater than 0.001%, greater than 0.01%, greater than 0.1%, greater than 0.5%, greater than 1%, greater than 2%, greater than 5%, about 10%, greater than 10%, less than 10%, less than 5%, less than 2%, less than 1%, less than 0.5%, less than 0.1%, less than 0.01%, or less than 0.001%, based on the weight of all the components.

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

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

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

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

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

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

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

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

The residence time of the composition depends on the erosion rate of the water erodible polymers used in the formulation and their respective concentrations. The erosion rate may be adjusted, for example, by mixing together components with different solubility characteristics or chemically different polymers, such as hydroxyethyl cellulose and hydroxypropyl cellulose; by using different molecular weight grades of the same polymer, such as mixing low and medium molecular weight hydroxyethyl cellulose; by using excipients or plasticizers of various lipophilic values or water solubility characteristics (including essentially insoluble components); by using water soluble organic and inorganic salts; by using crosslinking agents such as glyoxal with polymers such as hydroxyethyl cellulose for partial crosslinking; or by post-treatment irradiation or curing, which may alter the physical state of the film, including its crystallinity or phase transition, once obtained. These strategies might be employed alone or in combination in order to modify the erosion kinetics of the film. Upon application, the pharmaceutical composition film adheres to the mucosal surface and is held in place. Water absorption softens the composition, thereby diminishing the foreign body sensation. As the composition rests on the mucosal surface, delivery of the drug occurs. Residence times may be adjusted over a wide range depending upon the desired timing of the delivery of the chosen pharmaceutical and the desired lifespan of the carrier. Generally, however, the residence time is modulated between about a few seconds to about a few days. Preferably, the residence time for most pharmaceuticals is adjusted from about 5 seconds to about 24 hours. More preferably, the residence time is adjusted from about 5 seconds to about 30 minutes. In addition to providing drug delivery, once the composition adheres to the mucosal surface, it also provides protection to the treatment site, acting as an erodible bandage. Lipophilic agents can be designed to slow down erodibility to decrease disintegration and dissolution.

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

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

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

 The amount of pharmaceutically active component to be used depends on the desired treatment strength and the composition of the layers, although preferably, the pharmaceutical component comprises from about 0.001% to about 99%, more preferably from about 0.003 to
15 about 75%, and most preferably from about 0.005% to about 50% by weight of the composition, including, more than 0.005%, more than 0.05%, more than 0.5%, more than 1%, more than 5%, more than 10%, more than 15%, more than 20%, more than 30%, about 50%, more than 50%, less than 50%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, less than 1%, less than 0.5%, less than 0.05%, or less than 0.005%. The amounts of other components
20 may vary depending on the drug or other components but typically these components comprise no more than 50%, preferably no more than 30%, and most preferably no more than 15% by total weight of the composition.

 The thickness of the film may vary, depending on the thickness of each of the layers and the number of layers. As stated above, both the thickness and amount of layers may be adjusted
25 in order to vary the erosion kinetics. Preferably, if the composition has only two layers, the thickness ranges from 0.005 mm to 2 mm, preferably from 0.01 to 1 mm, and more preferably from 0.1 to 0.5 mm, including greater than 0.1 mm, greater than 0.2 mm, about 0.5 mm, greater than 0.5 mm, less than 0.5 mm, less than 0.2 mm, or less than 0.1 mm. The thickness of each layer may vary from 10 to 90% of the overall thickness of the layered composition, and
30 preferably varies from 30 to 60%, including greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 70%, greater than 90%, about 90%, less

than 90%, less than 70%, less than 50%, less than 40%, less than 30%, less than 20%, or less than 10%. Thus, the preferred thickness of each layer may vary from 0.01 mm to 0.9 mm, or from 0.03 to 0.5 mm.

As one skilled in the art will appreciate, when systemic delivery, e.g., transmucosal or transdermal delivery is desired, the treatment site may include any area in which the film is capable of delivery and/or maintaining a desired level of pharmaceutical in the blood, lymph, or other bodily fluid. Typically, such treatment sites include the oral, esophageal, aural, ocular, anal, nasal, or vaginal mucosal tissue, as well as, the skin. If the skin is to be employed as the treatment site, then usually larger areas of the skin wherein movement will not disrupt the adhesion of the film, such as the upper arm or thigh, are preferred.

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

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

EXAMPLES

IM study in Minipig-Dipivefrin/Prodrugs

This study was conducted to compare the pharmacokinetic profile of epinephrine following intramuscular (IM) administration of L-dipivefrin and epinephrine prodrugs (AQEP-01 (A), AQEP-02 (B), AQEP-03 (C) and AQEP-04 (D)) in male Yucatan miniature swine. Yucatan minipigs (n=4 males per group) were weighed and weights were recorded. The morning of the study, the vascular access port (VAP) of each animal was checked for proper functioning. Minipigs with viable VAP were removed from the home cage and placed in a holding sling. The animals were fasted overnight prior to dose administration and for the duration of PK blood collections.

