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UTILITY PATENT APPLICATION TRANSMITTAL <i>(Only for new nonprovisional applications under 37 CFR 1.53(b))</i>	Attorney Docket No.	18460.0028
	First Named Inventor	Alexander Mark Schobel
	Title	PHARMACEUTICAL COMPOSITIONS WITH ENHANCED PERMEATION
	Express Mail Label No.	

APPLICATION ELEMENTS <i>See MPEP chapter 600 concerning utility patent application contents.</i>	ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
1. ☐ Fee Transmittal Form (PTO/SB/17 or equivalent) 2. ☐ Applicant asserts small entity status. See 37 CFR 1.27 3. ☐ Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent. 4. ☒ Specification [Total Pages <u>78</u>] Both the claims and abstract must start on a new page. (See MPEP § 608.01(a) for information on the preferred arrangement) 5. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets <u>33</u>] 6. Inventor's Oath or Declaration [Total Pages _____] (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e)) a. ☐ Newly executed (original or copy) b. ☐ A copy from a prior application (37 CFR 1.63(d)) 7. ☒ Application Data Sheet * See note below. See 37 CFR 1.76 (PTO/AIA/14 or equivalent) 8. CD-ROM or CD-R in duplicate, large table, or Computer Program (Appendix) ☐ Landscape Table on CD 9. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. – c. are required) a. ☐ Computer Readable Form (CRF) b. ☐ Specification Sequence Listing on: i. ☐ CD-ROM or CD-R (2 copies); or ii. ☐ Paper c. ☐ Statements verifying identity of above copies	ACCOMPANYING APPLICATION PAPERS 10. ☐ Assignment Papers (cover sheet & document(s)) Name of Assignee _____ 11. ☐ 37 CFR 3.73(c) Statement ☐ Power of Attorney (when there is an assignee) 12. ☐ English Translation Document (if applicable) 13. ☐ Information Disclosure Statement (PTO/SB/08 or PTO-1449) ☐ Copies of citations attached 14. ☐ Preliminary Amendment 15. ☐ Return Receipt Postcard (MPEP § 503) (Should be specifically itemized) 16. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed) 17. ☐ Nonpublication Request Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent. 18. ☐ Other: _____ _____ _____ _____

*Note: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 must be included in an Application Data Sheet (ADS).
 (2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS					
☒ The address associated with Customer Number: <u>27890</u> OR ☐ Correspondence address below					
Name					
Address					
City	State	Zip Code			
Country	Telephone	Email			
Signature	/Harold H. Fox REG#41498/		Date	October 3, 2017	
Name (Print/Type)	Harold H. Fox		Registration No. (Attorney/Agent)	41,498	

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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

IPR2025-00874

Aquestive Therapeutics, Inc. v. Iono Pharma, LLC

Iono's Exhibit 2005

EX2005, Page 1

Privacy Act Statement

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

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

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

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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0028
		Application Number	
Title of Invention	PHARMACEUTICAL COMPOSITIONS WITH ENHANCED PERMEATION		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

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

Inventor Information:

Inventor	1				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Alexander	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 Dermont Drive				
Address 2					
City	Whitehouse Station	State/Province	NJ		
Postal Code	08889	Country i	US		

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

Mailing Address of Inventor:

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

Inventor	3				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					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0028
		Application Number	
Title of Invention	PHARMACEUTICAL COMPOSITIONS WITH ENHANCED PERMEATION		

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

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).			
☐ An Address is being provided for the correspondence information of this application.			
Customer Number	27890		
Email Address	ipdocketing@stepoe.com	Add Email	Remove Email
Email Address	hfox@stepoe.com	Add Email	Remove Email

Application Information:

Title of the Invention	PHARMACEUTICAL COMPOSITIONS WITH ENHANCED PERMEATION		
Attorney Docket Number	18460.0028	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	33	Suggested Figure for Publication (if any)	

Filing By Reference:

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

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

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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0028
		Application Number	
Title of Invention	PHARMACEUTICAL COMPOSITIONS WITH ENHANCED PERMEATION		

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	☐	Limited Recognition (37 CFR 11.9)
Customer Number	27890		

Domestic Benefit/National Stage Information:

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

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

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation in part of	15717856	2017-09-27
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation in part of	15587376	2017-05-04
Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15587376	Claims benefit of provisional	62331993	2016-05-05
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			Add

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0028
		Application Number	
Title of Invention	PHARMACEUTICAL COMPOSITIONS WITH ENHANCED PERMEATION		

Foreign Priority Information:

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

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

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

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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	18460.0028
		Application Number	
Title of Invention	PHARMACEUTICAL COMPOSITIONS WITH ENHANCED PERMEATION		

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	18460.0028
		Application Number	
Title of Invention	PHARMACEUTICAL COMPOSITIONS WITH ENHANCED PERMEATION		

Applicant Information:

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

Applicant	1	Remove
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section. Clear		
☒ Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:		
Name of the Deceased or Legally Incapacitated Inventor:		
If the Applicant is an Organization check here. ☒		
Organization Name	MONOSOL RX, LLC	
Mailing Address Information For Applicant:		
Address 1	30 TECHNOLOGY DRIVE	
Address 2		
City	WARREN	State/Province NJ
Country	US	Postal Code 07059
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	18460.0028
		Application Number	
Title of Invention	PHARMACEUTICAL COMPOSITIONS WITH ENHANCED PERMEATION		

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

Signature:

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)	2017-10-03	
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	18460.0028
		Application Number	
Title of Invention	PHARMACEUTICAL COMPOSITIONS WITH ENHANCED PERMEATION		

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

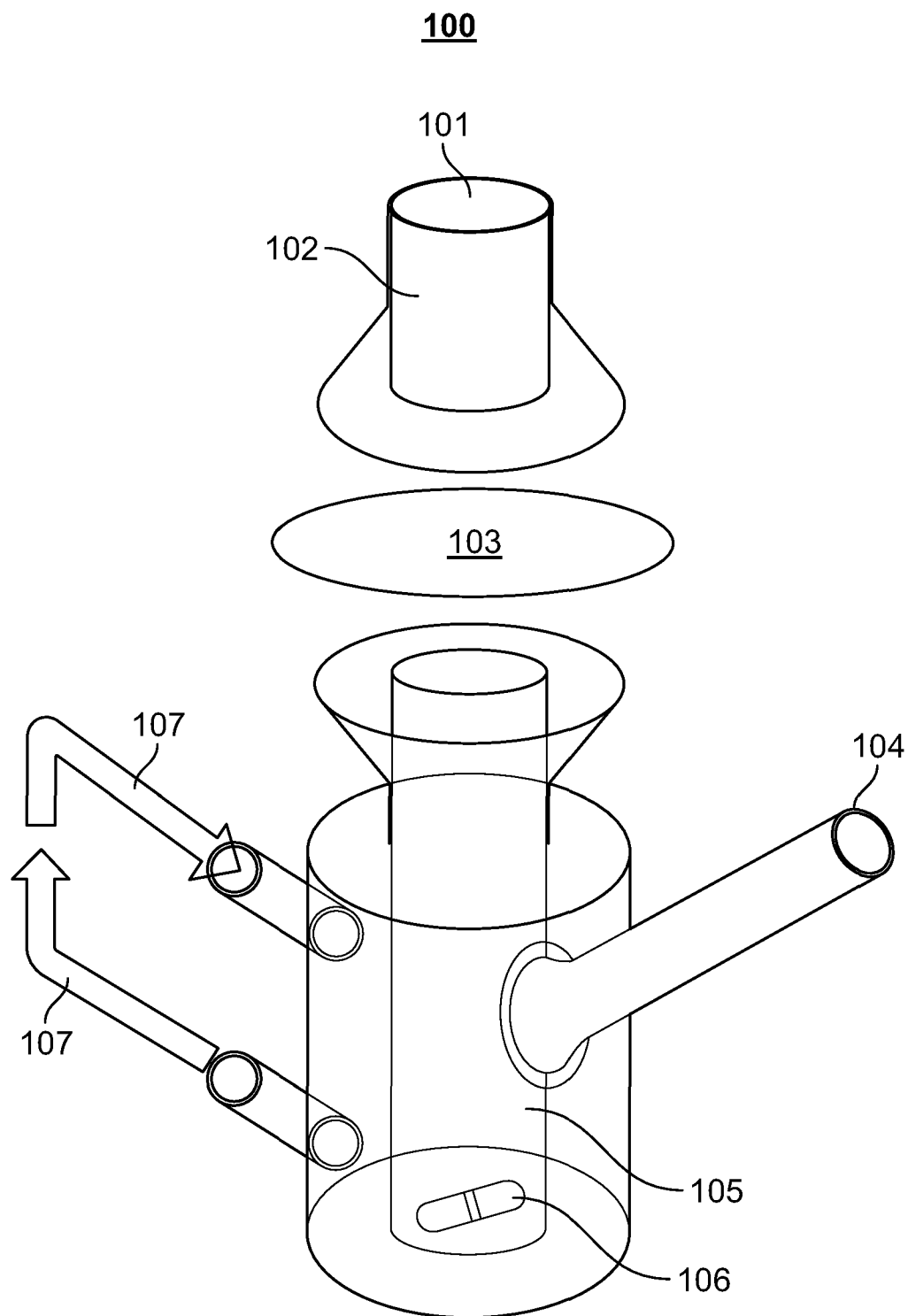


FIG. 1A

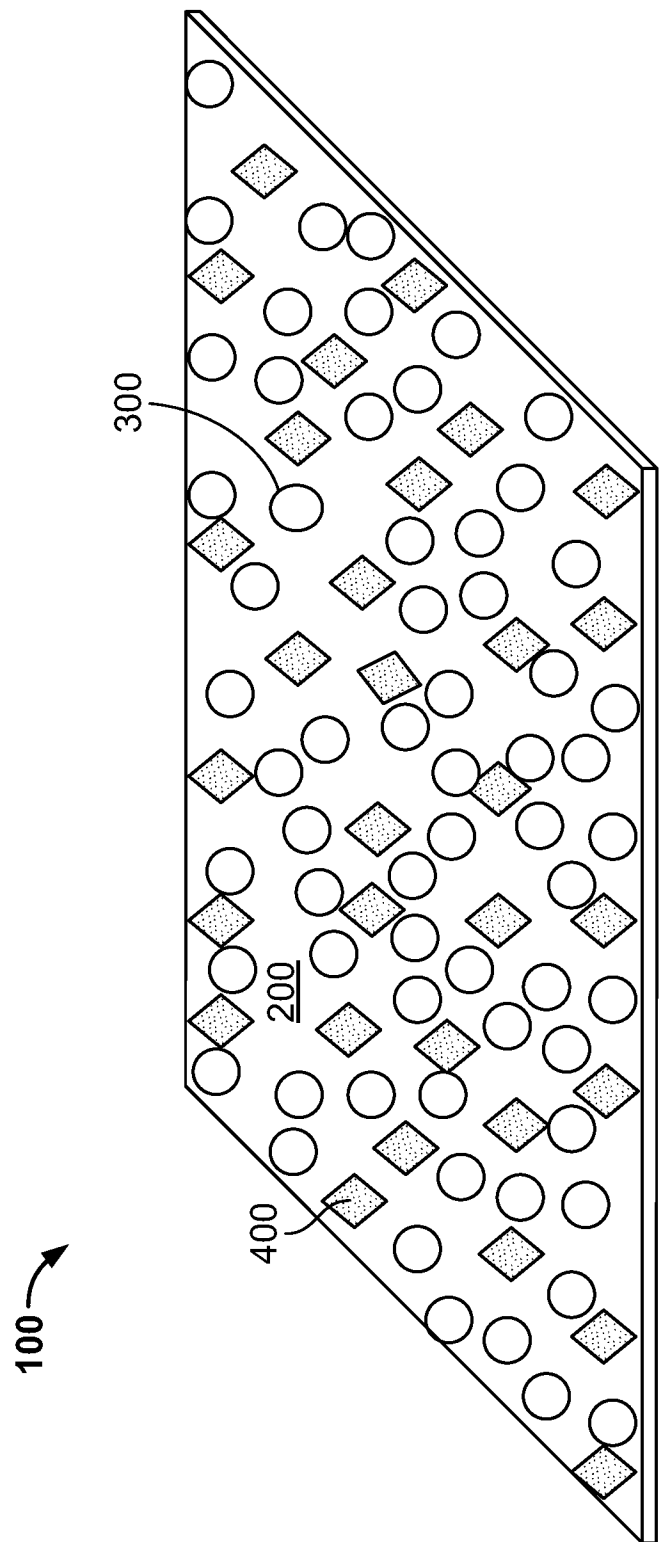
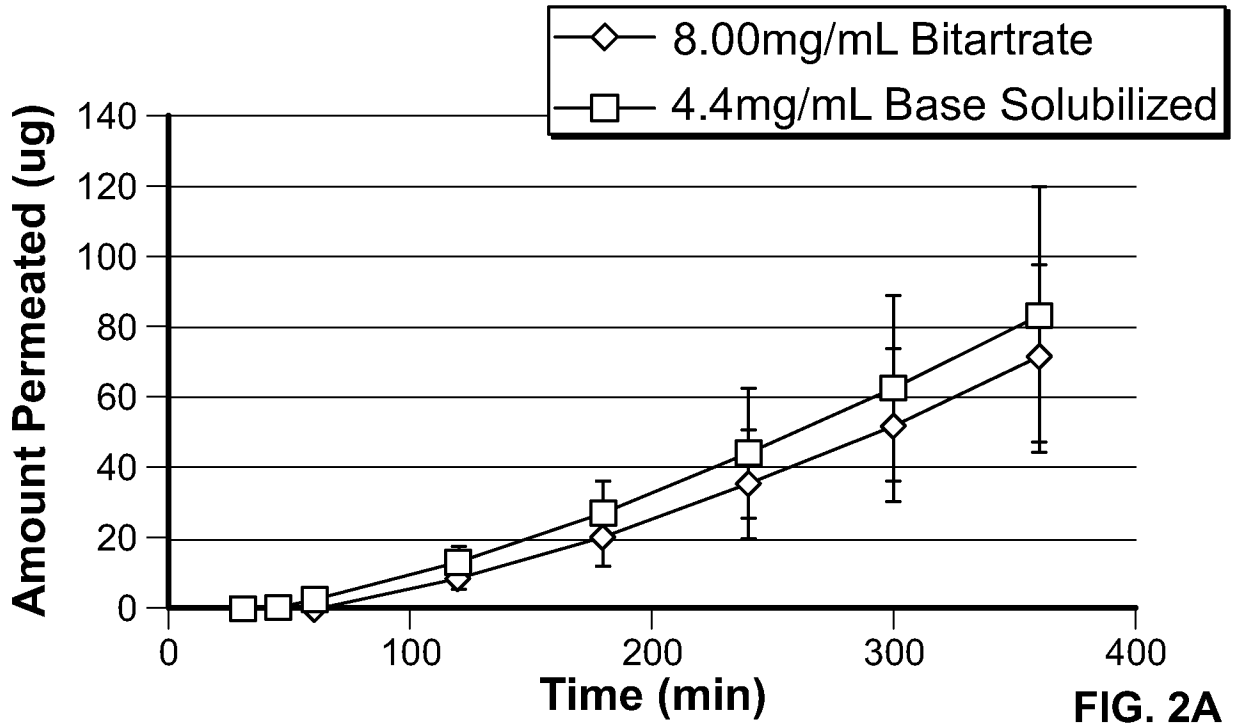


FIG. 1B

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Average Amount Permeated vs Time