Dosing of L-Dipivefrin or other epinephrine prodrugs (AQEP-01 (A), AQEP-02 (B), AQEP-03 (C) and AQEP-04 (D)) solution was done (2mg/animal) through IM route. All the formulations were prepared fresh on the day of dosing and maintained on wet ice until dosing. The dose was injected in the rear hind limb. Prior to administering, the plunger of the syringe was aspirated and observed for any blood that may flow into the syringe. If no blood was observed, it was verified that the needle was in proper placement, and the test articles were administered.

Pharmacokinetic blood sample collections were done through vascular access port at 0 (pre-dose), 2, 5, 10, 12, 15, 17, 20, 25, 30, 40, 60, 90 and 120 minutes, 3hr, 4 hr, 6hr and 8hr post dose. At each specified time-point, 6 mL of whole blood was collected into blood collection tubes containing K₂EDTA as the anticoagulant and sodium metabisulfite as stabilizer. Sodium metabisulfite was at a concentration of 8.9mM, pH 3 (60µL/6 mL of whole blood of the 890 mM stock solution). SigmaFast (600 µL of SigmaFast 1x solution to 6 mL of whole blood) was added immediately to the tubes as the enzyme arresting agent. The tubes were inverted several times for mixing upon addition of SigmaFast solution. All blood samples were centrifuged within 30 minutes of collection at 3000 RPM for 15 minutes at ~4°C. The resulting plasma was obtained and stored at approximately -70 degrees. The analysis of epinephrine was done using LC-MS/MS method.

Example 1

Referring to **Fig. 1A** and **Fig. 1B**, dipivefrin, a prodrug for epinephrine was tested in a 24 mg soluble film (DSF) and compared to Epipen in terms of achieving epinephrine plasma concentrations (in pg/ml) over time in humans. The study showed that surprisingly, the prodrug achieved comparable epinephrine concentrations were achieved in less than 0.6 hour, for example between 0.4-0.6 hours.

Example 2

Referring to **Fig. 2A** and **Fig. 2B**, the figures show results from projected increase in prodrug dosing from 24 mg, to 30 mg and 36 mg of dipivefrin soluble film as compared to the Epipen. As shown in the figure, the increased dose provides a curve shift to the left, resulting in achieving similar epinephrine plasma concentrations in a shorter time compared to lower doses.

5 **Example 3 - In vitro Human Whole Blood Hydrolysis Assay**

To identify epinephrine prodrugs with faster hydrolysis using human whole blood in vitro, epinephrine levels in plasma was measured. Fresh healthy human whole blood was collected in blood collection tubes and preincubated for 30 min at 37°C. After incubation, in the presence of stabilizer, the whole blood was fortified at a final concentration of 1 μ M of
 10 dipivefrin or prodrugs (AQEP-03, AQEP-04, AQEP-05, AQEP-06, AQEP-07, AQEP-08, AQEP-09, AQEP-10, AQEP-11, AQEP-12, and AQEP-13 for each time point separately. After addition, samples were mixed thoroughly and incubated at 37°C for different time points up to 6 hours. After incubation, whole blood samples at each time point was removed, quenched, and centrifuged to separate the plasma. Plasma samples were analyzed for epinephrine concentrations
 15 using established LC-MS/MS method

Referring to **Fig. 3A** and **3B**, the results show that the newly synthesized prodrug AQEP-10 has achieved significantly higher plasma levels of epinephrine in much less time including less than 30 minutes, less than 20 minutes, less than 15 minutes, less than 10 minutes, and less than 5 minutes. Note that in this study, $t=0$ is not a true zero as there is an approximately 3-5min
 20 lag for mixing of the components prior to addition of the stabilizer that stops enzymatic hydrolysis.

In general, prodrugs AQEP-05, AQEP-08, AQEP-09 and AQEP-10 and AQEP-11 having ester groups showed faster hydrolysis in human whole blood compared to L-Dipivefrin. The data indicates that one or more of these prodrugs can be used in place of or in addition to L-Dipivefrin
 25 as a combination of prodrugs. Surprisingly, increasing the number of carbons did not affect the rate of hydrolysis. Unexpectedly, prodrugs AQEP-12 with carbonate group showed faster hydrolysis in human whole blood compared to L-Dipivefrin, in a manner similar to AQEP-10 with ester group. Unpredictably, prodrug AQEP-04 having ester groups showed faster hydrolysis in human whole blood, but did not permeate as well, compared to L-Dipivefrin. Prodrugs AQEP-
 30 06 or AQEP-07 with carbamate groups did not show any hydrolysis in the blood. This is consistent with literature that carbamate compounds are resistant to plasma esterases. Finally,

prodrug AQEP-03 (with dimethyl amino group) showed minimal hydrolysis and increased gradually at later timepoints.

5 **Example 4**

Referring to **Fig. 4**, Prodrugs AQEP-04 and AQEP-05 were tested similarly in the manner of Example 31. Using human whole blood in vitro, epinephrine levels in plasma was measured. Whole blood was collected from 2 donors. Compounds were incubated at 1 μ M conc with Stabilizer. Plasma was separated after stopping the enzyme reaction at different timepoints. Samples were extracted and analyzed by LC-MS method. Rapid conversion and higher levels of epinephrine was seen for Prodrugs AQEP-04 and AQEP-05, compared to L-Dipivefrin. This shows that AQEP-04 or AQEP-05 can be combined with L-Dipivefrin ('Combo' drug) to achieve faster and sustained exposure to epinephrine in plasma and achieve improved results over Epipen.

15 **Example 53**

Referring to **Fig. 5**, Prodrugs AQEP-03, AQEP-06, and AQEP-07 were tested similarly in the manner of Example 31. Using human whole blood in vitro, epinephrine levels in plasma was measured. Whole blood was collected from 2 donors. Compounds were incubated at 1 μ M conc with Stabilizer. Plasma was separated after stopping the enzyme reaction at different timepoints. Samples were extracted and analyzed by LC-MS method. Prodrugs AQEP-03, AQEP-06, and AQEP-07 did not show faster hydrolysis in human blood, compared to L-Dipivefrin.

Example 6 – Intramuscular Study in Minipig for Prodrugs

Applicants sought to identify epinephrine prodrugs with higher permeability and slower hydrolysis after intramuscular (IM) administrations. This study was conducted to compare the pharmacokinetic profile of epinephrine following intramuscular (IM) administration of L-dipivefrin and epinephrine prodrugs (AQEP-01 (A), AQEP-02 (B), AQEP-03 (C) and AQEP-04 (D)) in male Yucatan miniature swine. Yucatan minipigs were weighed and in the morning of the study, the vascular access port (VAP) of each animal was checked for proper functioning. Minipigs with viable VAP were removed from the home cage and placed in a holding sling. The animals were fasted overnight prior to dose administration and for the duration of PK blood collections. .

Dosing of L-Dipivefrin or other epinephrine prodrugs (AQEP-01 (A), AQEP-02 (B), AQEP-03 (C) and AQEP-04 (D)) solution was done (2mg/animal) through IM route. The dose was injected in the rear hind limb. Pharmacokinetic blood sample collections were done through vascular access port at 0 (pre-dose), 2, 5, 10, 12, 15, 17, 20, 25, 30, 40, 60, 90 and 120 minutes, 3hr, 4 hr, 6hr and 8hr post dose. At each specified time-point, 6 mL of whole blood was collected into blood collection tubes containing anticoagulant and stabilizer. Protease inhibitor cocktail was added and the tubes were inverted several times for mixing. All blood samples were centrifuged and the resulting plasma was analyzed for epinephrine using LC-MS/MS method.

10

Group	No. of Animals (Male)	Test Article	Dose Route	Target Dose Level (mg/animal)	Dipi Dose Conc. (mg/mL)	Target Dose Amount (mL/animal)
1	4	L-Dipivefrin Solution	IM	2	2	1 mL
2	4	Prodrug A Solution	IM	2	2	1 mL
3	4	Prodrug B Solution	IM	2	2	1 mL
4	4	Prodrug C Solution	IM	2	2	1 mL
5	4	Prodrug D Solution	IM	2	2	1 mL

The following conversion was observed

	Actual Dose used	Conversion ratio	Epinephrine Dose Equivalence (mg)
L-Dipivefrin	2mg (0.1mg/kg)	0.52	1.04
AQEP-01	2mg (0.1mg/kg)	0.39	0.78
AQEP-02	2mg (0.1mg/kg)	0.44	0.88
AQEP-03	2mg (0.1mg/kg)	0.51	1.01
AQEP-04	2mg (0.1mg/kg)	0.43	0.86

Referring to **Fig. 6A** and **Fig. 6B**, the figures show normalization to epinephrine equivalent dose of L-dipivefrin and showing average epinephrine plasma concentration. Prodrug, AQEP-04 had higher C_{max} and AUC compared to Prodrugs 01, 02 and 03 (AQEP-04>AQEP-02>AQEP-03>AQEP-01). L-dipivefrin showed C_{max} (1.94 ng/ml) and AUC (256.8 ng/ml*min) compared to other Epinephrine prodrugs. Faster hydrolysis (T_{max}=5 min), with

15

sufficient plasma levels (0.5ng/ml) up to 4 hrs was seen. Faster hydrolysis was seen (Tmax=5 min) with AQEP-04, but Cmax and AUC was less compared to L-Dipivefrin.