Average Flux vs. Time

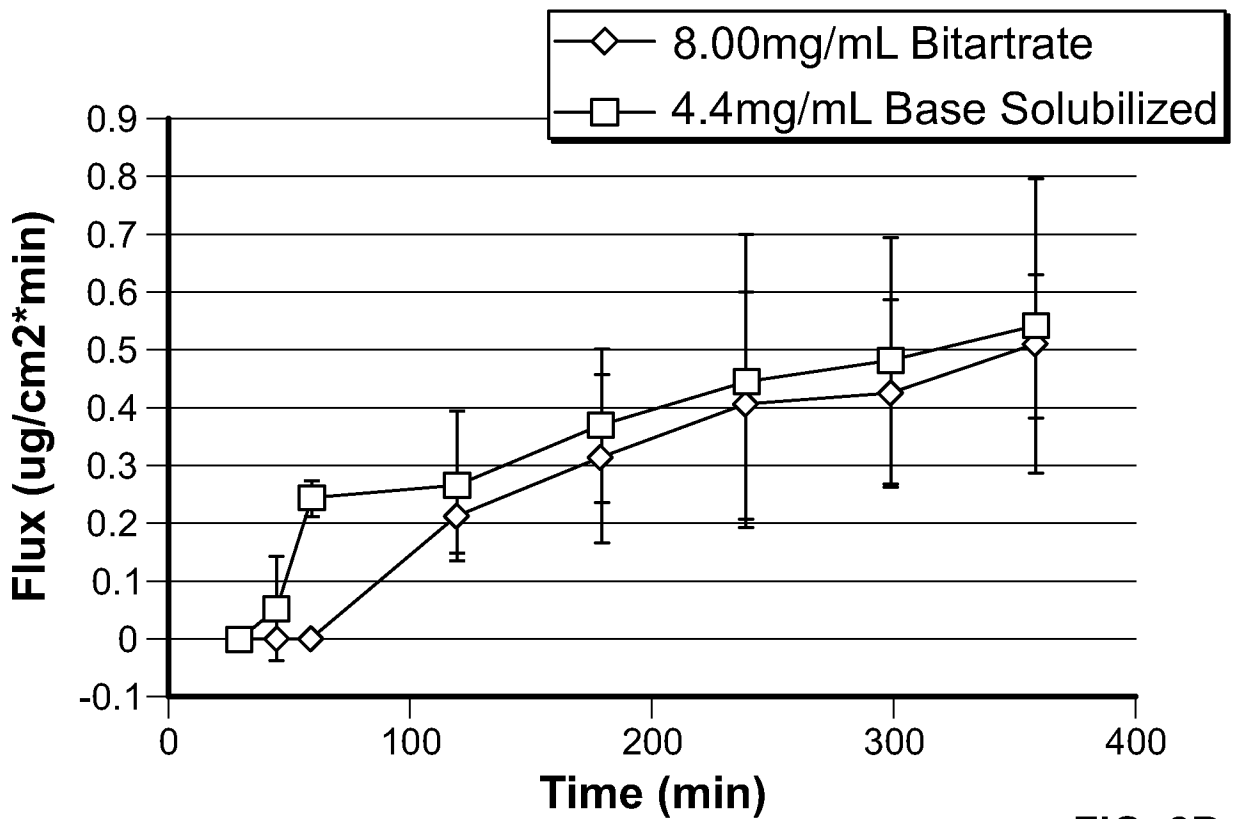


FIG. 2B

Ex-Vivo Permeation of Epinephrine Bitartrate as a Function of Concentration

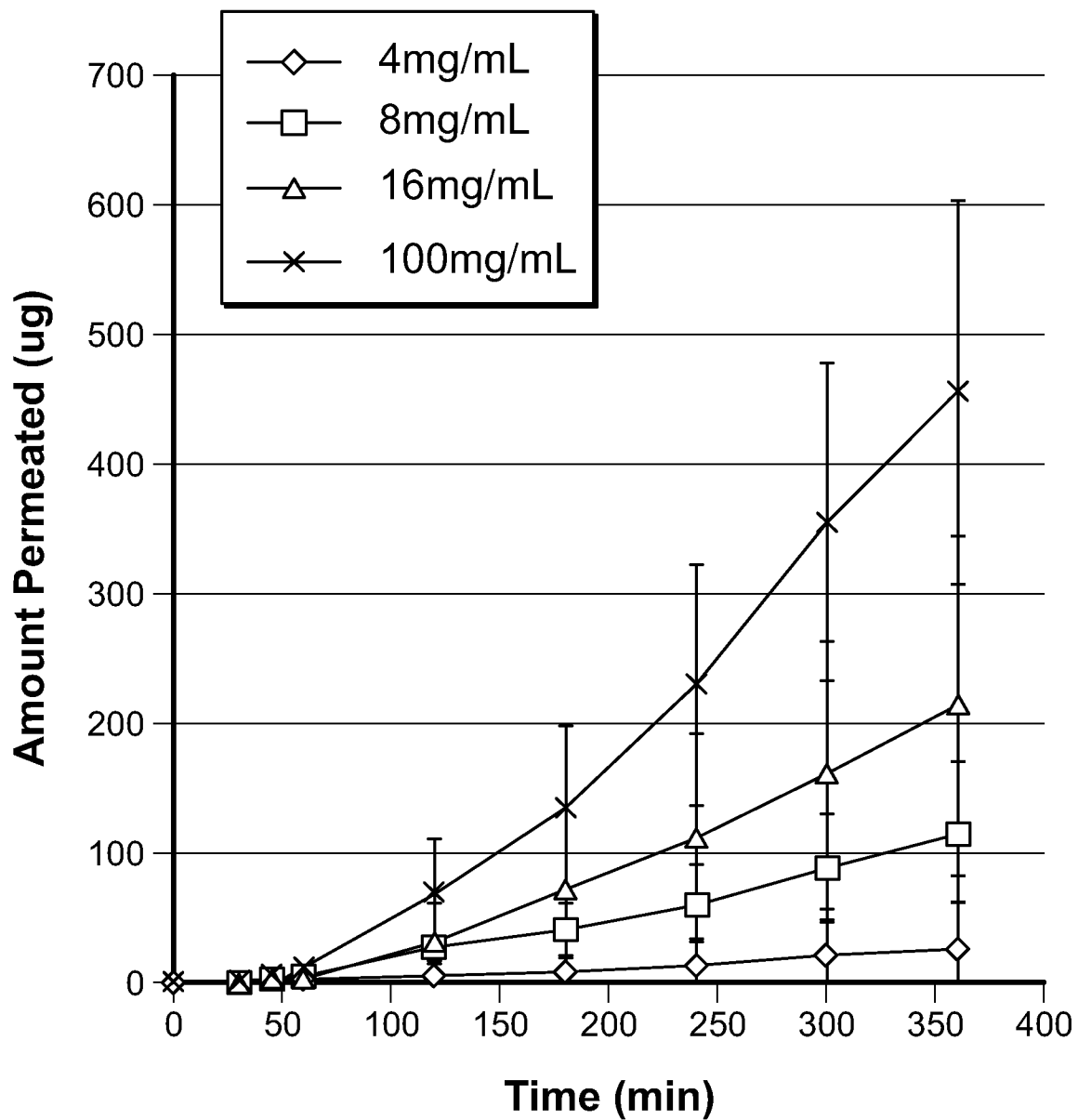


FIG. 3

Permeation of Epinephrine Bitartrate as a Function of Solution pH

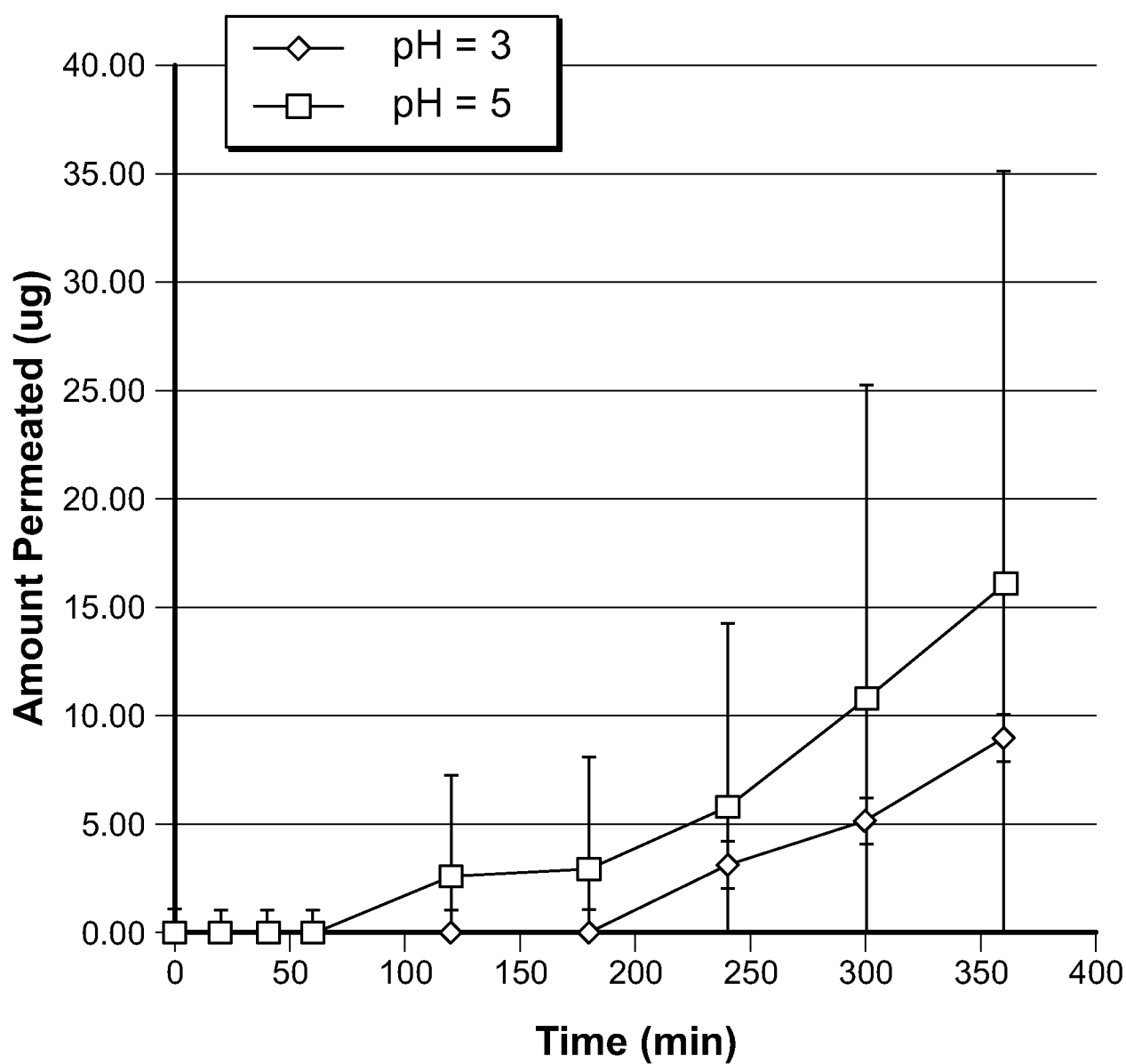


FIG. 4

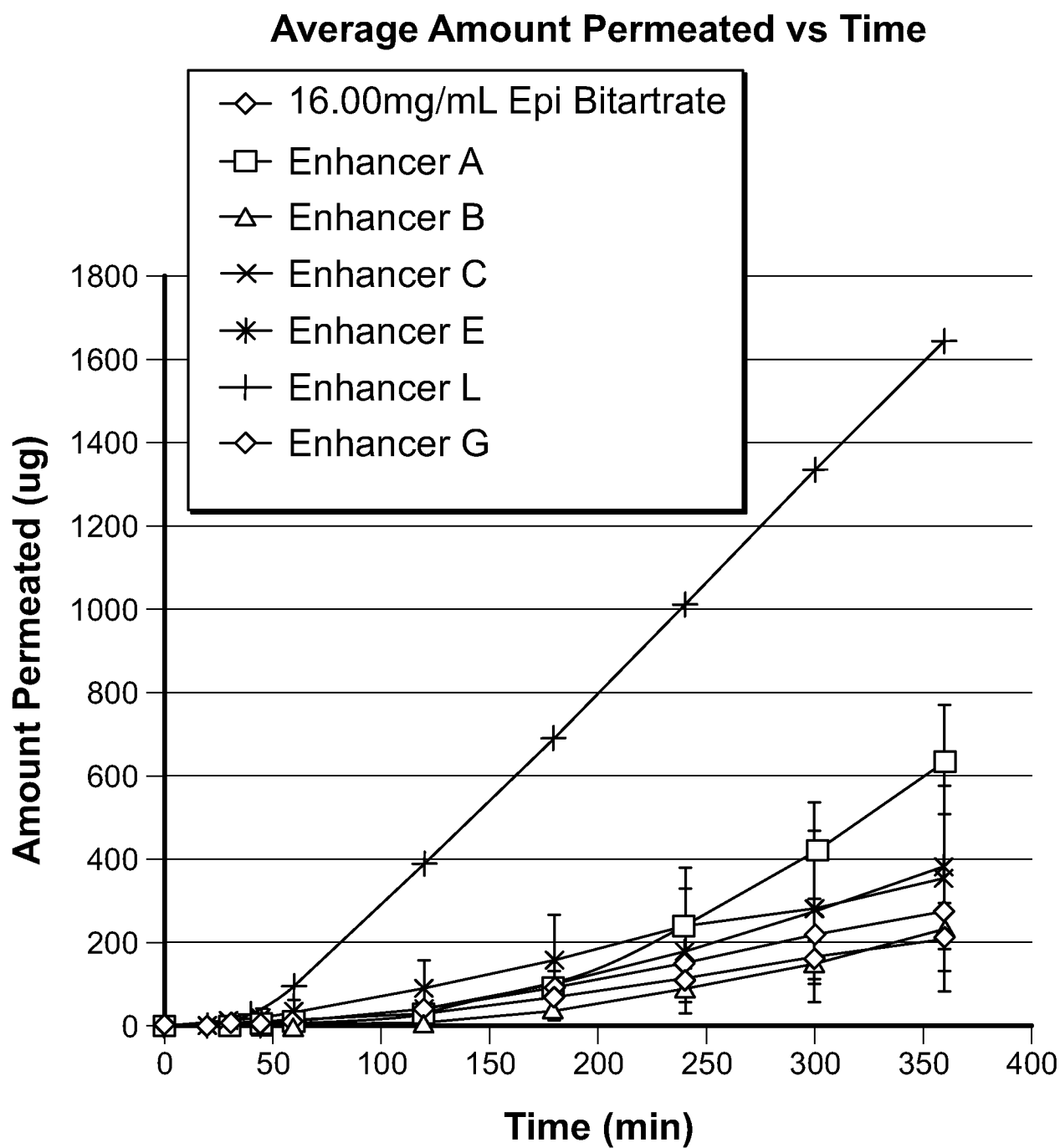


FIG. 5

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Epinephrine Release from Different Polymer Platforms