Example 7 – Hydrolysis Testing after IV Exposure

Referring to **Figs. 7A** and **7B**, hydrolysis assay was performed with the following prodrugs as test articles: L-dipivefrin, AQEP-03, and AQEP-05. Hydrolysis was analyzed after intravenous (IV) administrations. All Groups were tested at the following time intervals: 0 (predose), 2, 5, 10, 12, 15, 17, 20, 25, 30, 40, 60, 90 and 120 minutes and 3hr, 4 hr, 6hr and 8hr post dose.

Group	No. of Animals (Male)	Test Article	Dose Route	Target Dose Level* (mg/animal)	Dipivefrin Dose Conc. (mg/mL or mg/DF)	Target Dose Amount (mL or DF/animal)
1	3	L-Dipivefrin Solution	IV	2.0	2.0	1 mL
2	3	Prodrug AQEP-03 Solution	IV	2.06	2.06	1 mL
3	3	Prodrug AQEP-05 Solution	IV	2.05	2.05	1 mL

The following pharmacokinetic (PK) parameters were observed.

	L-Dipivefrin	AQEP-03	AQEP-05	
			With outlier animal	Without outlier animal
AUC ₀₋₁ (ng/ml*min)	243.8	60.4	457.8	584.9
AUC ₀₋₃₀ (ng/ml*min)	109.1	8.1	137.8	196.8
Cmax (ng/ml)	7.3	0.46	11.4	16.6
Tmax (min)	2	17	2	2

Rapid conversion of Prodrug AQEP-05 to epinephrine was seen after IV administration, compared to L-Dipivefrin. Approximately 2-fold increase in the AUC and Cmax was observed. Similar Tmax (2 minutes) was seen.

5 **Example 8 - Intramuscular (IM) and subcutaneous (SC) administrations of L-Dipivefrin**

This study was conducted to compare the pharmacokinetic profile of L-dipivefrin administered through intramuscular (IM) and subcutaneous (SC) routes to epinephrine (Epipen, 0.3 mg) (Mfg: Mylan) in male Yucatan miniature swine. . The study measured epinephrine exposure, conversion of dipivefrin to epinephrine and pharmacokinetic (PK) parameters.

Yucatan minipigs were weighed and in the morning of the study, the vascular access port (VAP) of each animal was checked for proper functioning. Minipigs with viable VAP were removed from the home cage and placed in a holding sling. The animals were fasted overnight prior to dose administration and for the duration of PK blood collections.

15 Dosing of L-Dipivefrin (0.6, 1 and 2 mg/animal) solution was administered through IM or SC routes, whereas Epipen was injected through IM route. For IM route, L-Dipivefrin solutions or Epipen were injected in the rear hind limb. For SC route, L-Dipivefrin solutions were dosed on the animal's neck, just behind the right ear.

20 Pharmacokinetic blood sample collections were done through vascular access port at 0 (pre-dose), 2, 5, 10, 12, 15, 17, 20, 25, 30, 40, 60, 90 and 120 minutes, 3hr, 4 hr, 6hr and 8hr post dose. At each specified time-point, 6 mL of whole blood was collected into blood collection tubes containing anticoagulant and stabilizer. Protease inhibitor cocktail was added and the tubes were inverted several times for mixing. All blood samples were centrifuged and the resulting plasma was analyzed for dipivefrin and epinephrine using LC-MS/MS method.

25

Group	No. of Animals (Male)	Test Article	Dose Route	Target Dose Level (mg/animal)	Epi/Dipivefrin Dose Conc. (mg/mL)	Target Dose Amount (mL /animal)
1	1	Placebo	IM	0	0	1 mL
2	3	Epipen	IM	0.3	1 mg/ml	0.3 ml

3	3	Dipivefrin (Alc-L) Solution	IM	0.6	0.6 mg/mL	1 mL
4	3	Dipivefrin (Alc-L) Solution	IM	1	1 mg/mL	1 mL
5	3	Dipivefrin (Alc-L) Solution	IM	2	2 mg/mL	1 mL
6	3	Dipivefrin (Alc-L) Solution	SC	0.6	0.6 mg/mL	1 mL
7	3	Dipivefrin (Alc-L) solution	SC	1	1 mg/mL	1 mL
8	3	Dipivefrin (Alc-L) Solution	SC	2	2 mg/mL	1 mL

PK Blood /Plasma Sample Collections were collected for all Groups: 0 (predose), 2, 5, 10, 12, 15, 17, 20, 25, 30, 40, 60, 90 and 120 minutes and 3hr, 4 hr, 6hr and 8hr post dose.

5 Referring to **Fig. 8A**, average epinephrine plasma concentration was collected over time for intramuscular and subcutaneous administration of L-dipivefrin (0.6 mg, 1 mg and 2 mg) and compared to the Epipen.

Referring to **Fig. 8B**, intramuscular (IM) administration was performed and average epinephrine plasma concentration was measured.

10 Referring to **Fig. 8C**, subcutaneous (SC) administration, and average epinephrine plasma concentration was measured.

Example 9

15 Referring to **Fig. 9A**, a comparison of IM & SC administration of L-dipivefrin 0.6 mg was performed and average epinephrine plasma concentration was measured, using the same protocol as in Example 38. Referring to **Fig. 9B**, the same comparison was drawn using 1 mg of L-dipivefrin. Referring to **Fig. 9C**, the same comparison was drawn using 2 mg of L-dipivefrin.

Example 10

Referring to **Fig. 10**, average dipivefrin plasma concentration vs time profiles were obtained over time for 0.6 mg, 1 mg and 2 mg of dipivefrin using intramuscular (IM) administration and subcutaneous (SC) administration.

Example 11

Referring to **Fig. 11A**, conversion of dipivefrin to epinephrine was measured for 0.6 mg, 1 mg and 2 mg of dipivefrin using intramuscular (IM) administration.

Referring to **Fig. 11 B**, conversion of dipivefrin to epinephrine was measured for 0.6 mg, 1 mg and 2 mg of dipivefrin using subcutaneous (SC) administration.

The following PK parameters were observed.

	EPI AUC 0-t (min* ng/ml)	EPI Tmax (min)	EPI Cmax (mean, ng/ml)	DIPI AUC 0-t (min* ng/ml)	DIPI Tmax (min)	DIPI Cmax (mean, ng/ml)
Placebo	0	-	-	0	-	-
Epipen	71.02	5	0.403	-	-	-
L- Dipivefrin IM 0.6mg	62.85	20	0.387	2.6	5	0.285
L- Dipivefrin IM 1 mg	123.1	10	0.851	15.63	10	0.632
L- Dipivefrin IM 2 mg	208.2	10	1.35	29.79	5	0.882
L- Dipivefrin SC 0.6mg	83.13	2	0.48	18.25	17	0.602
L- Dipivefrin SC 1 mg	248.2	17	1.17	80.14	10	2.34
L- Dipivefrin SC 2 mg	490.9	17	2.89	197.6	17	5.2

Example 12- Alternative Administration of Dipivefrin

Referring to **Fig. 12A**, a comparison was performed for IM and SC administration of dipivefrin as compared to the EpiPen. It was determined that 0.6mg dipivefrin was equivalent to 0.3mg epinephrine. No apparent difference in IM vs SC vs EpiPen.

Referring to **Fig. 12B**, the dose response (epinephrine plasma levels) was obtained as a function of route of administration.

Referring to **Fig. 12C**, dose response (epinephrine plasma levels) as a function of route of administration.

The results show that dose response varies by route of administration. It was found that ~2.5X higher dose response in AUC and Cmax for SC vs. IM. Statistically significant only at 2mg in this data set ($p < 0.05$). Equivalent at dose of interest 0.6mg Dipivefrin (equivalent to EpiPen). Effect at dose of EpiPen Jr (0.15mg Epi = 0.3mg Dipivefrin).

Comparable plasma Epinephrine levels were observed after IM and SC administrations of L-Dipivefrin at all doses tested, except 2 mg dose where SC administration showed higher levels of Epinephrine than IM administration. It is expected that a threshold is crossed at 1 mg changing the distribution to the body (depo effect)

Conversion of Dipivefrin to Epinephrine was seen after IM and SC administrations of L-Dipivefrin at all doses tested. Dose dependent effects were seen in the plasma epinephrine exposure (AUC) after IM and SC administrations of L-Dipivefrin. The onset of epinephrine response was very similar in both IM and SC administrations and comparable to EpiPen.

Example 13—In Vitro Human Whole Blood Assay

Referring to **Fig. 13A**, prodrugs AQEP-08, AQEP-09 and AQEP-10 were tested against L-dipivefrin for their resulting epinephrine concentration in human plasma (ng/ml) over time (min). Note: $t=0$ is not a true zero as there is an approximately 3-5min lag for mixing of the components prior to addition of the stabilizer that stops enzymatic hydrolysis. Prodrugs AQEP-08, AQEP-09, and AQEP-10 showed faster hydrolysis in human blood, compared to L-Dipivefrin.

Further, as shown in Figure **13B**, Prodrugs AQEP-11, AQEP-12, and AQEP-13 showed faster hydrolysis in human blood, compared to L-Dipivefrin.

Referring to **Fig. 13C**, the graph indicates a comprehensive comparison of various prodrugs tested against dipivefrin for resulting epinephrine concentration in human plasma (ng/ml) over time (min). Note: $t=0$ is not a true zero as there is an approximately 3-5min lag for mixing of the components prior to addition of the stabilizer that stops enzymatic hydrolysis.