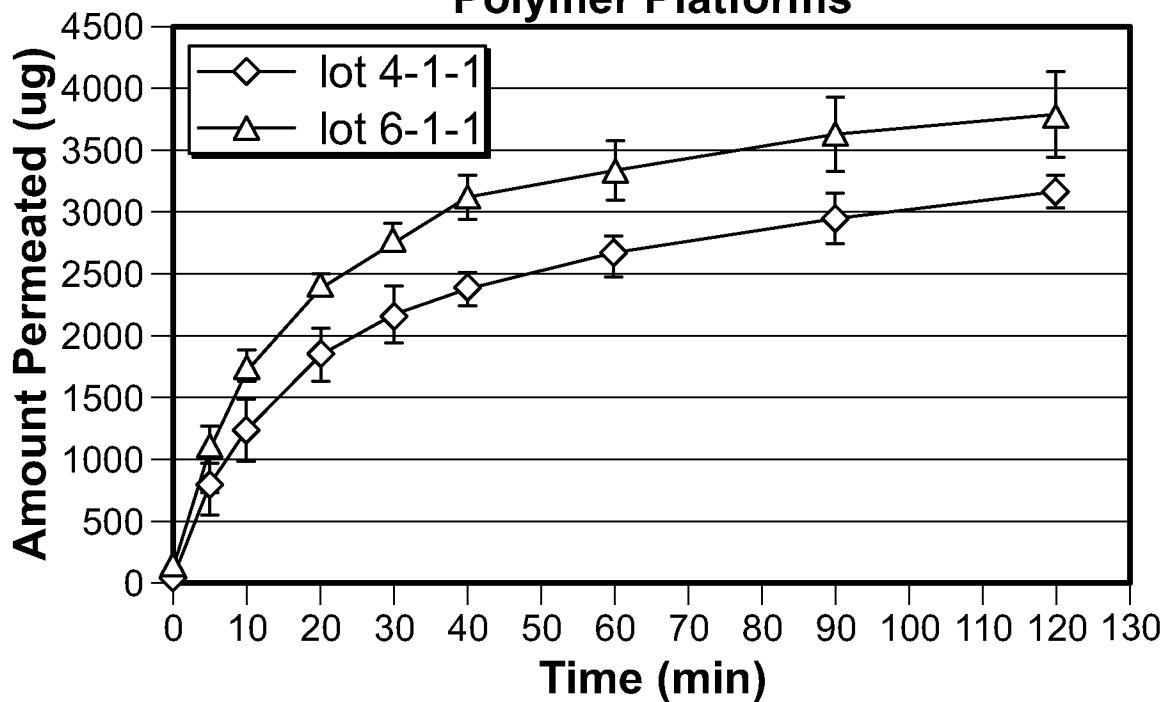


FIG. 6A

Impact of Enhancers on Epinephrine Release

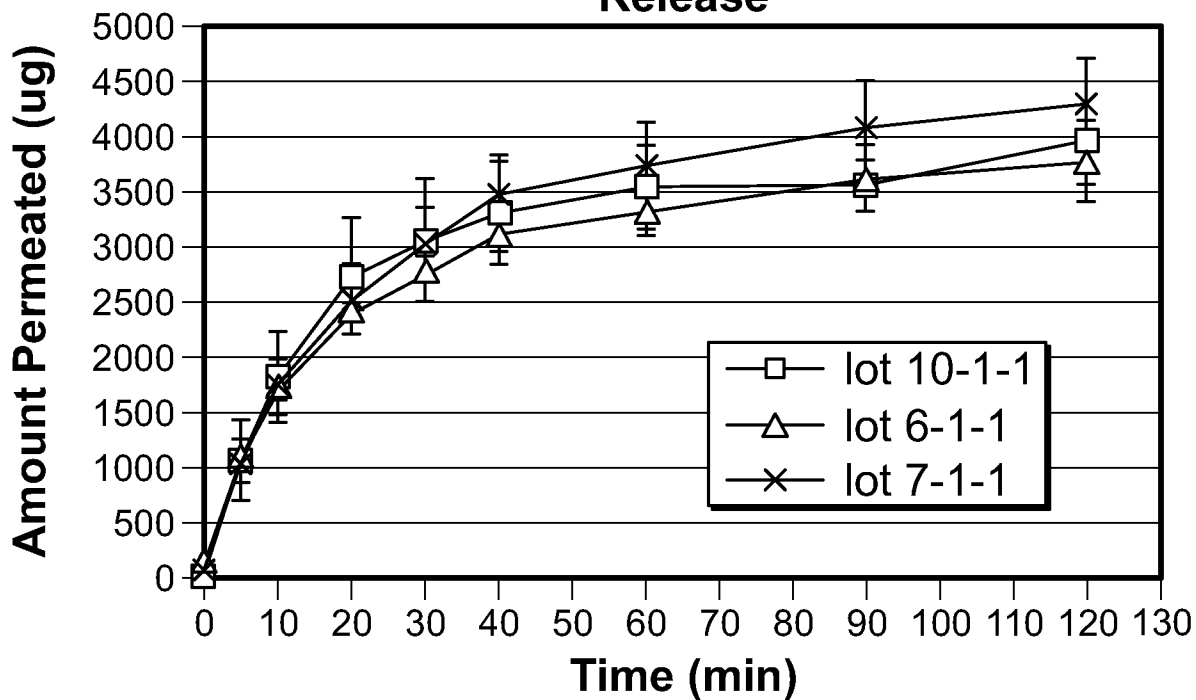


FIG. 6B

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

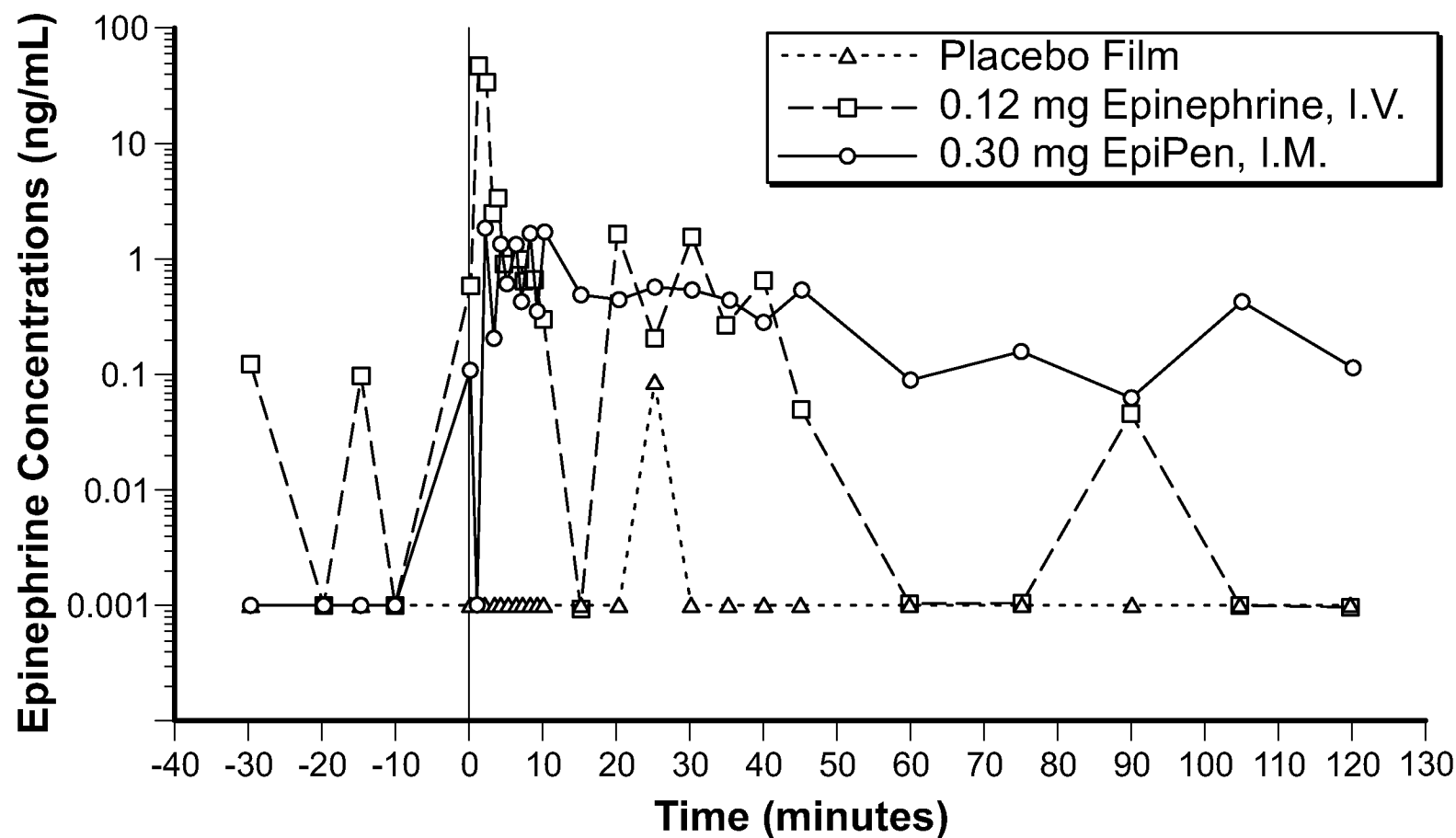


FIG. 7

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

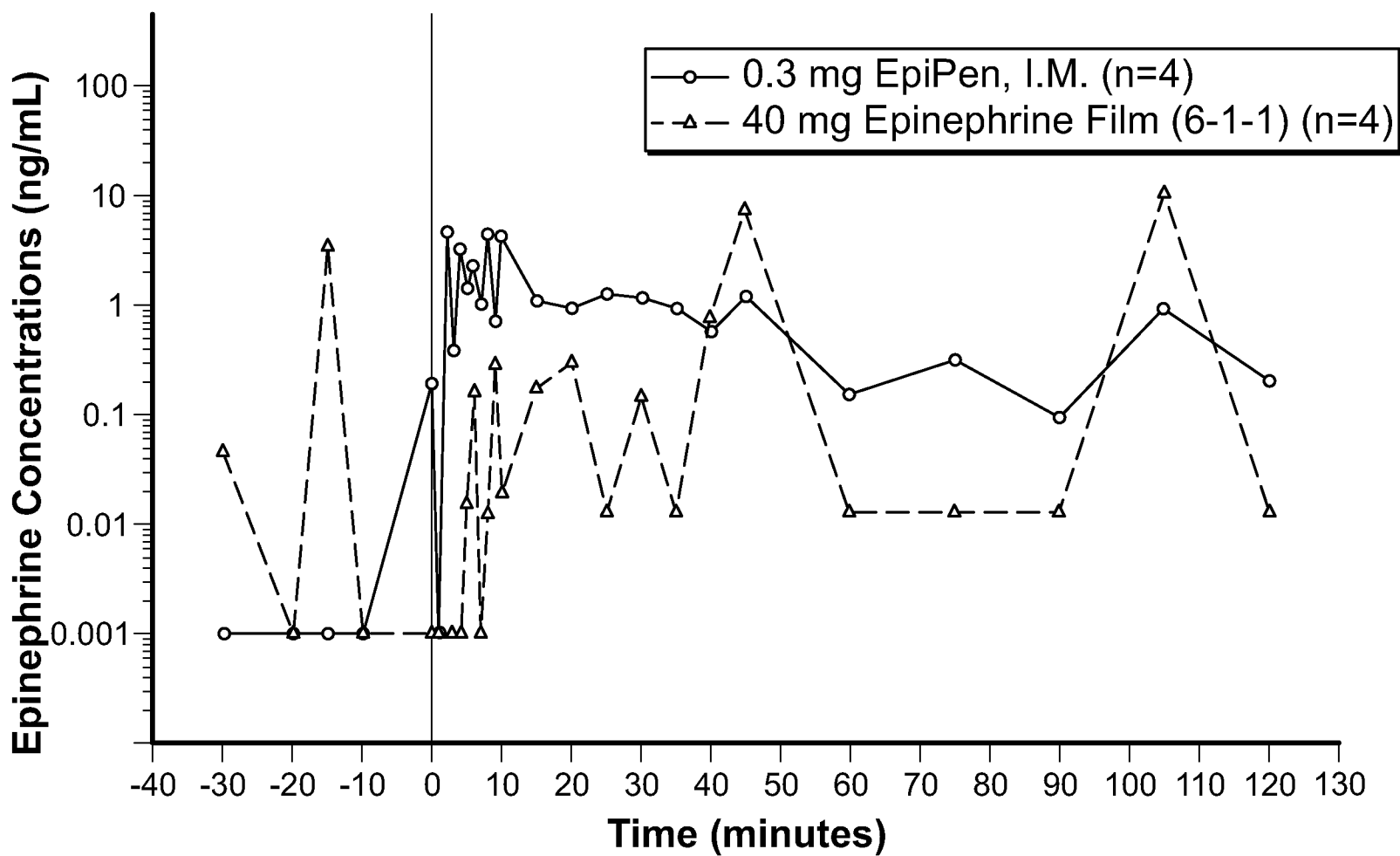


FIG. 8

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

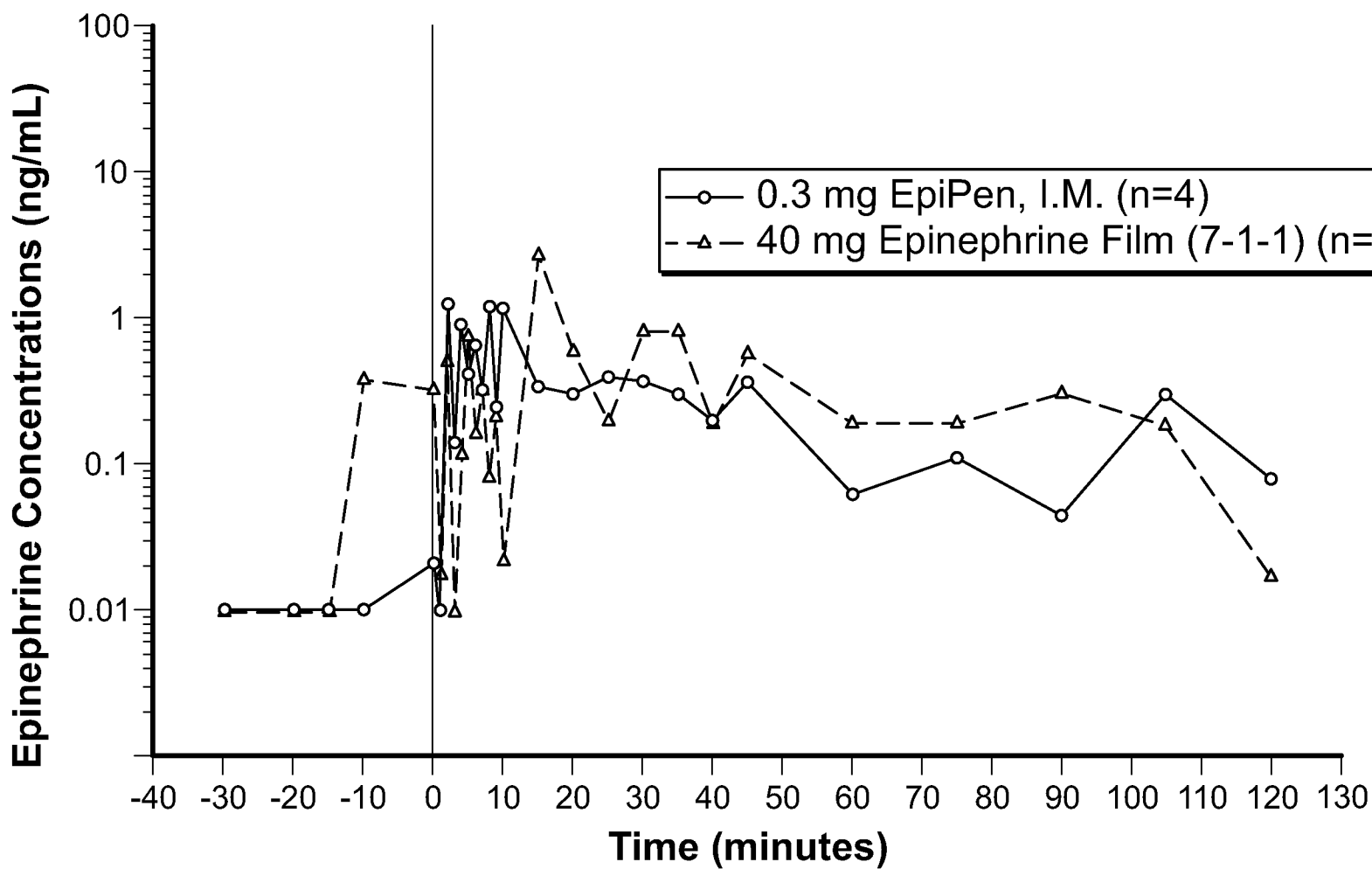


FIG. 9

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

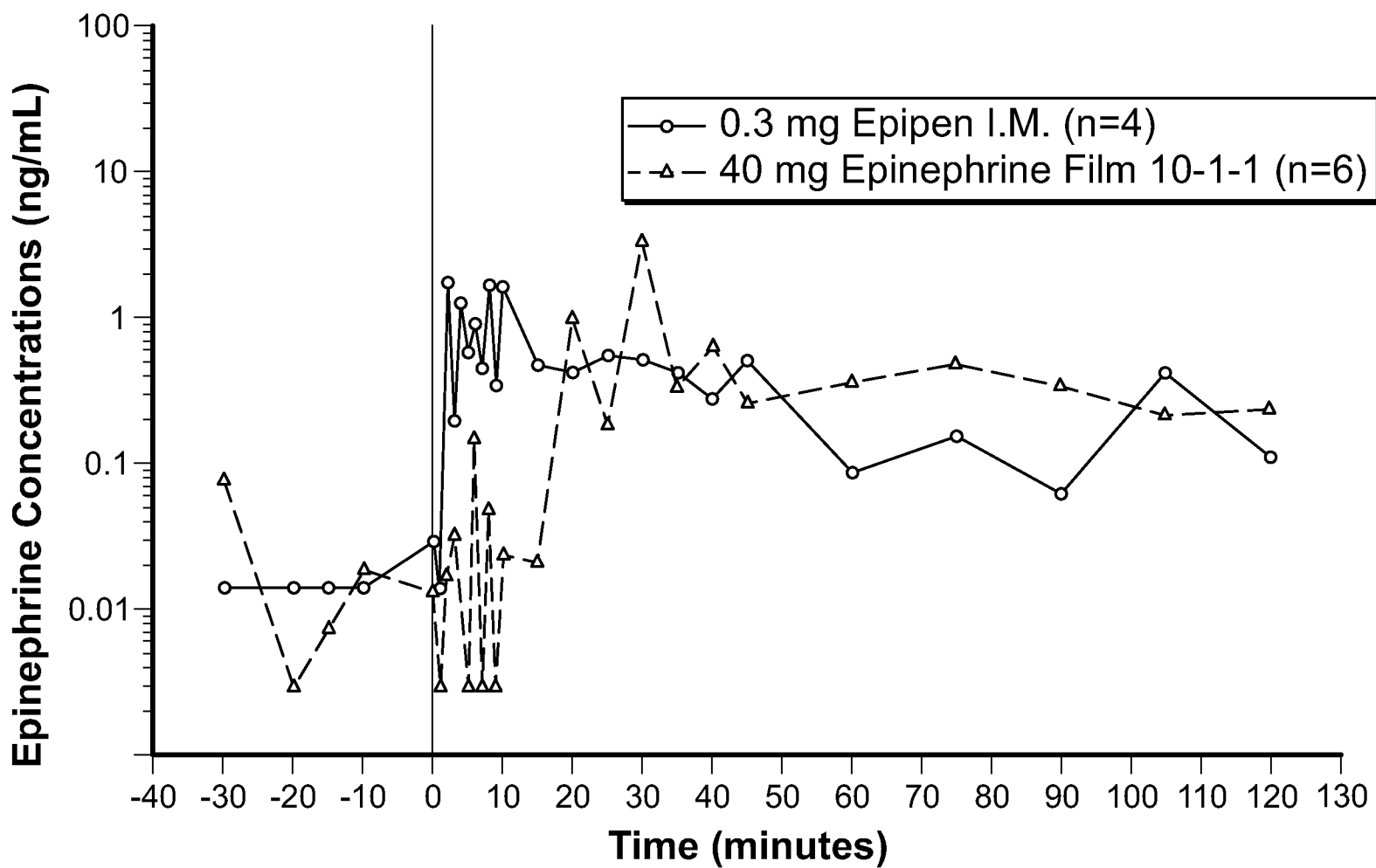


FIG. 10

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

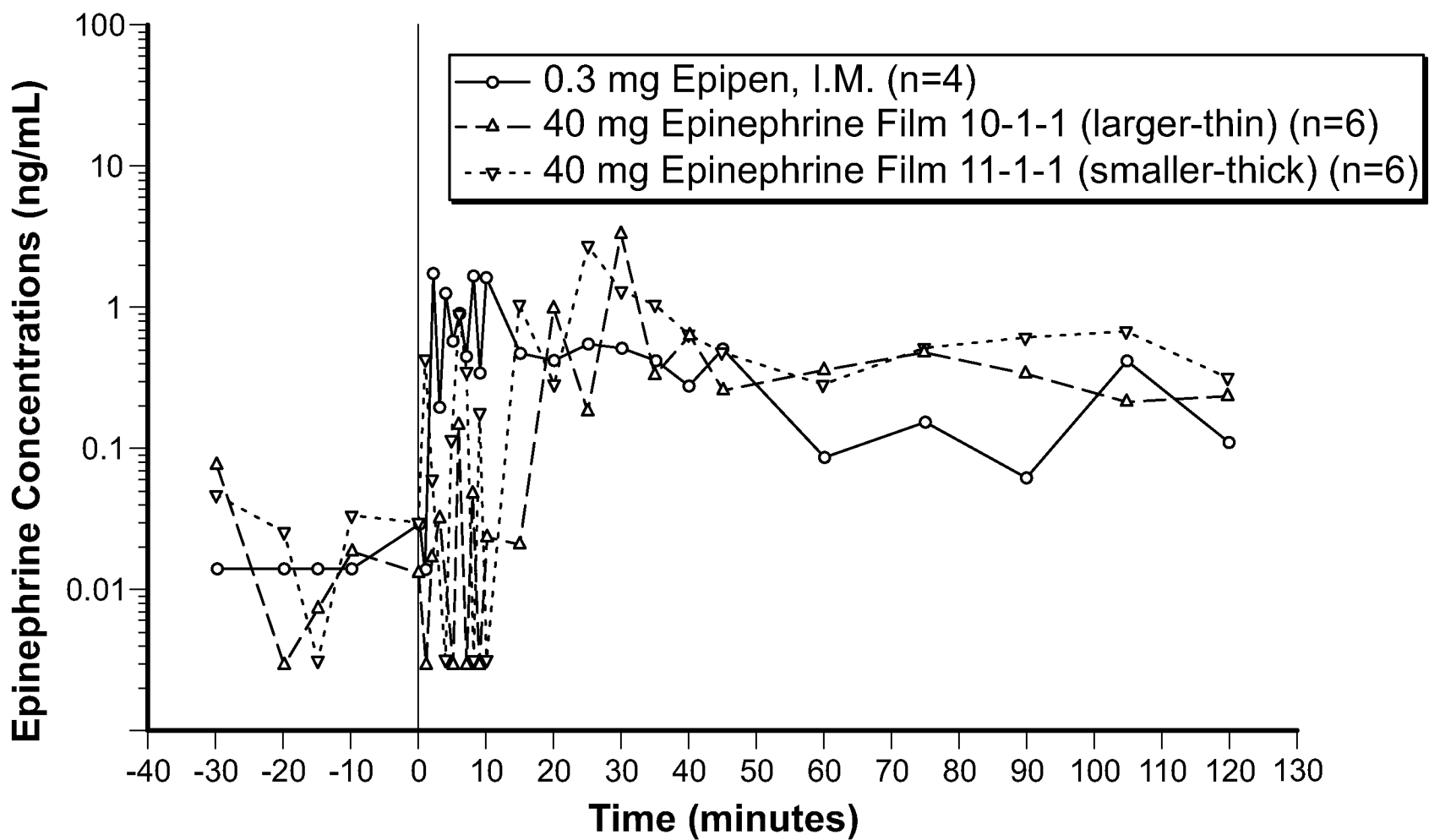


FIG. 11

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