- 5 Prodrugs AQEP-08, AQEP-09, and AQEP-10 showed faster hydrolysis in human blood, compared to L-Dipivefrin.

The results showed prodrug AQEP-04 (with similar ester groups) showed faster hydrolysis in human whole blood, but did not permeate higher than L-Dipivefrin. However, prodrugs AQEP-05, AQEP-08, AQEP-09 and AQEP-10 (with ester groups) showed surprisingly
10 faster hydrolysis in human whole blood while also showing effective permeation.

Prodrugs AQEP-06 or AQEP-07 (with carbamate groups) did not show any hydrolysis in the blood (consistent with literature that carbamate compounds are resistant to plasma esterases, Imai et al, 2012). Prodrug AQEP-03 (with dimethyl amino group) showed minimal hydrolysis and increased gradually at later timepoints.

- 15 The data indicates that the a pharmaceutically effective composition can include prodrugs AQEP-05, AQEP-08, AQEP-09, AQEP-10, AQEP-11, AQEP-11, AQEP-12, and AQEP-13 alone or in combination with each other and/or L-Dipivefrin.

20 **Example 14– Prodrug Selection**

Referring to **Fig. 14A**, of the various prodrugs tested for permeation and hydrolysis, AQEP-05, AQEP-08, AQEP-09 and AQEP-10. **Fig. 14B** shows the ex vivo permeation data for AQEP-09 compared to L-dipivefrin.

25 **Example 15 – Hydrolysis Comparison**

Referring to Fig. 45, the graph indicates a study comparing in vitro human whole blood hydrolysis data for those prodrugs having acceptable levels of permeation.

30 **Example 16 – Carbon Length Effect on Permeation**

Conventionally, it would be expected that increasing lipophilicity would increase permeation of a compound based in increasing ability to cross a transmucosal barriers including surface epithelial cells, intercellular space, and a basement membrane.

Referring to **Fig. 16**, the graph indicates the results from a study of flux vs. carbon chain length. An unexpected result was obtained in that increasing lipophilicity did not result in enhanced permeation. The prodrug AQEP-11 having 5 carbon straight chain was tested, and unexpectedly permeation dropped. Thus, permeation was not always enhanced with increased
5 lipophilicity.

Other embodiments are within the scope of the following claims.

CLAIMS:

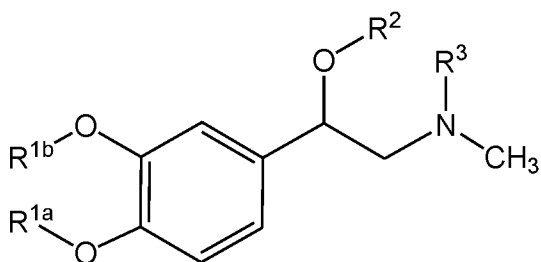
What is claimed is:

1. A method of treating a medical condition in a human subject comprising:
administering a composition including a prodrug and a permeation enhancer from a
5 matrix;
the permeation enhancer promoting permeation of the prodrug through a mucosal tissue
to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in
the human subject in less than one hour.
2. The method of claim 1, wherein the matrix has a permeation enhancer to prodrug ratio is
10 1000:1 to 1:1000 by weight.
3. The method of claim 1, wherein the permeation enhancer to prodrug ratio is 100:1 to
1:100 by weight.
4. The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 1:50
by weight.
- 15 5. The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 1:1
by weight.
6. The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 10:1
by weight.
7. The method of claim 1, wherein the permeation enhancer to prodrug ratio is 10:1 to 1:10
20 by weight.
8. The method of claim 1, further including administering a pharmaceutically active
ingredient with the prodrug.
9. A method of treating a medical condition in a human subject comprising:
administering a composition including a prodrug from a matrix;
25 delivering the prodrug through a mucosal tissue to achieve an effective plasma
concentration of a pharmaceutically active form of the prodrug in the human subject in less than
one hour.
10. The method of claim 1, wherein the prodrug comprises 0.01-90% of the matrix by %
weight.
- 30 11. The method of claim 1, wherein the prodrug comprises 0.1-50% of the matrix by %
weight.

12. The method of claim 1, wherein the permeation enhancer comprises 1-50% of the matrix by % weight.
13. The method of claim 1, wherein the permeation enhancer comprises 5-25% of the matrix by % weight
- 5 14. The method of claim 1, wherein the pharmaceutically active form of the prodrug has a Tmax of less than 240 minutes.
15. The method of claim 1, wherein the prodrug has a Tmax of less than 120 minutes.
16. The method of claim 1, wherein the prodrug has a Tmax of less than 60 minutes.
17. The method of claim 1, wherein the prodrug has a Cmax of 0.1 pg/ml-50,000 pg/ml.
- 10 18. The method of claim 1, wherein prodrug has particle size of no more than 100 microns.
19. The method of claim 1, wherein the prodrug and permeation enhancer concurrently penetrate the mucosal tissue.
20. The method of claim 1, wherein the prodrug is an ester of a pharmaceutically active form of the prodrug.
- 15 21. The method of claim 1, wherein the prodrug includes an alkyl ester of a pharmaceutically active form of the prodrug.
22. The method of claim 1, wherein the prodrug includes a butyl ester of a pharmaceutically active form of the prodrug.
23. The method of claim 1, wherein the prodrug includes an isopropyl ester pharmaceutically
- 20 active form of the prodrug.
24. The method of claim 1, wherein the prodrug includes an ethyl ester pharmaceutically active form of the prodrug.
25. The method of claim 1, wherein the prodrug includes an ester of epinephrine.
26. The method of claim 1, wherein at least half of the administered prodrug is converted
- 25 inless than 240 minutes.
27. The method of claim 1, wherein at least half of the administered prodrug is converted inless than 120 minutes.
28. The method of claim 1, wherein at least half of the administered prodrug is converted inless than 60minutes.

29. The method of claim 1, wherein the prodrug converts to produce a concentration of active compound of of 20 pg/ml to about 20 ng/ml of active compound in a period of less than 120 minutes.
30. The method of claim 1, wherein the matrix is applied as chewable or gelatin based dosage form, inhalation dosage form, capsule, lyophilized solid dosage unit, mist, powder, spray, liquid, gum, gel, cream, film or tablet.
31. The method of claim 1, wherein the matrix is pharmaceutical film as a residence time of less than 90 minutes in an oral cavity.
32. The method of claim 1, wherein the matrix is pharmaceutical film as a residence time of less than 60 minutes in an oral cavity.
33. The method of claim 1, wherein the matrix is pharmaceutical film has a residence time of less than 15 minutes in an oral cavity.
34. The method of claim 1, wherein administering the prodrug stimulates one or more adrenergic receptors.
35. The method of claim 1, wherein administering the prodrug does not activate the alpha 1 adrenergic receptor.
36. The method of claim 1, wherein administering the prodrug minimizes a side effect of epigastric pain.
37. The method of claim 1, wherein the medical condition is in a spectrum of anaphylaxis.
38. The method of claim 1, wherein the medical condition is an allergic reaction.
39. The method of claim 1, wherein the medical condition is a cardiac abnormality.
40. The method of claim 1, wherein the medical condition is a pulmonary abnormality.
41. The method of claim 1, wherein the permeation enhancer includes a phenylpropanoid.
42. The method of claim 1, wherein the phenylpropanoid is a eugenol or eugenol acetate.
43. The method of claim 1, wherein the phenylpropanoid is a cinnamic acid, cinnamic acid ester, cinnamic aldehyde or hydrocinnamic acid.
44. The method of claim 1, wherein the phenylpropanoid is a chavicol.
45. The method of claim 1, wherein the phenylpropanoid is a safrole.
46. The method of claim 1, wherein the permeation enhancer includes an essential oil extract of a clove plant.
47. The method of claim 1, wherein the permeation enhancer is synthetic.

48. The method of claim 1, wherein the permeation enhancer is biosynthetic.
49. The method of claim 1, wherein the permeation enhancer is natural.
50. The method of claim 1, wherein the permeation enhancer includes 150-95% eugenol.
51. The method of claim 1, wherein the permeation enhancer includes a terpenoid, terpene or
5 a sesquiterpene.
52. The method of claim 1, wherein the permeation enhancer includes a benzyl alcohol.
53. The method of claim 1, wherein the permeation enhancer includes farnesol.
54. The method of claim 1, wherein the permeation enhancer includes a self-emulsifying
excipient.
- 10 55. The method of claim 1, wherein the matrix includes a mucoadhesive water soluble
polymer.
56. The method of claim 1, wherein the permeation enhancer includes linoleic acid.
57. The method of claim 1, wherein the composition including a prodrug includes more than
one prodrug with each prodrug being a derivative of a pharmaceutically active ingredient.
- 15 58. The method of claim 1, wherein one of the prodrugs is dipivefrin.
59. The method of claim 54, wherein the first prodrug is a first ester of epinephrine and the
second prodrug is a second ester of epinephrine, the first ester of epinephrine and the second
ester of epinephrine being different.
60. The method of claim 1, wherein the prodrug is a compound of formula (I), wherein



(I)

- 20 each of R^{1a}, R^{1b}, R² and R³, independently, can be H, C1-C16 acyl, alkyl aminocarbonyl,
alkyloxycarbonyl, phenacyl, sulfate or phosphate, or R^{1a} and R^{1b} together, R^{1a} and R² together,
R^{1a} and R³ together, R^{1b} and R² together, R^{1b} and R³ together, or R² and R³ together form a cyclic
structure including a dicarbonyl, disulfate or diphosphate moiety, provided that one of R¹, R² and
25 R³ is not H, or a pharmaceutically acceptable salt thereof.