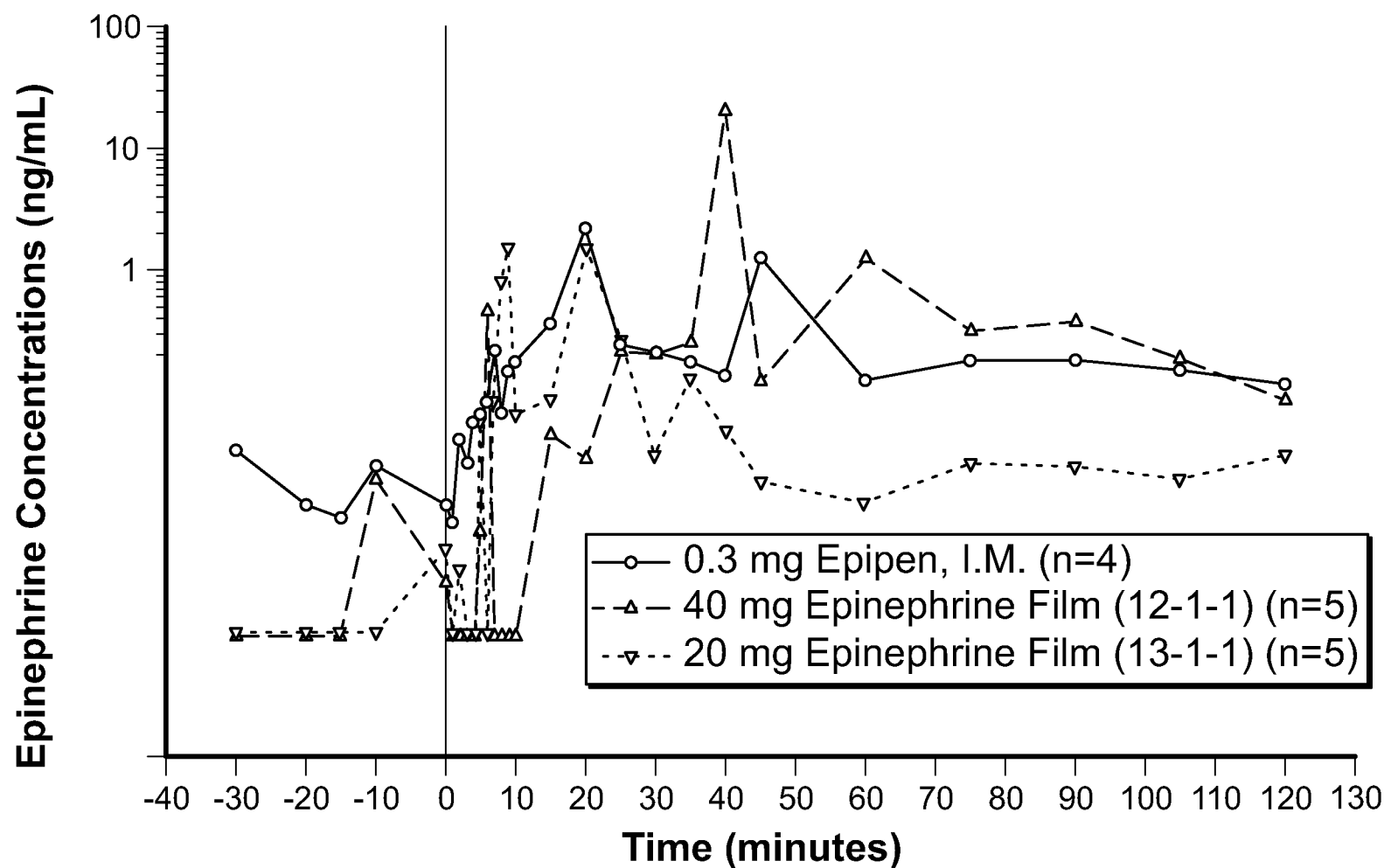


FIG. 12

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

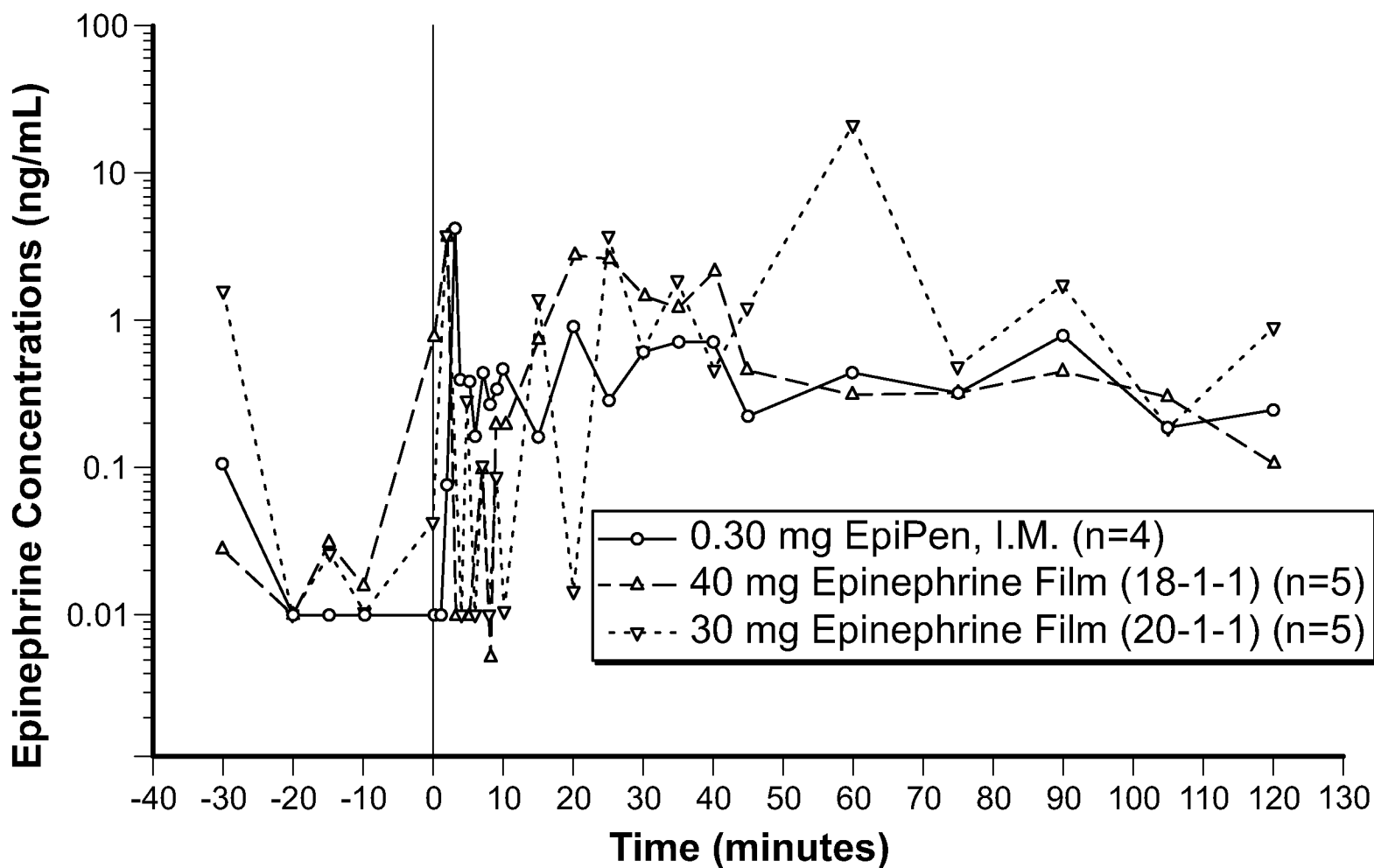


FIG. 13

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

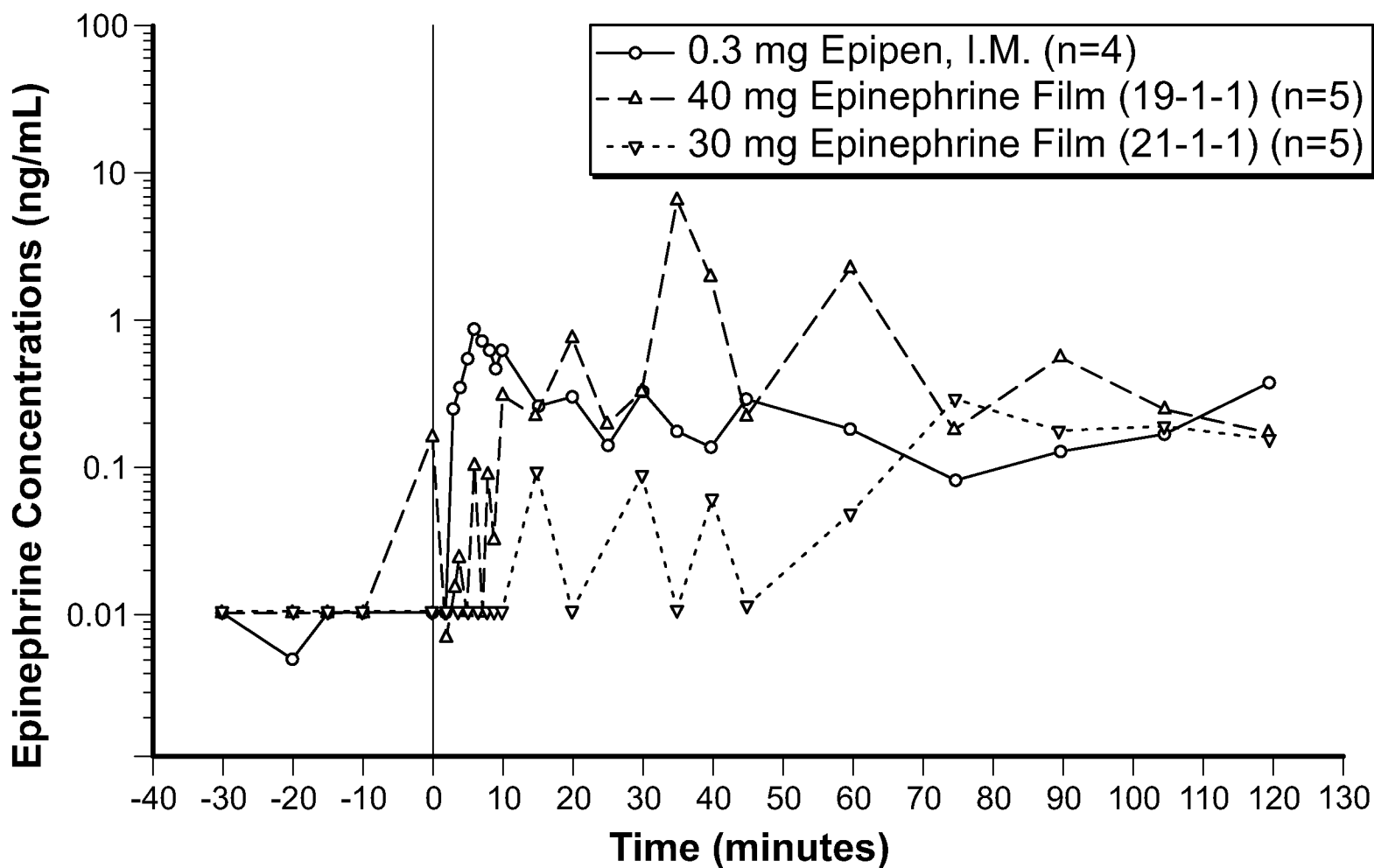


FIG. 14

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Average Amount Permeated vs Time

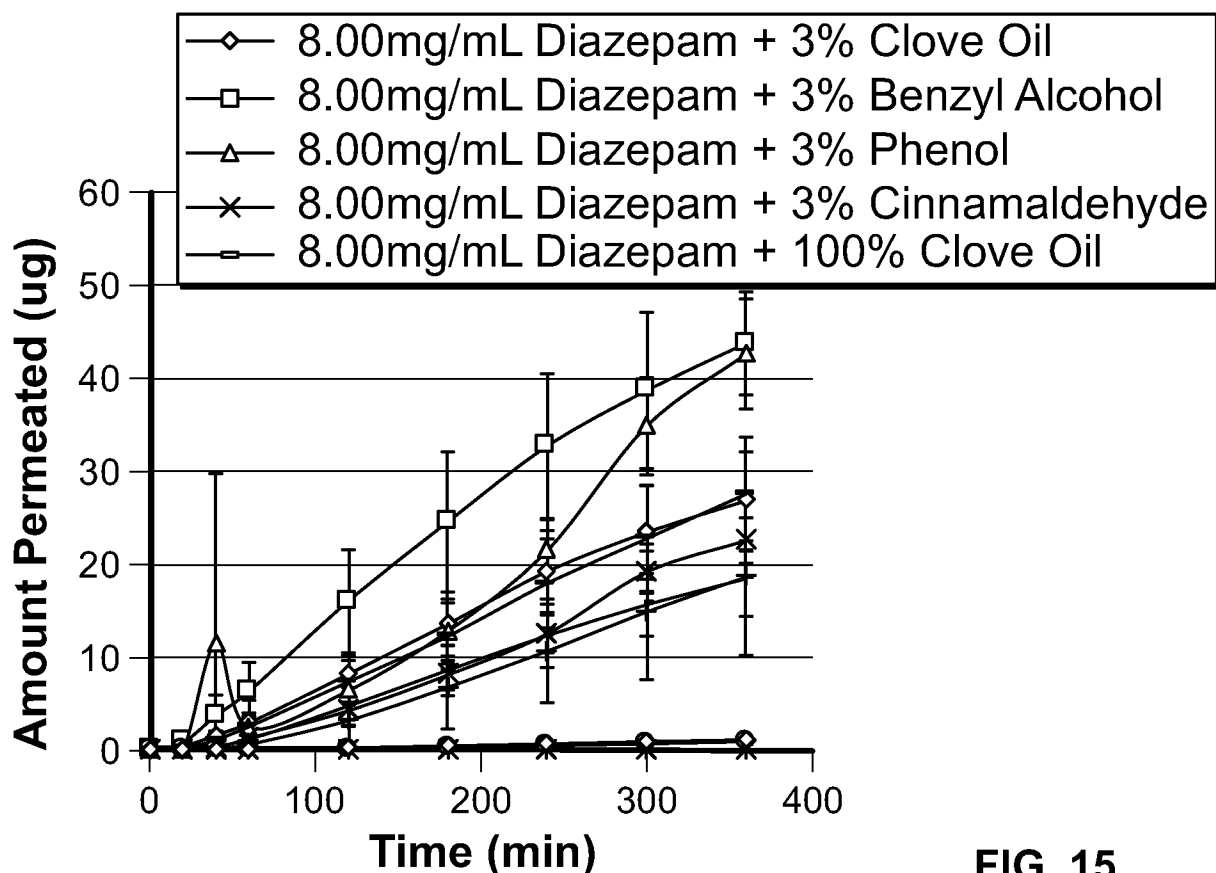


FIG. 15

Average Flux vs Time

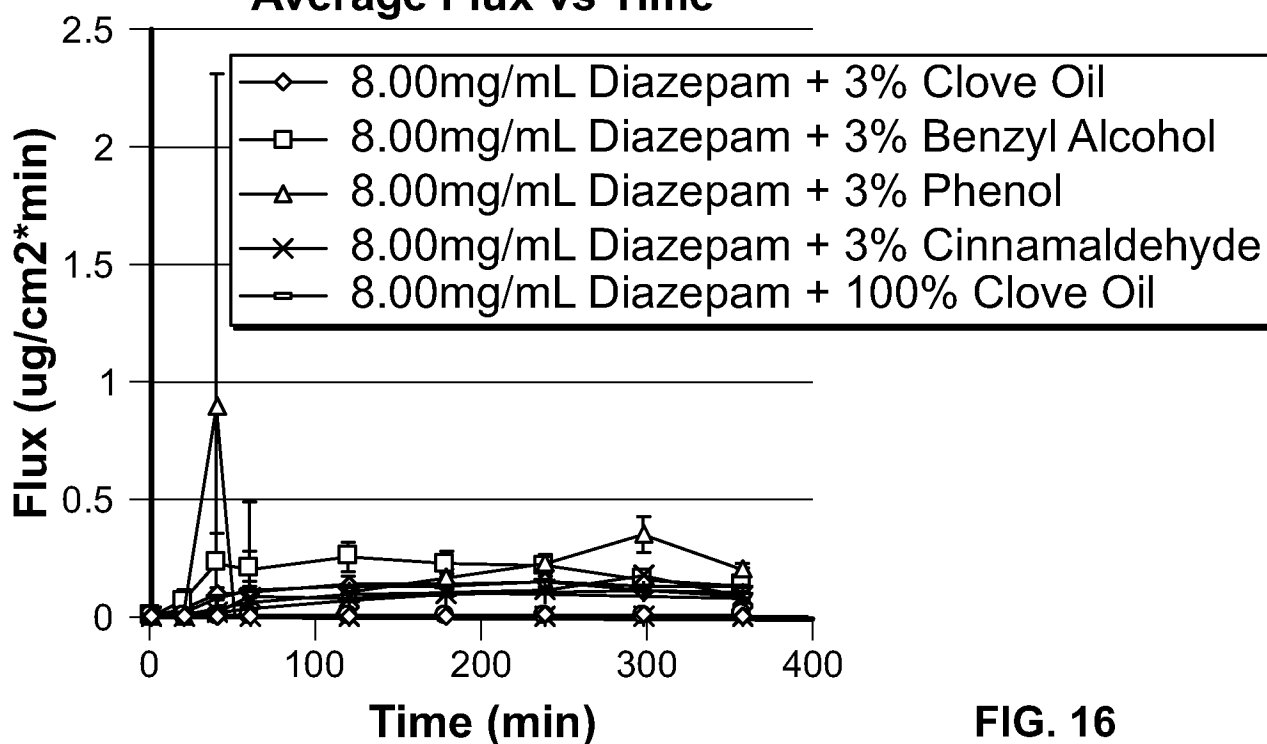
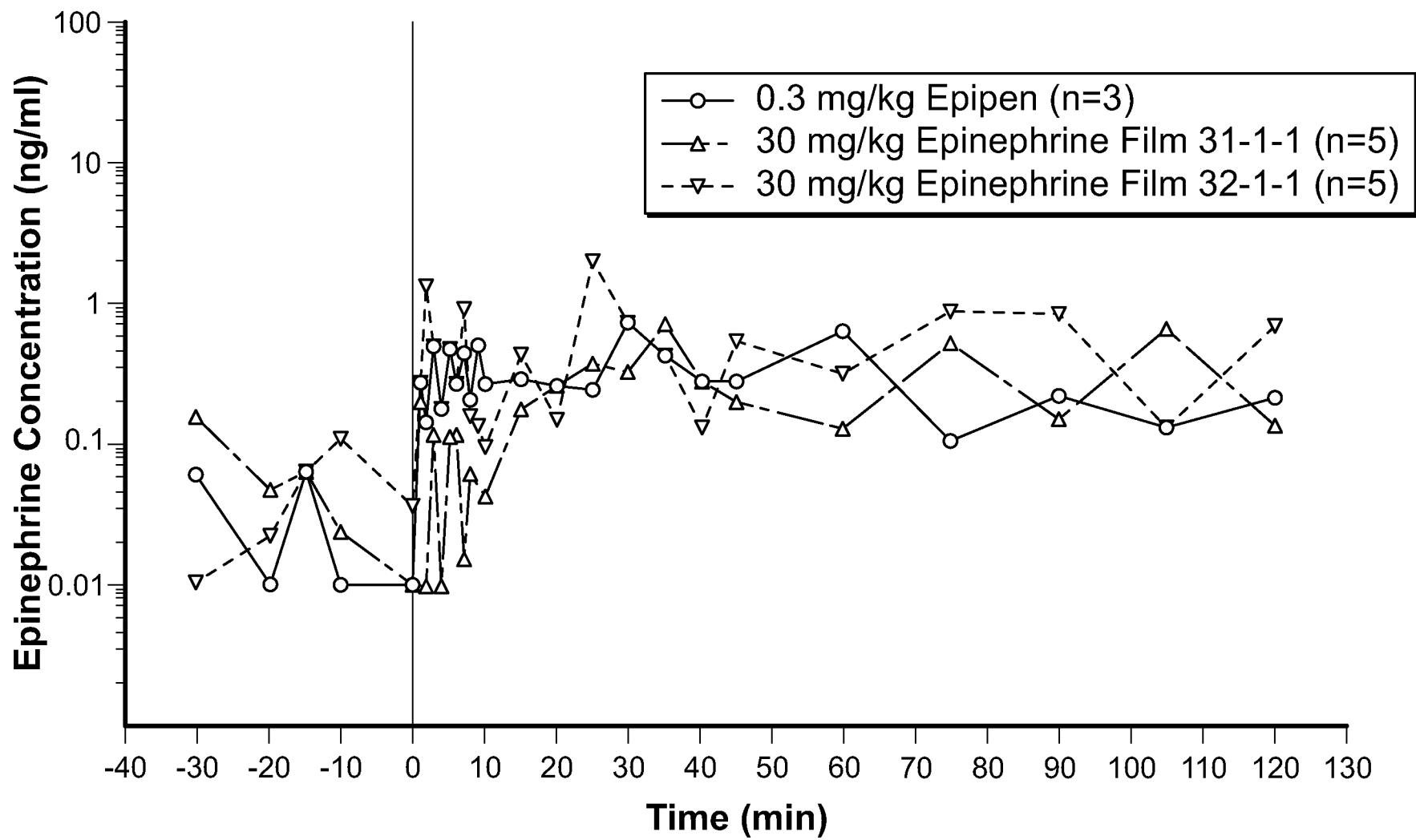


FIG. 16

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



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FIG. 17

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

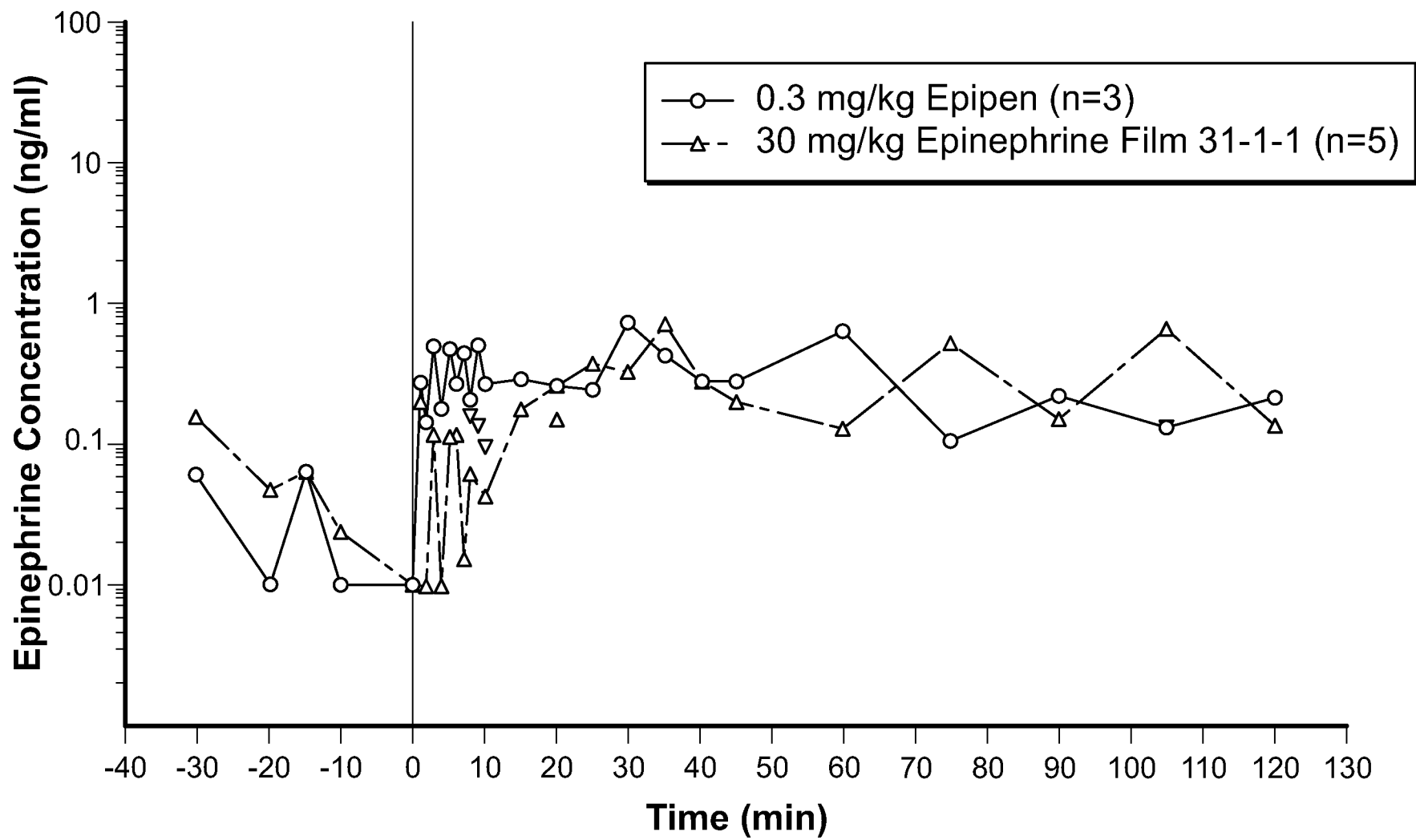
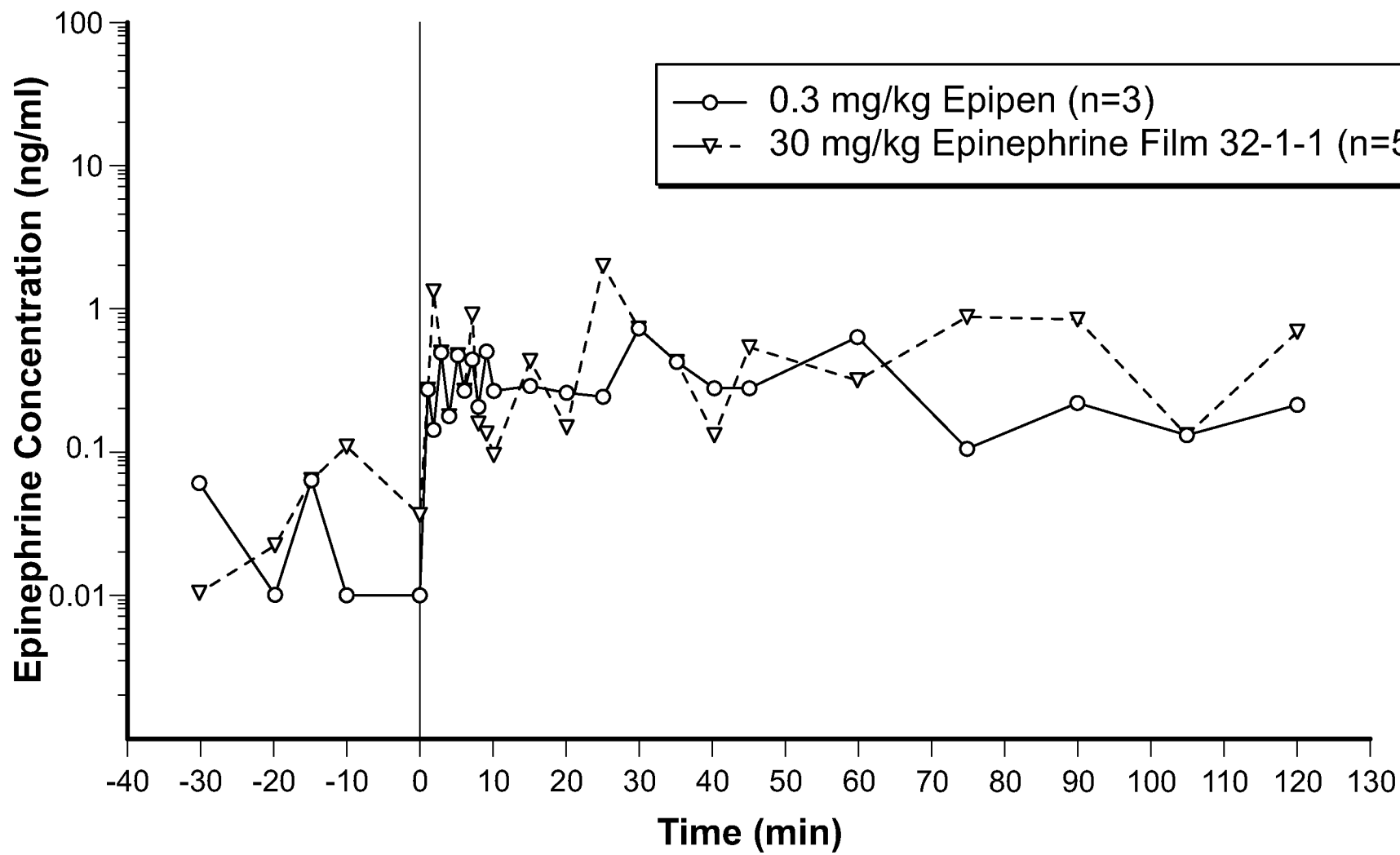


FIG. 18

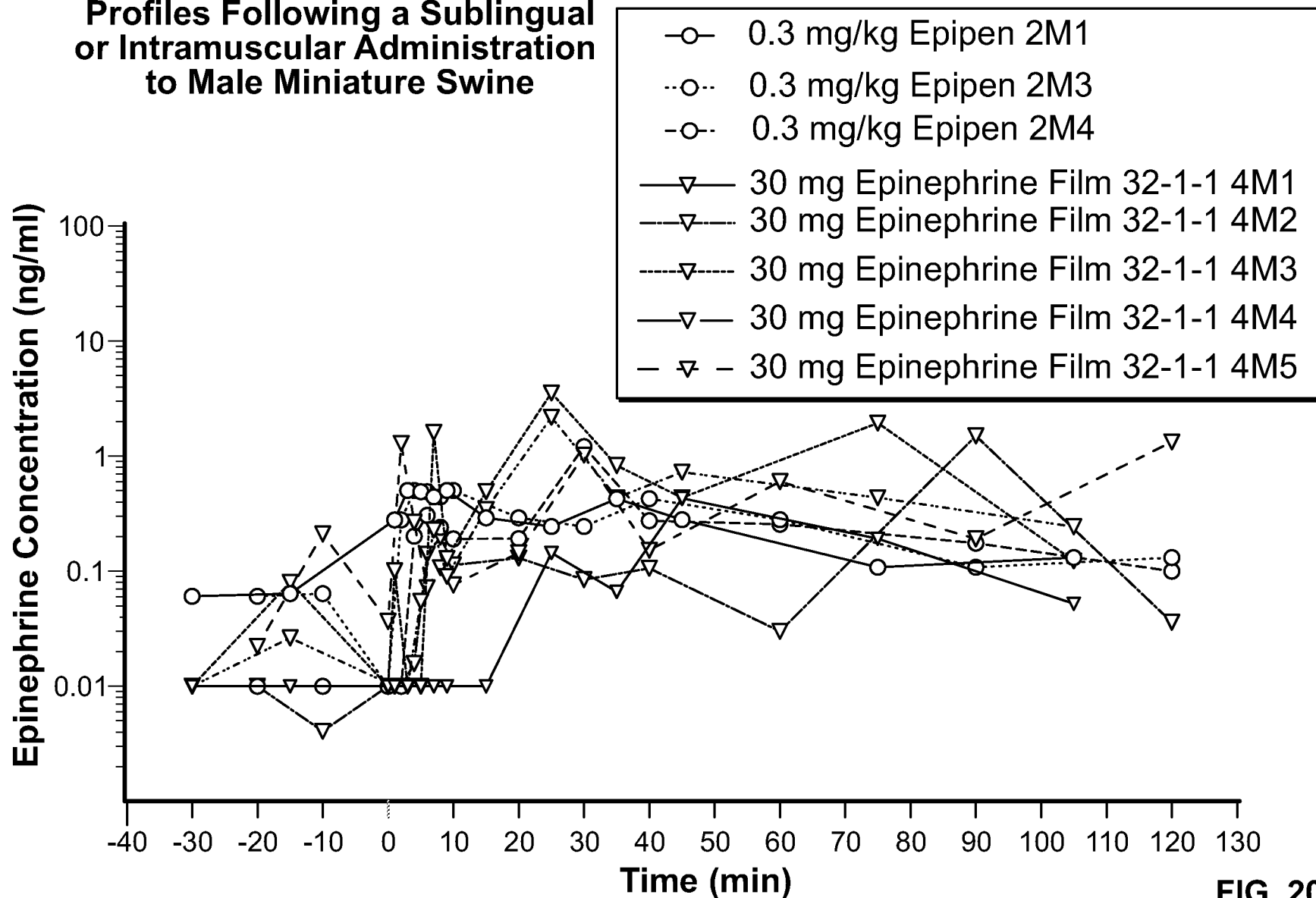
Epinephrine Plasma Concentration vs Time Profiles Following a Sublingual or Intramuscular Administration to Male Miniature Swine



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FIG. 19

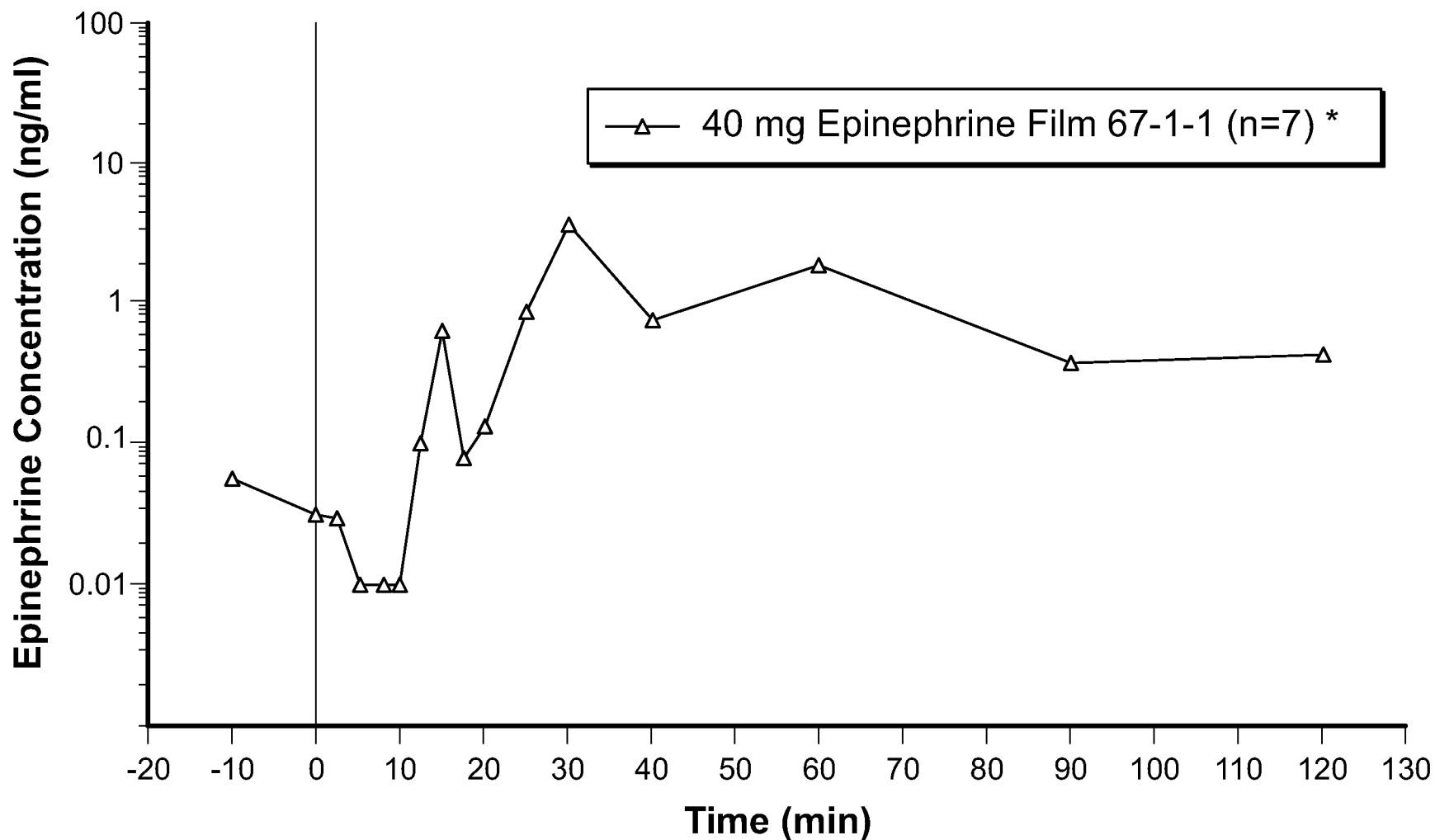
Epinephrine Plasma Concentration vs Time **Profiles Following a Sublingual** **or Intramuscular Administration** **to Male Miniature Swine**



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FIG. 20

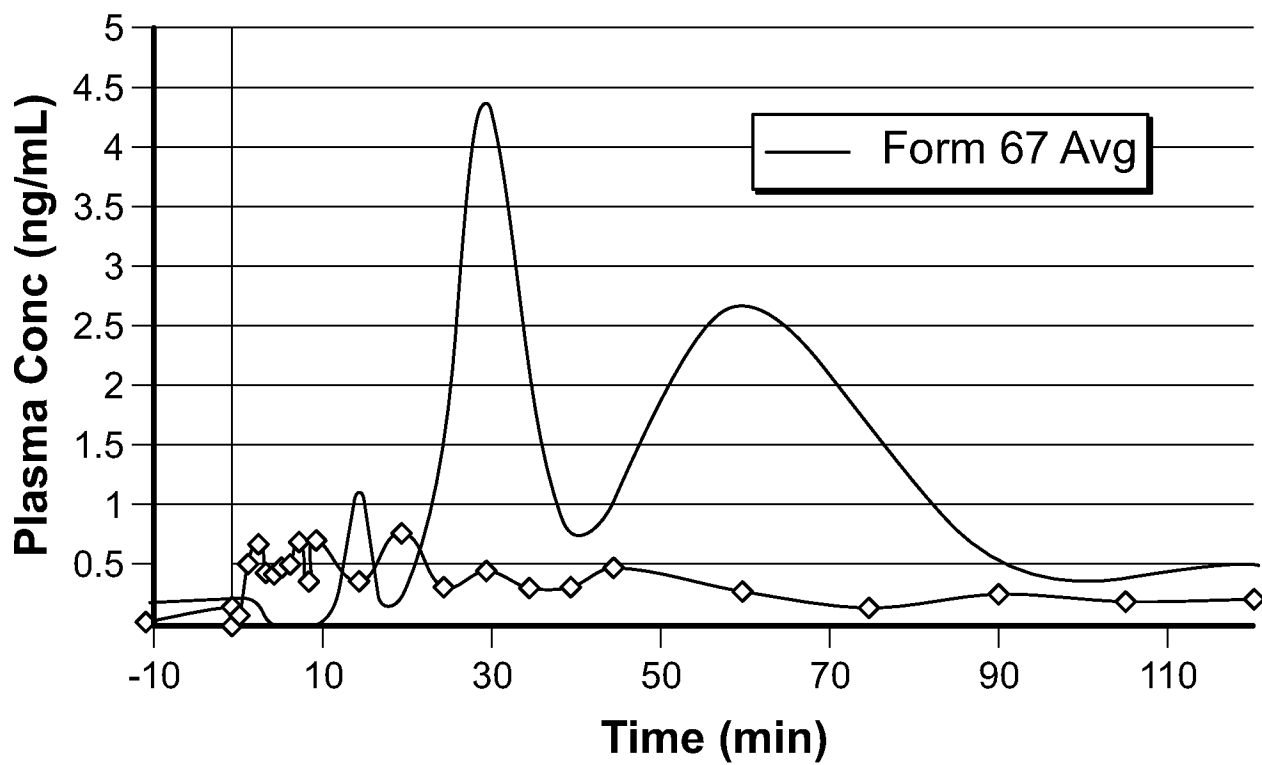
Epinephrine Plasma Concentration vs Time Profiles Following a Sublingual Administration to Male Miniature Swine



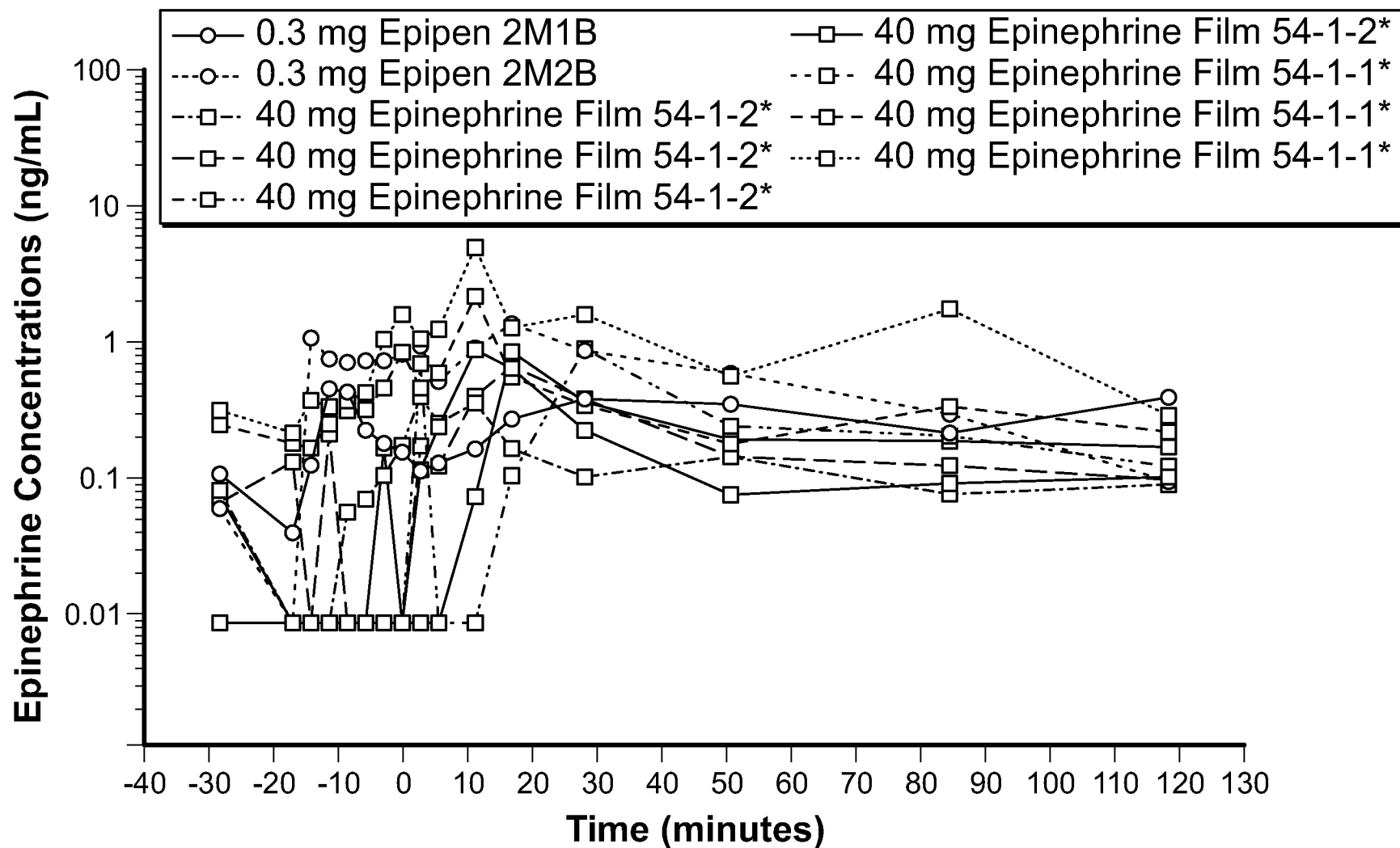
* Epinephrine Film Formulation also Contains 6% Clove Oil and 6% Labrasol

FIG. 21

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Formulation 67-40mg epi with 6% Clove + 6% Labrasol**FIG. 22**