61. The method of claim 60, wherein R^2 and R^3 are H and each R^{1a} and R^{1b} , independently, is ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl.
62. A method of treating a medical condition comprising
5 administering a prodrug from a matrix, the prodrug being converted to provide a concentration of 20 pg/ml to about 20 ng/ml of active compound in less than 240 minutes.
63. The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 350 pg/ml of active compound in less than 120 minutes.
64. The method of claim 62, wherein the prodrug is converted to provide a concentration of
10 200 pg/ml to about 350 pg/ml of active compound in less than 100 minutes.
65. The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 350 pg/ml of active compound in less than 60 minutes.
66. The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 350 pg/ml of active compound in less than 45 minutes.
- 15 67. The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 350 ng/ml of active compound in less than 30 minutes.
68. The method of claim 62, wherein the prodrug converts to create a sustained concentration of 200 pg/ml to about 350 pg/ml.
69. The method of claim 62, further including administering a pharmaceutically active
20 ingredient with the prodrug.
70. The method of claim 62 in which less than 100% of the prodrug is converted.
71. The method of claim 62 in which 100% of the prodrug is converted.
72. A method of treating a medical condition comprising
administering a prodrug, the prodrug converting to produce a concentration of active
25 compound of between 20 pg/ml to about 20 ng/ml in a period of less than 240 minutes.
73. The method of claim 72 in which less than 100% of the prodrug is converted.
74. The method of claim 72 in which 100% of the prodrug is converted.
- 30 75. The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg of epinephrine for a duration of at least 15 minutes.

76. The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg of epinephrine for a duration of at least 30 minutes.
77. The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg of epinephrine for a duration of at least 1 hours.
- 5 78. The method of claim 59, wherein the prodrug produced therapeutic levels over 100 pg of epinephrine for a duration of at least 4 hours.

ABSTRACT

Pharmaceutical compositions include a prodrug of epinephrine are described.

SCORE Placeholder Sheet for IFW Content

Application Number: 62929737

Document Date: 11/01/2019

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		
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.)

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

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

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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.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1	
		Application Number		
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT			
Customer Number	27890			
Email Address	ipdocketing@step toe.com	Add Email	Remove Email	
Email Address	hfox@step toe.com	Add Email	Remove Email	

Application Information:

Title of the Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		
Attorney Docket Number	18460.0039P1	Small Entity Status Claimed	☐
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	18	Suggested Figure for Publication (if any)	

Filing By Reference:

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

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

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

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.			
Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	27890		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

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.

Foreign Priority Information:

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

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Remove
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Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.



NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

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.

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☐ 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.

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

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.

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☒ Assignee
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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. ☒

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

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.

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Address 2			
City	WARREN	State/Province	NJ
Country ⁱ	US	Postal Code	07059
Phone Number		Fax Number	
Email Address			

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

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	/Harold H. Fox, Reg.# 41498/		Date (YYYY-MM-DD)	2019-11-26	
First Name	Harold	Last Name	Fox	Registration Number	41,498

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	18460.0039P1
		Application Number	
Title of Invention	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

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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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the international Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	37857956
Application Number:	62929737
International Application Number:	
Confirmation Number:	1064
Title of Invention:	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT
First Named Inventor/Applicant Name:	Alexander Mark Schobel
Customer Number:	27890
Filer:	Harold H. Fox/Linda Fielding
Filer Authorized By:	Harold H. Fox
Attorney Docket Number:	18460.0039P1
Receipt Date:	26-NOV-2019
Filing Date:	
Time Stamp:	04:40:18
Application Type:	Provisional

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	0039P1UPDATEDADS.pdf	144984	no	9
			43cd86b72e3247ead69d995a7da24c50193009c3		

Warnings:

Information:	
This is not an USPTO supplied ADS fillable form	
Total Files Size (in bytes):	144984
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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
62/929,737	11/01/2019		280	18460.0039P1		

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

CONFIRMATION NO. 1064
FILING RECEIPT



Date Mailed: 12/06/2019

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 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 identifying the requested changes, preferably by 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)

Alexander Mark Schobel, Vero Beach, FL;
Stephen Paul Wargacki, Annandale, NJ;
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Applicant(s)

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Power of Attorney:

Harold Fox--41498

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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

If Required, Foreign Filing License Granted: 12/05/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 62/929,737**

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

Non-Publication Request: No

Early Publication Request: No

Title

PRODRUG COMPOSITIONS AND METHODS OF TREATMENT

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

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