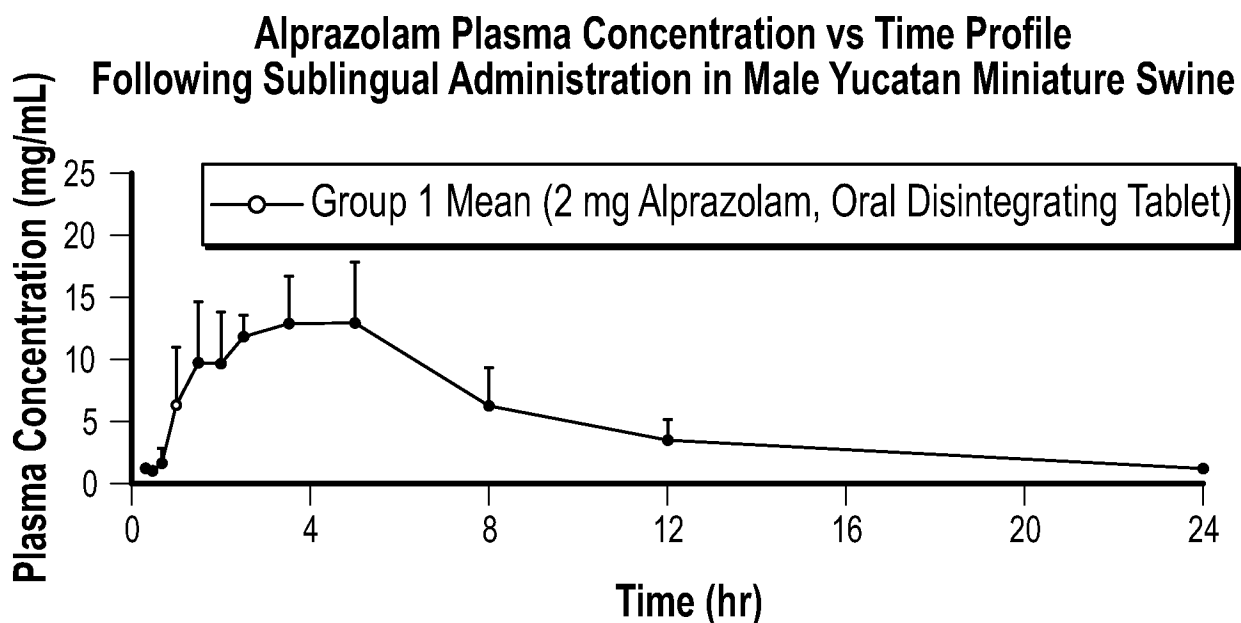
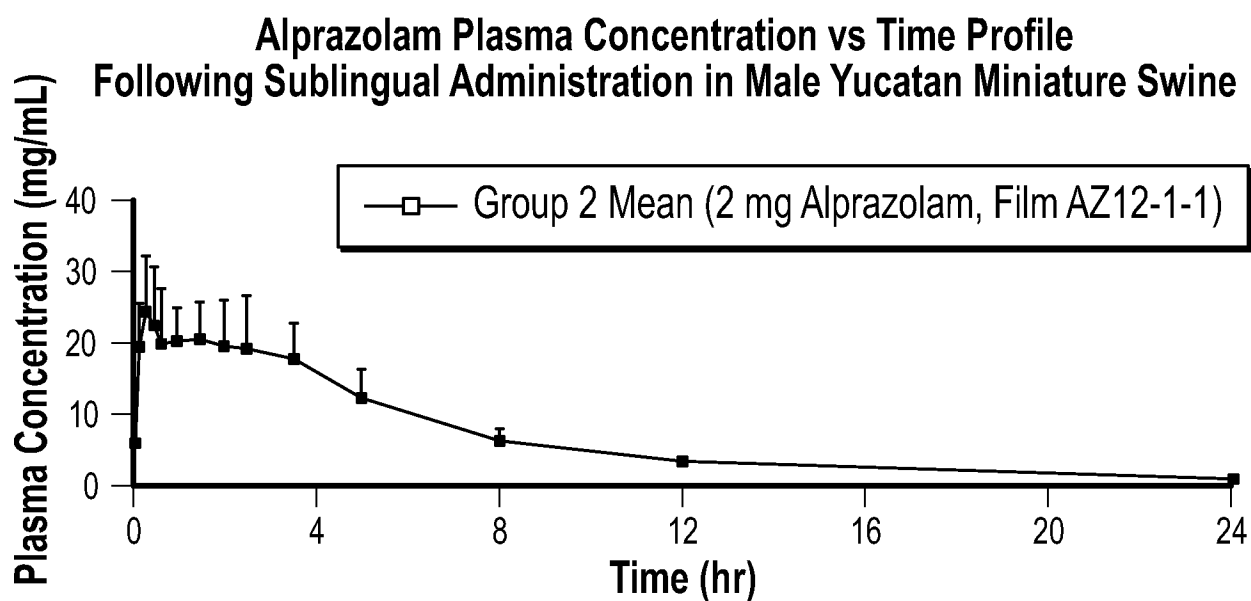
Epinephrine Plasma Concentration vs Time Profiles Following a Sublingual or Intramuscular Administration to Male Miniature Swine



* Epinephrine Film Formulation also Contains 9% Clove Oil and 3% Labrasol

FIG. 23

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**FIG. 24A****FIG. 24B**

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**Alprazolam Plasma Concentration vs Time Profile Following
an Sublingual Administration in Male Yucatan Miniature Swine**

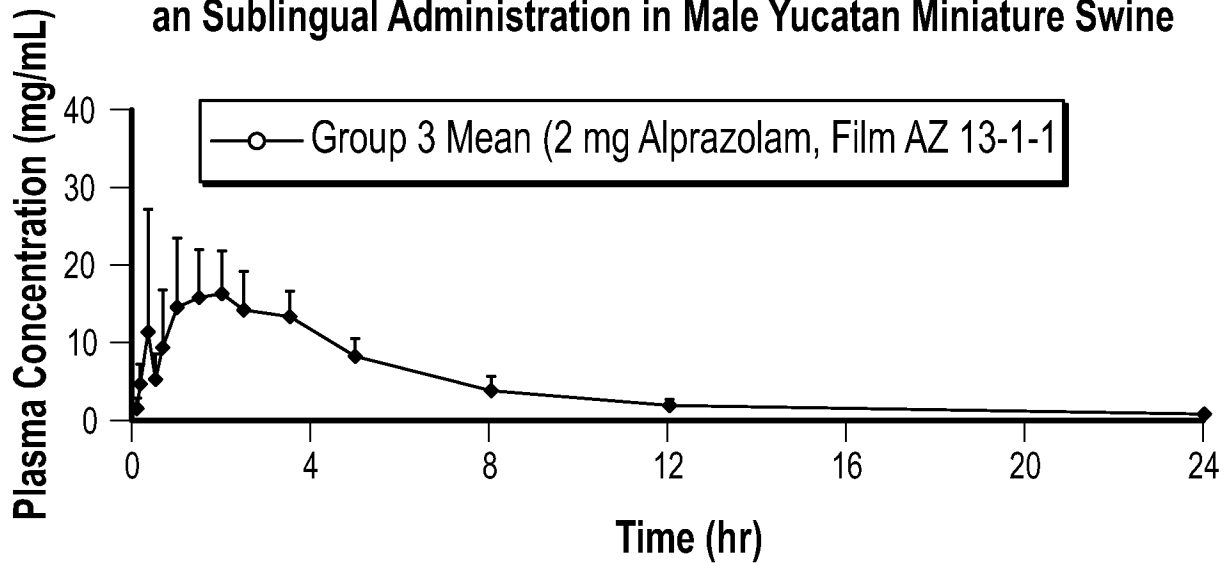


FIG. 24C

**Alprazolam Plasma Concentration vs Time Profiles Following a Sublingual
Administration of ODT or Pharm Film to Male Miniature Swine**

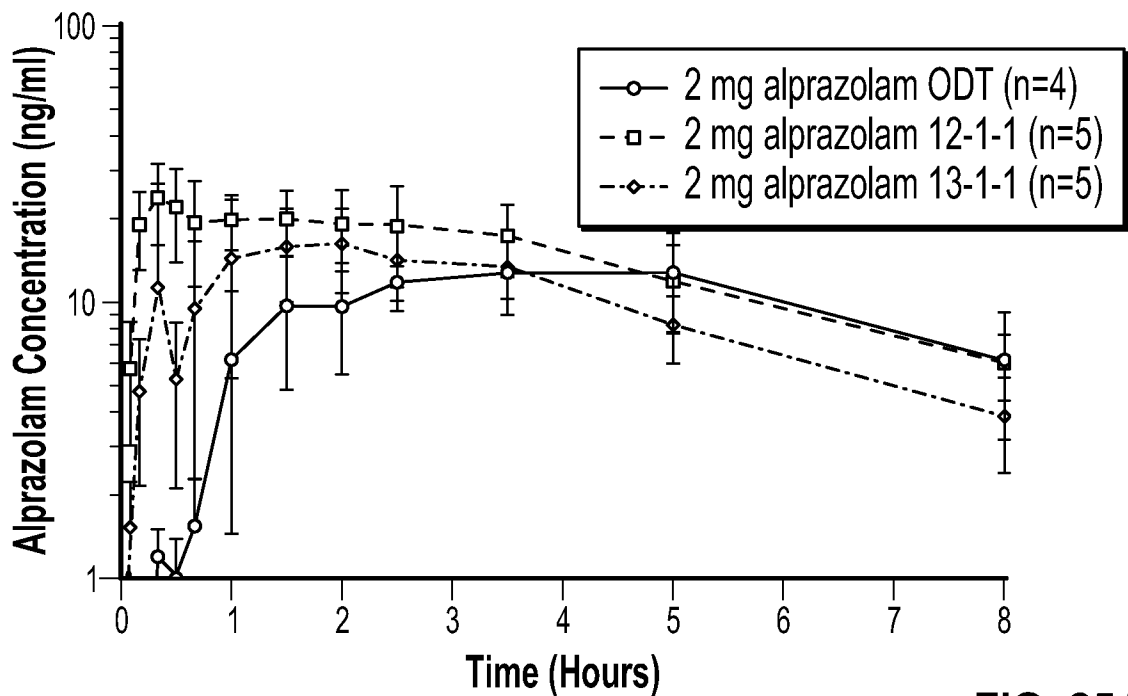
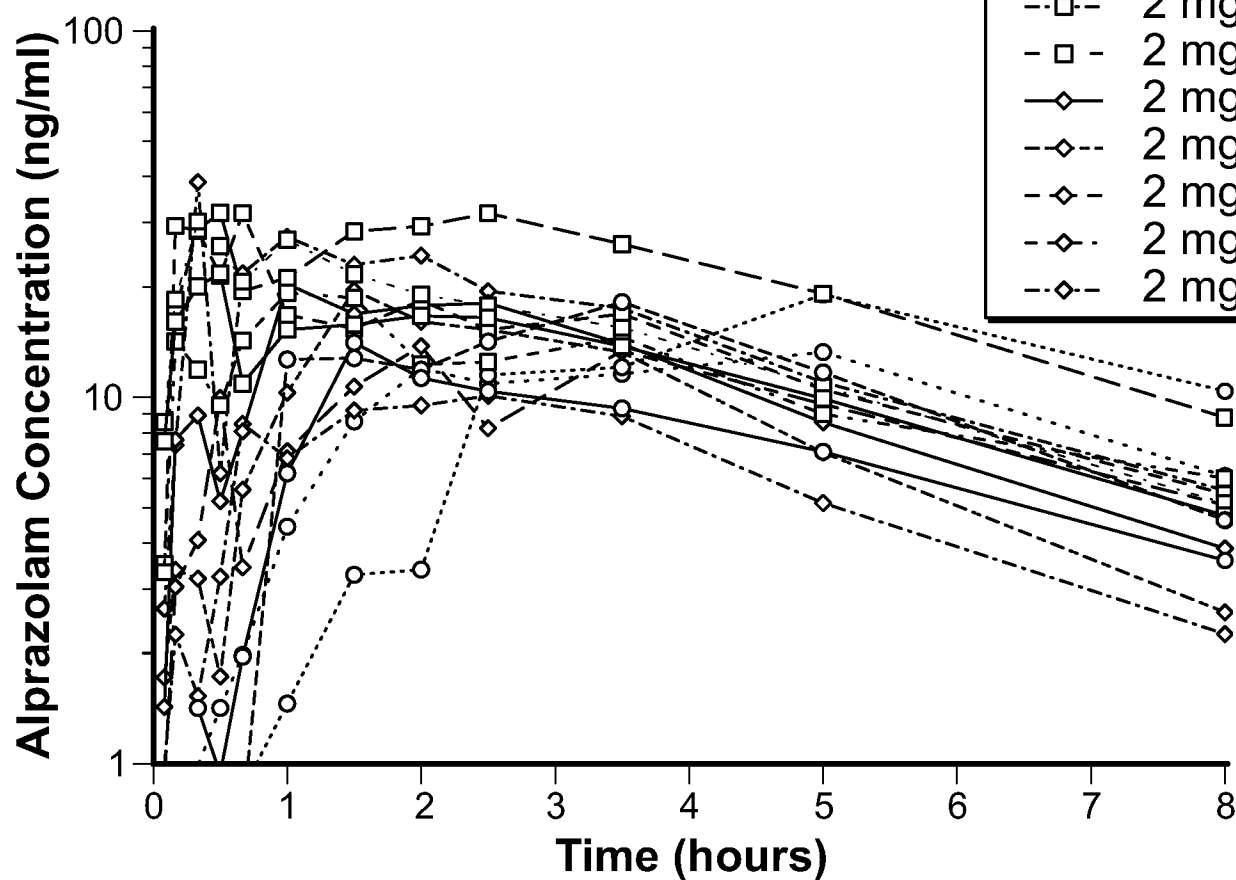


FIG. 25A

**Alprazolam Plasma Concentration vs Time
Profiles Following a Sublingual
Administration of ODT or PharmFilm
to Male Miniature Swine**



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FIG. 25B

Alprazolam Plasma Concentration vs Time Profiles Following a Sublingual Administration of ODT or PharmFilm to Male Miniature Swine

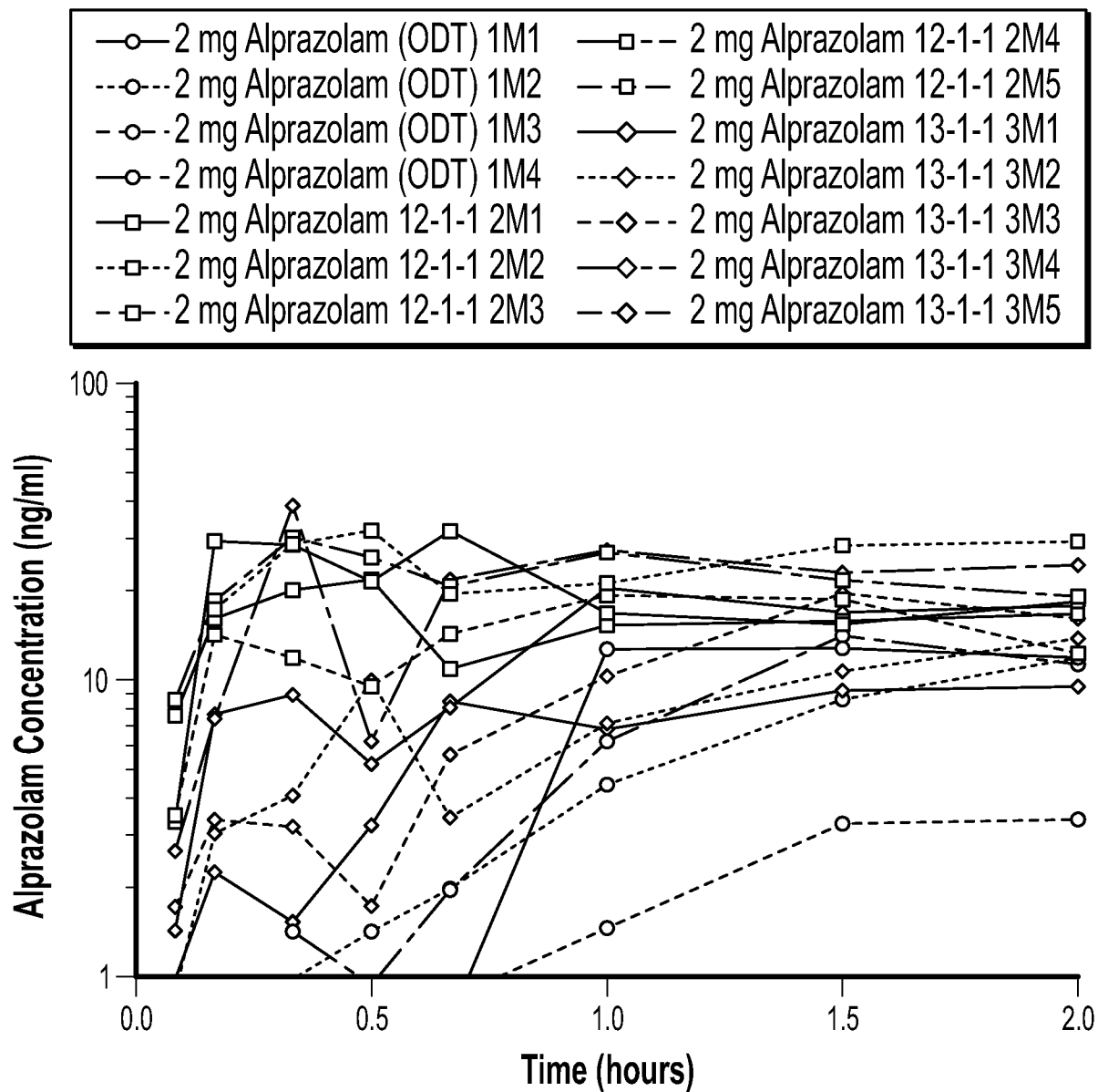


FIG. 25C

**Alprazolam Plasma Concentration vs Time Profiles
Following a Sublingual Administration of ODT
or PharmFilm to Male Miniature Swine**

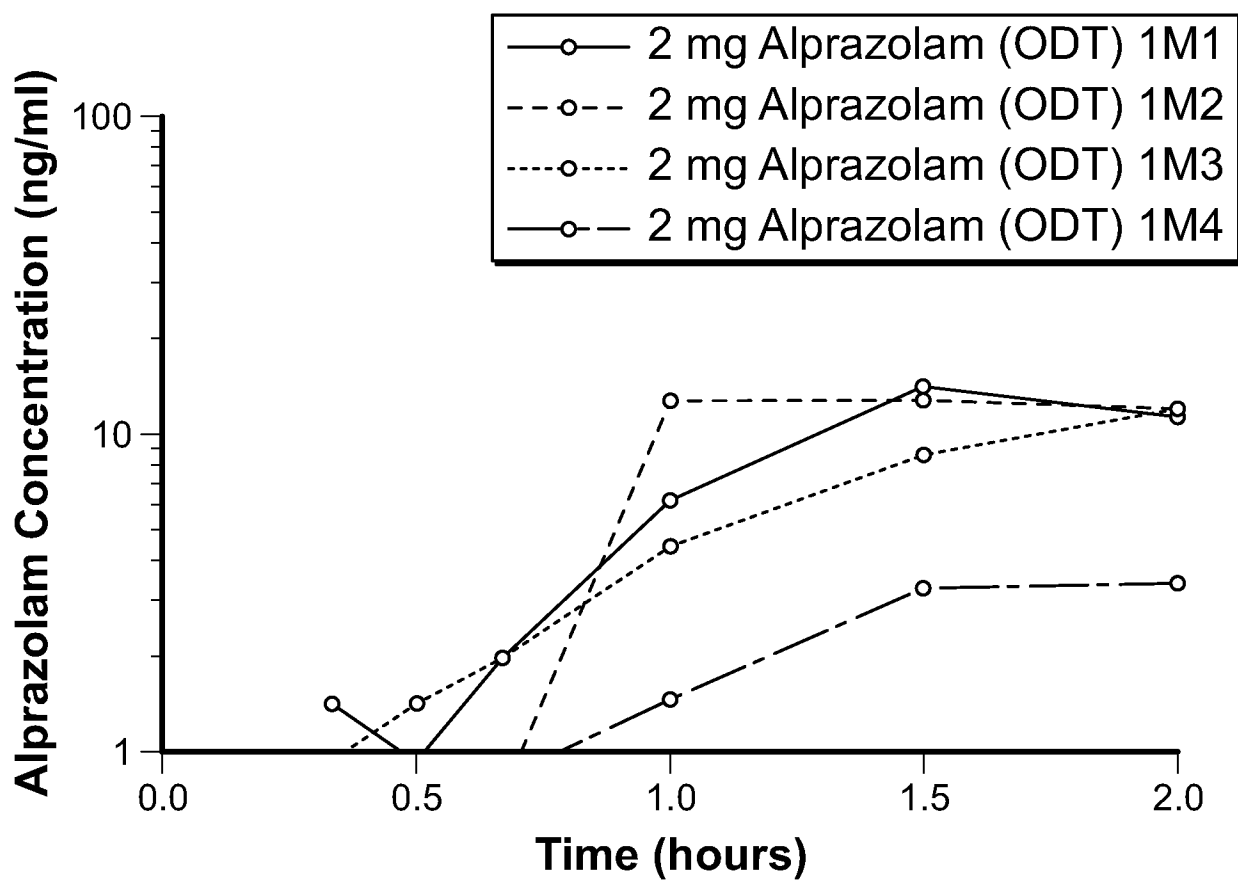


FIG. 26A

**Alprazolam Plasma Concentration vs Time Profiles
Following a Sublingual Administration of ODT
or PharmFilm to Male Miniature Swine**

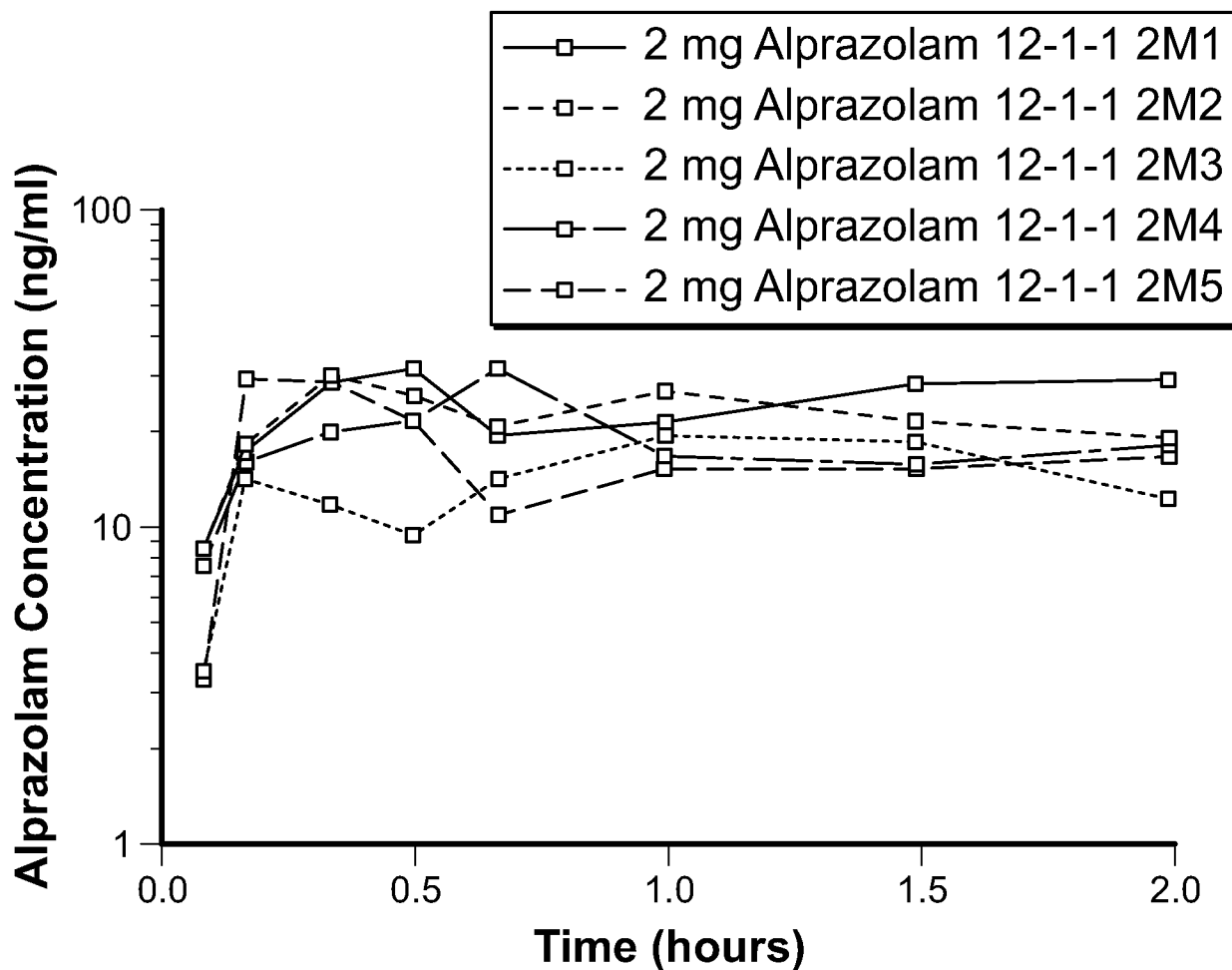


FIG. 26B

**Alprazolam Plasma Concentration vs Time Profiles
Following a Sublingual Administration of ODT
or PharmFilm to Male Miniature Swine**

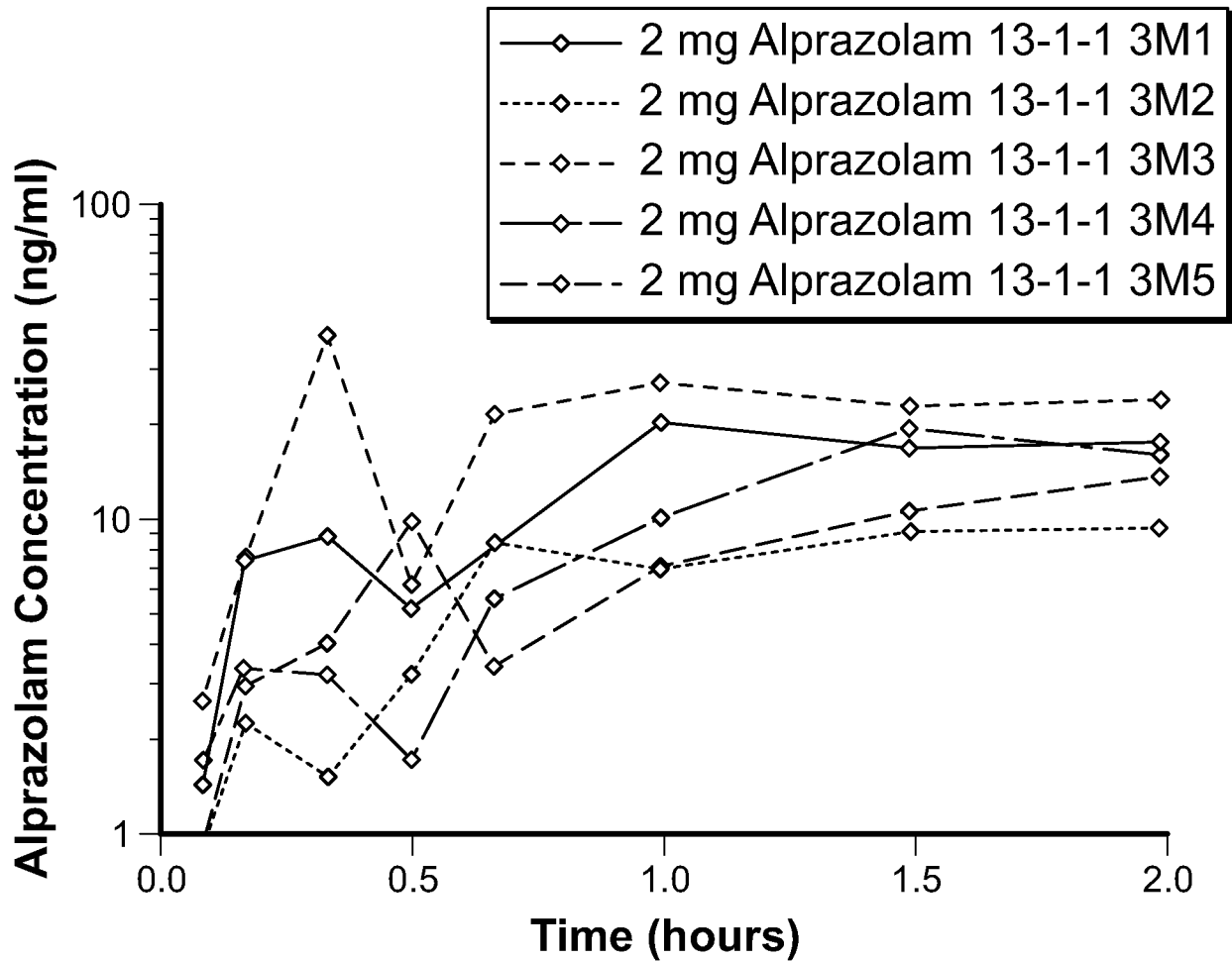


FIG. 26C

**Alprazolam Plasma Concentration vs Time Profile
Following Sublingual Administration in
Male Yucatan Miniature Swine**

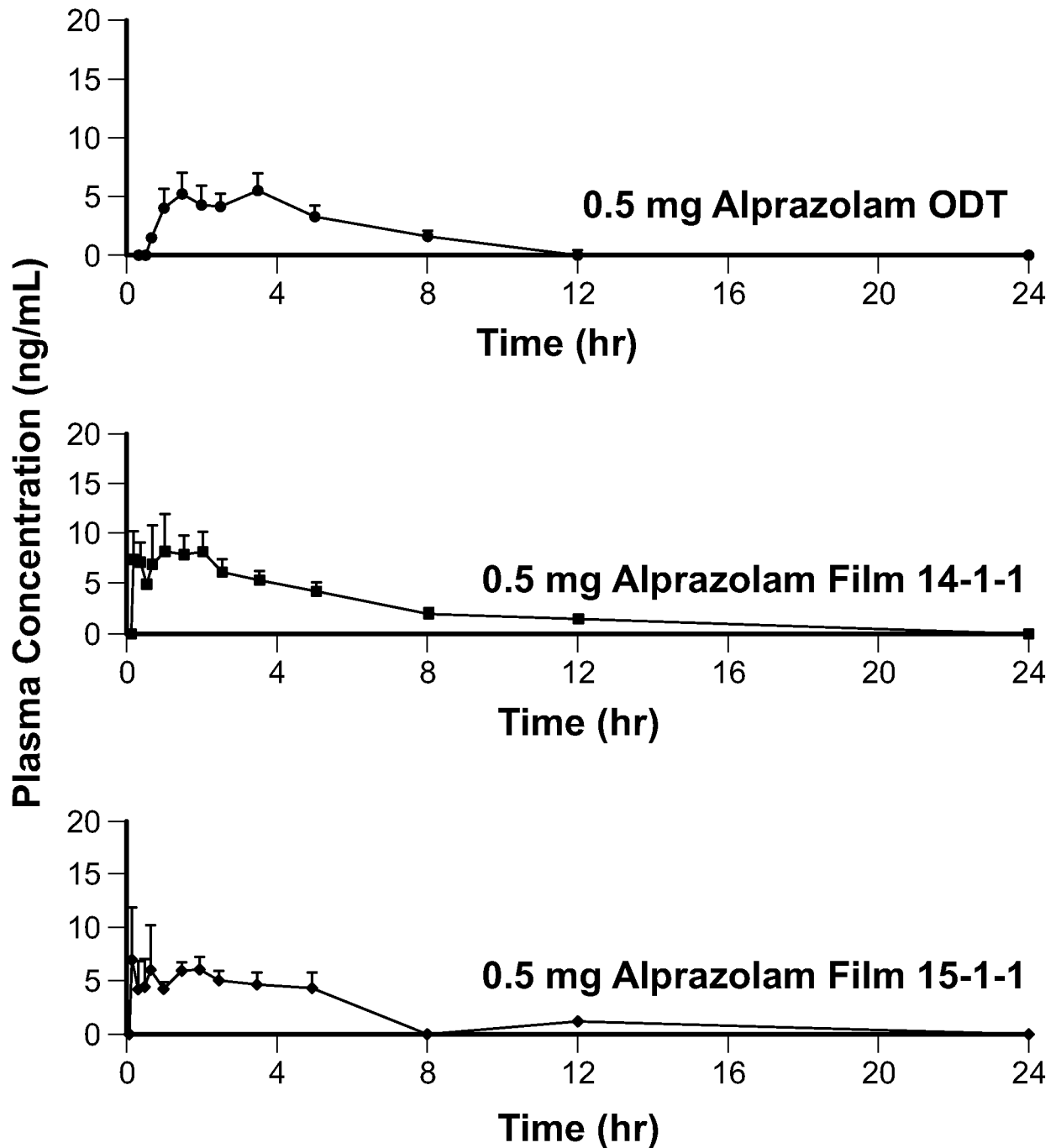


FIG. 27A

**Alprazolam Plasma Concentration vs Time Profiles
Following a Sublingual Administration of ODT
or PharmFilm to Male Miniature Swine**

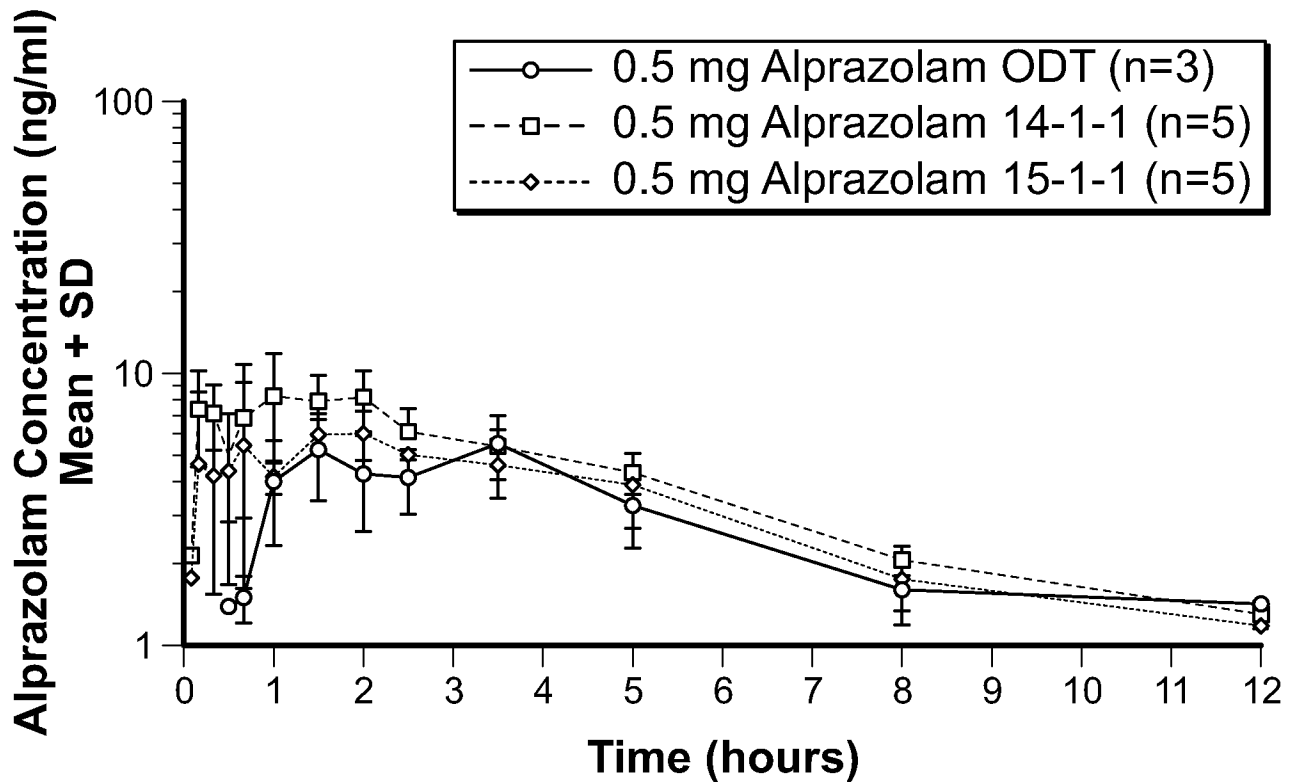


FIG. 27B

Alprazolam Plasma Concentration vs Time Profiles Following a Sublingual Administration of ODT or PharmFilm to Male Miniature Swine

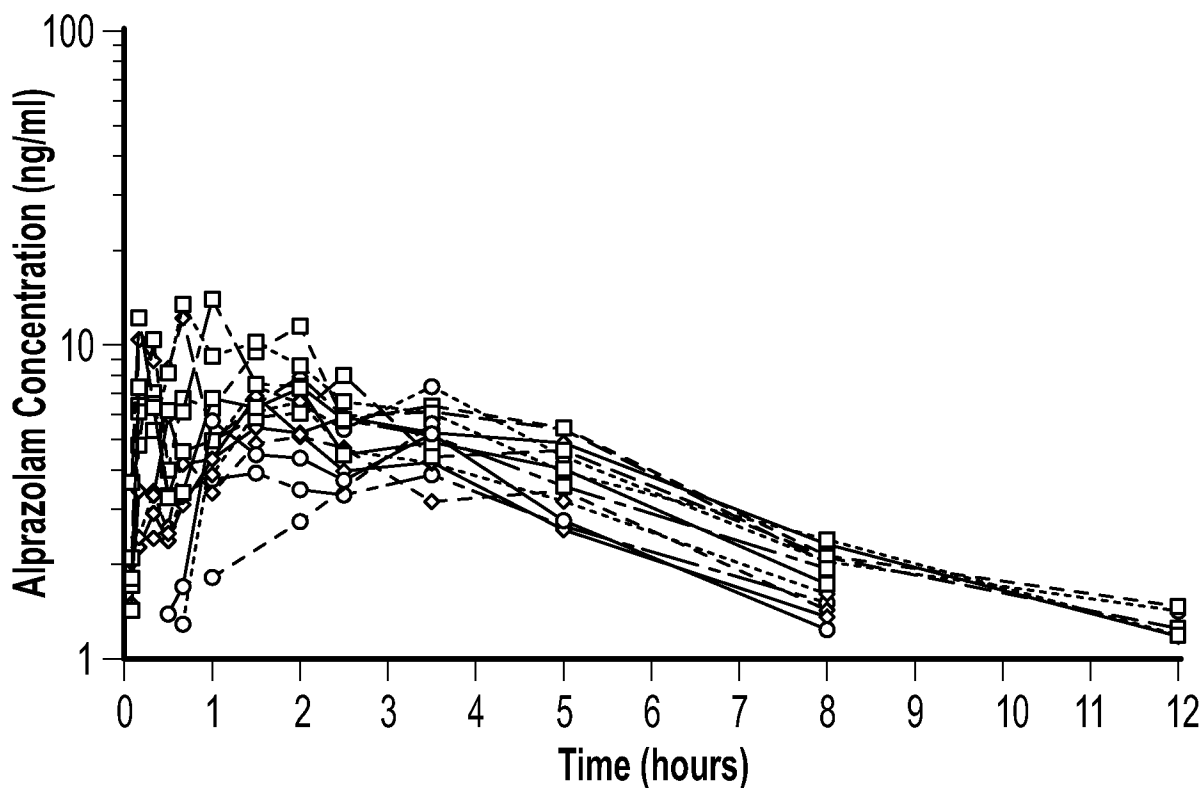
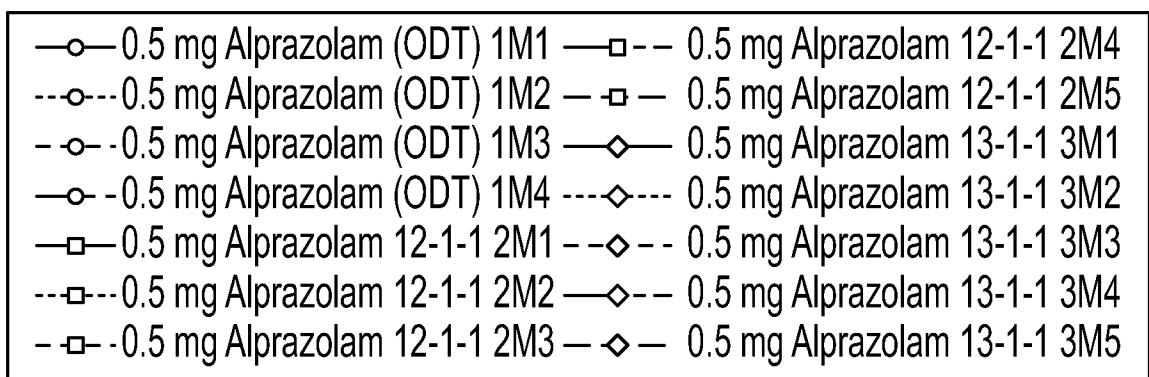


FIG. 27C

PHARMACEUTICAL COMPOSITIONS WITH ENHANCED PERMEATION

CLAIM FOR PRIORITY

This application is a continuation-in-part of U.S. Patent Application No. 15/717,856, filed September 27, 2017, which is a continuation-in-part of U.S. Patent Application No. 15/587,376, filed May 4, 2017, which claims priority under 35 U.S.C. §119(e) to U.S. Patent Application Serial No. 62/331,993 filed on May 5, 2016, each of which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

This invention relates to pharmaceutical compositions.

BACKGROUND

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

SUMMARY

In general a pharmaceutical composition can include a polymeric matrix, a pharmaceutically active component in the polymeric matrix, and an adrenergic receptor interacter. In certain embodiments, the pharmaceutical composition can further include a permeation enhancer. An adrenergic receptor interacter can be an adrenergic receptor blocker. The permeation enhancer can also be a flavonoid, or used in combination with a flavonoid.

In certain embodiments, the adrenergic receptor interacter can be a terpenoid, terpene or a C3-C22 alcohol or acid. The adrenergic receptor interacter can be a sesquiterpene. In certain embodiments, the adrenergic receptor interacter can include farnesol, linoleic acid, arachidonic acid, docosahexanoic acid, eicosapentanoic acid, or docosapentanoic acid, or combinations thereof.

In certain embodiments, a pharmaceutical composition can include a polymeric matrix, a pharmaceutically active component in the polymeric matrix, and an aporphine alkaloid interacter.

5 In other embodiments, a pharmaceutical composition can include a polymeric matrix, a pharmaceutically active component in the polymeric matrix, and a vasodilator interacter.

In certain embodiments, the pharmaceutical composition can be a film further comprising a polymeric matrix, the pharmaceutically active component being contained in the polymeric matrix.

In certain embodiments, the adrenergic receptor interacter can be a phytoextract.

10 In certain embodiments, the permeation enhancer can be a phytoextract.

In certain embodiments, the permeation enhancer can include a phenylpropanoid.

In other embodiments, the phenylpropanoid can be eugenol.

In certain embodiments, the pharmaceutical composition can include a fungal extract.

15 In certain embodiments, the pharmaceutical composition can include saturated or unsaturated alcohol.

In certain embodiments, the alcohol can be benzyl alcohol.

In some cases, the flavonoid, phytoextract, phenylpropanoid, eugenol, or fungal extract can be used as a solubilizer.

20 In other embodiments, the phenylpropanoid can be eugenol. In certain embodiments, the phenylpropanoid can be a eugenol acetate. In certain embodiments, the phenylpropanoid can be a cinnamic acid. In other embodiments, the phenylpropanoid can be a cinnamic acid ester. In other embodiments, phenylpropanoid can be a cinnamic aldehyde.

25 In other embodiments, the phenylpropanoid can be a hydrocinnamic acid. In certain embodiments, the phenylpropanoid can be chavicol. In other embodiments, the phenylpropanoid can be safrole.

In certain embodiments, the phytoextract can be an essential oil extract of a clove plant. In other examples, the phytoextract can be an essential oil extract of a leaf of a clove plant. The phytoextract can be an essential oil extract of a flower bud of a clove plant. In other embodiments, the phytoextract can be an essential oil extract of a stem of a clove plant.

In certain embodiments, the phytoextract can be synthetic. In certain embodiments, the phytoextract can include 20-95% eugenol, including 40-95% eugenol, and including 60-95% eugenol. In certain embodiments, the phytoextract can include 80-95% eugenol.

In other embodiments, the pharmaceutically active component can be epinephrine.

5 In certain embodiments, the pharmaceutically active component can be diazepam.

In certain embodiments, the pharmaceutically active component can be alprazolam.

In certain embodiments, the polymer matrix can include a polymer. In certain embodiments, the polymer can include a water soluble polymer.

In certain embodiments, the polymer can be a polyethylene oxide.

10 In certain embodiments, the polymer can be a cellulosic polymer. In certain embodiments, the cellulosic polymer can be hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethyl cellulose and/or sodium carboxymethylcellulose.

In certain embodiments, the polymer can include hydroxypropyl methylcellulose.

15 In certain embodiments, the polymer can include polyethylene oxide and/or hydroxypropyl methylcellulose.

In certain embodiments, the polymer can include polyethylene oxide and/or polyvinyl pyrrolidone.

20 In certain embodiments, the polymeric matrix can include polyethylene oxide and/or a polysaccharide.

In certain embodiments, the polymeric matrix can include polyethylene oxide, hydroxypropyl methylcellulose and/or a polysaccharide.

In certain embodiments, the polymeric matrix can include polyethylene oxide, a cellulosic polymer, polysaccharide and/or polyvinylpyrrolidone.

25 In certain embodiments, 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, propylene oxide co-polymers, collagen, albumin, poly-amino acids, 30 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 otherwise act as catalysts, emulsifiers and surfactants, which can stabilize emulsions, ultraviolet stabilizers, which can protect materials from harmful effects of ultraviolet radiation, UV
 5 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 formed by ultraviolet radiation.

In yet another aspect, the pharmaceutical composition has a suitable nontoxic, nonionic
 10 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
 15 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 agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetyl amino acid or salt thereof; (xv) an
 20 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
 25 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 making a pharmaceutical composition can include combining an
 30 adrenergic receptor interacter with a pharmaceutically active component and forming a

pharmaceutical composition including the adrenergic receptor interacter and the pharmaceutically active component.

The pharmaceutical composition can be a chewable or gelatin based dosage form, spray, gum, gel, cream, tablet, liquid or film.

5 In general, a pharmaceutical composition can be dispensed from a device. The device can dispense a pharmaceutical composition in a predetermined dose as a chewable or gelatin based dosage form, spray, gum, gel, cream, tablet, liquid or film. A device can include a housing that holds an amount of a pharmaceutical composition, including a polymeric matrix; a pharmaceutically active component in the polymeric matrix; and an adrenergic receptor
10 interacter and an opening that dispenses a predetermined amount of the pharmaceutical composition. The device can also dispense a pharmaceutical composition including a permeation enhancer including a phenylpropanoid and/or a phytoextract

In certain embodiments, a pharmaceutical composition can include a polymeric matrix, a pharmaceutically active component in the polymeric matrix; and a permeation enhancer
15 including a phenylpropanoid and/or a phytoextract.

In certain embodiments, a pharmaceutical composition can include a polymeric matrix; a pharmaceutically active component in the polymeric matrix; and an interacter that creates increased blood flow or enables a flushing of the tissue to modify transmucosal uptake of the pharmaceutically active component.

20 In certain embodiments, a pharmaceutical composition can include a polymeric matrix; a pharmaceutically active component in the polymeric matrix; and an interacter that has a positive or negative heat of solution which are used as aids to modify (increase or decrease) transmucosal uptake.

In other embodiments, a pharmaceutical composition includes a polymeric matrix, a pharmaceutically active component in the polymeric matrix, and an interacter, the composition
25 contained in a multilayer film having at least one side where the edges are coterminous.

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

BRIEF DESCRIPTION OF THE FIGURES

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

5 Referring to **Figure 1B**, a pharmaceutical composition is a film 100 comprising a polymeric matrix 200, the pharmaceutically active component 300 being contained in the polymeric matrix. The film can include a permeation enhancer 400.

Referring to **Figures 2A** and **2B**, the graphs show the permeation of an active material from a composition. Referring to **Figure 2A**, this graph shows average amount of active material permeated vs. time, with 8.00 mg/mL epinephrine bitartrate and 4.4 mg/mL epinephrine base solubilized.

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

Referring to **Figure 3**, this graph shows ex-vivo permeation of epinephrine bitartrate as a function of concentration. Referring to **Figure 4**, this graph shows permeation of epinephrine bitartrate as a function of solution pH. Referring to **Figure 5**, this graph shows the influence of enhancers on permeation of epinephrine, indicated as amount permeated as a function of time.

Referring to **Figure 6A** and **6B**, these graphs show the release of epinephrine on polymer platforms (6A) and the effect of enhancers on its release (6B), indicated as amount permeated (in μg) vs. time. Referring to **Figure 7**, this graph shows a pharmacokinetic model in the male Yucatan, miniature swine. The study compares a 0.3 mg Epipen, a 0.12 mg Epinephrine IV and a placebo film.

Referring to **Figure 8**, this graph shows the impact of no enhancer on the concentration profiles of a 40 mg Epinephrine film vs 0.3 mg Epipen. Referring to **Figure 9**, this graph shows the impact of Enhancer A (Labrasol) on the concentration profiles of a 40 mg Epinephrine film vs 0.3 mg Epipen, Referring to **Figure 10**, this graph shows the impact of Enhancer L (clove oil) on the concentration profiles of two 40 mg Epinephrine films (10-1-1) and (11-1-1) vs. a 0.3 mg Epipen.

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

Referring to **Figure 12**, this graph shows the concentration profiles for varying doses of Epinephrine films in a constant matrix for Enhancer L (clove oil) vs. a 0.3 mg Epipen. Referring to **Figure 13**, this graph shows the concentration profiles for varying doses of Epinephrine films in a constant matrix for Enhancer L (clove oil) vs. a 0.3 mg Epipen.

5 Referring to **Figure 14**, this graph shows the concentration profiles for varying doses of Epinephrine films in a constant matrix for Enhancer A (Labrasol) vs. a 0.3 mg Epipen.

Referring to **Figure 15**, this graph shows the influence of enhancers on permeation of diazepam, indicated as amount permeated as a function of time.

10 Referring to **Figure 16**, this graph shows the average flux as a function of time (diazepam + enhancers).

Referring to **Figure 17**, this graph shows the impact of Farnesol and Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen.

15 Referring to **Figure 18**, this graph shows the impact of Farnesol on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen.

Referring to **Figure 19**, this graph shows the impact of Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen.

20 Referring to **Figure 20**, this graph shows the impact of Farnesol and Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen.

Referring to **Figure 21**, this graph shows the impact of Enhancer A (Labrasol) in combination with Enhancer L (clove oil) on the concentration profiles of a 40 mg Epinephrine films (also shown in Fig. 22), in logarithmic view.

25 Referring to **Figure 22**, this graph shows the impact of Enhancer A (Labrasol) in combination with Enhancer L (clove oil) on the concentration profiles of a 40 mg Epinephrine films vs. the average data collected from 0.3 mg Epipens.

Referring to **Figure 23**, this graph shows the impact of Enhancer A (Labrasol) in combination with Enhancer L (clove oil) on the concentration profiles of a 40 mg Epinephrine films, shown as separate animal subjects.

Referring to **Figure 24A**, this graph shows the alprazolam plasma concentration as a function of time following sublingual administration of alprazolam oral disintegrating tablets (ODT).

5 Referring to **Figure 24B**, this graph shows the alprazolam plasma concentration as a function of time following sublingual administration of alprazolam pharmaceutical composition films.

Referring to **Figure 24C**, this graph shows the alprazolam plasma concentration as a function of time following sublingual administration of alprazolam pharmaceutical composition films.

10 Referring to **Figure 25A**, this graph shows mean alprazolam plasma concentration as a function of time following sublingual administration of alprazolam ODTs and alprazolam pharmaceutical composition films.

Referring to **Figure 25B**, this graph shows the alprazolam plasma concentration as a function of time following sublingual administration.

15 Referring to **Figure 25C**, this graph shows the alprazolam plasma concentration as a function of time following sublingual administration.

Referring to **Figure 26A**, this graph shows the alprazolam plasma concentration as a function of time following sublingual administration of alprazolam ODTs.

20 Referring to **Figure 26B**, this graph shows the alprazolam plasma concentration as a function of time following sublingual administration of alprazolam pharmaceutical composition films.

Referring to **Figure 26C**, this graph shows the alprazolam plasma concentration as a function of time following sublingual administration of alprazolam pharmaceutical composition films.

25 Referring to **Figure 27A**, this graph shows mean alprazolam plasma concentration as a function of time following sublingual administration of alprazolam ODTs and pharmaceutical composition films.

30 Referring to **Figure 27B**, this graph shows mean alprazolam plasma concentration as a function of time following sublingual administration of alprazolam ODTs and pharmaceutical composition films.

Referring to **Figure 27C**, this graph shows the alprazolam plasma concentration as a function of time following sublingual administration of alprazolam ODTs and pharmaceutical composition films.

DETAILED DESCRIPTION

5 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
10 mucosa, allowing drugs diffusing from the oral mucosa to have direct access to systemic circulation. This also offers increased convenience and therefore increased compliance in patients. For certain drugs, or pharmaceutically active components, a permeation enhancer can help to overcome the mucosal barrier and improve permeability. Permeation enhancers reversibly modulate the penetrability of the barrier layer in favor of drug absorption. Permeation
15 enhancers facilitate transport of molecules through the epithelium. 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 and mucosal residence time.

A pharmaceutical composition can be designed to deliver a pharmaceutically active
20 component in a deliberate and tailored way. However, solubility and permeability of the pharmaceutically active component in vivo, in particular, in the mouth of a subject, can vary tremendously. A particular class of permeation enhancer can improve the uptake and bioavailability of the pharmaceutically active component in vivo. In particular, when delivered to the mouth via a film, the permeation enhancer can improve the permeability of the
25 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
30 100%, 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

5 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

10 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 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;

15 (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 effectively combined, associated, contained, encapsulated or bound resulting in stabilization of

20 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. There are many reasons why the oral mucosa might be an attractive site for the delivery

25 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

30 removed easily in the case of an emergency. However, like the skin, the buccal mucosa acts as a barrier to the absorption of xenobiotics, which can hinder the permeation of compounds across

this tissue. Consequently, the identification of safe and effective penetration enhancers has become a major goal in the quest to improve oral mucosal drug delivery.

Chemical penetration enhancers are substances that 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.

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 500–600 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/min⁻¹/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 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

attributed to contents extruded from the membrane-coating granules into the epithelial intercellular spaces.

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

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

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

A chemical penetration enhancer, or absorption promoter, is a substance added to a pharmaceutical formulation in order to increase the membrane permeation or absorption rate of 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.

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.

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 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.

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

The permeation enhancer can be a phytoextract. A phytoextract can be an essential oil or
 10 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 acid, a cinnamic acid ester, a cinnamic aldehyde, a hydrocinnamic acid, chavicol, or safrole, or a
 15 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% to 15% eugenol acetate. The extract can also include caryophyllene. The extract can also include
 20 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 or 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 fusidate; glycocholate or deoxycholate and their salts; fatty acids and derivatives such as sodium laurate,
 25 oleic acid, oleyl alcohol, monoolein, or palmitoylcarnitine; chelators such as disodium EDTA, sodium citrate and sodium laurylsulfate, azone, sodium cholate, sodium 5-methoxysalicylate, sorbitan laurate, glyceryl monolaurate, octoxynonyl-9, laureth-9, polysorbates, sterols, or glycerides, such as caprylocaproyl polyoxylglycerides, e.g., Labrasol. The permeation enhancer can include phytoextract derivatives and/or monolignols. The permeation enhancer can also be a
 30 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), which is incorporated by reference herein. Specifically, vasorelaxant effects of eugenol have
 5 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,
 10 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
 15 metabolic fuel (storage and transport energy), essential components of all membranes and gene regulators. For review, see Rustan A.C. and Drevon, 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
 20 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
 25 and 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
 30 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, Spannhake, 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 eicosapentaenoic acid (EPA) and docosahexaenoic acid (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.

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 -adrenoceptor 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 $\alpha 1$ -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.

$\alpha 1$ -adrenergic receptors can be a main receptor for fatty acids. For example, saw palmetto extract (SPE), widely used for the treatment of benign prostatic hyperplasia (BPH), has been reported to bind $\alpha 1$ -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, myristic acid, palmitic acid and linoleic acid. Lauric acid and oleic acid can bind noncompetitively to $\alpha 1$ -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 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 selected and/or designed based on, e.g., 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 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, preferably a C7-C18 alcohol or acid. 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 or amide. For example, the adrenergic receptor interacter 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; 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.

For example, the penetration enhancer(s) can be used as a pretreatment alone or in combination with at least one API 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.

Applicants have found that microneedles could 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 0.0025 mm to about 0.250 mm, or a film can have a somewhat thicker thickness of from about 0.250 mm to about 1.0 mm. For some films, the thickness may be even larger, i.e., greater than about 1.0 mm or thinner, i.e., less than about 0.0025 mm. 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, and 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 the compound, 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.

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, 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, 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.

For example, the pharmaceutically active component can be buprenorphine, naloxone, acetaminophen, riluzole, clobazam, Rizatriptan, propofol, methyl salicylate, monoglycol

salicylate, aspirin, mefenamic acid, flufenamic acid, indomethacin, diclofenac, alclofenac,
 diclofenac sodium, ibuprofen, ketoprofen, naproxen, pranoprofen, fenoprofen, sulindac,
 fenclofenac, clidanac, flurbiprofen, fentiazac, bufexamac, piroxicam, phenylbutazone,
 oxyphenbutazone, clofezone, pentazocine, mepirizole, tiaramide hydrochloride, hydrocortisone,
 5 predonisolone, dexamethasone, triamcinolone acetonide, fluocinolone acetonide, hydrocortisone
 acetate, predonisolone acetate, methylpredonisolone, dexamethasone acetate, betamethasone,
 betamethasone valerate, flumetasone, fluorometholone, beclomethasone dipropionate,
 fluocinonide, edaravone, lurasidone, esomeprazole, lumateperone, naldmedine, doxylamine,
 pyridoxine, diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine,
 10 chlorpheniramine hydrochloride, chlorpheniramine maleate isothipendyl hydrochloride,
 tripeleminamine hydrochloride, promethazine hydrochloride, methdilazine hydrochloride
 dibucaine hydrochloride, dibucaine, lidocaine hydrochloride, lidocaine, benzocaine, p-
 buthylaminobenzoic acid 2-(diethylamino) ethyl ester hydrochloride, procaine hydrochloride,
 tetracaine, tetracaine hydrochloride, chlorprocaine hydrochloride, oxyprocaine hydrochloride,
 15 mepivacaine, cocaine hydrochloride, piperocaine hydrochloride, dyclonine, dyclonine
 hydrochloride, thimerosal, phenol, thymol, benzalkonium chloride, benzethonium chloride,
 chlorhexidine, povidone iodide, cetylpyridinium chloride, eugenol, trimethylammonium
 bromide, naphazoline nitrate, tetrahydrozoline hydrochloride, oxymetazoline hydrochloride,
 phenylephrine hydrochloride, tramazoline hydrochloride, thrombin, phytonadione, protamine
 20 sulfate, aminocaproic acid, tranexamic acid, carbazochrome, carbaxochrome sodium sulfanate,
 rutin, hesperidin, sulfamine, sulfathiazole, sulfadiazine, homosulfamine, sulfisoxazole,
 sulfisomidine, sulfamethizole, nitrofurazone, penicillin, meticillin, oxacillin, cefalotin,
 cefalordin, erythromycin, lincomycin, tetracycline, chlortetracycline, oxytetracycline,
 metacycline, chloramphenicol, kanamycin, streptomycin, gentamicin, bacitracin, cycloserine,
 25 salicylic acid, podophyllum resin, podolifox, cantharidin, chloroacetic acids, silver nitrate,
 protease inhibitors, thymidine kinase inhibitors, sugar or glycoprotein synthesis inhibitors,
 structural protein synthesis inhibitors, attachment and adsorption inhibitors, and nucleoside
 analogues such as acyclovir, penciclovir, valacyclovir, and ganciclovir, heparin, insulin, LHRH,
 TRH, interferons, oligonucleotides, calcitonin, octreotide, omeprazole, fluoxetine, ethinylestradiol,
 30 amiodipine, paroxetine, enalapril, lisinopril, leuprolide, prevastatin, lovastatin, norethindrone,
 risperidone, olanzapine, albuterol, hydrochlorothiazide, pseudoephedrine, warfarin, terazosin,

cisapride, ipratropium, busprione, methylphenidate, levothyroxine, zolpidem, levonorgestrel, glyburide, benazepril, medroxyprogesterone, clonazepam, ondansetron, losartan, quinapril, nitroglycerin, midazolam versed, cetirizine, doxazosin, glipizide, vaccine hepatitis B, salmeterol, sumatriptan, triamcinolone acetonide, goserelin, beclomethasone, granisteron, desogestrel, alprazolam, estradiol, nicotine, interferon beta 1A, cromolyn, fosinopril, digoxin, fluticasone, bisoprolol, calcitriol, captopril, butorphanol, clonidine, premarin, testosterone, sumatriptan, clotrimazole, bisacodyl, dextromethorphan, nitroglycerine, nafarelin, dinoprostone, nicotine, bisacodyl, goserelin, or granisetron. In certain embodiments, the pharmaceutically active component can be epinephrine, a benzodiazepine such as diazepam or lorazepam or alprazolam.

10 **Epinephrine, Diazepam and Alprazolam Examples**

In one example, a composition including epinephrine or its salts or esters can have a biodelivery profile similar to that of epinephrine administered by injection, for example, using an EpiPen. Epinephrine can be present in an amount of from about .01 mg to about 100 mg per dosage, for example, at a 0.1 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. In another example, a composition including diazepam can have a biodelivery profile similar to that of a diazepam tablet or gel, or better. Diazepam or its salts can be present in an amount of from about 0.5 mg to about 100 mg per dosage, for example, at a 0.5 mg, 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.

In another example, a composition (e.g., including alprazolam, diazepam or 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; (iii) a phospholipid additive, mixed micelle, liposome, or carrier; (iv) an alcohol; (v) an enamine; (vi) an NO donor compound; (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-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; 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 diazepam and alprazolam.

Treatment or Adjunctive Treatment

Status epilepticus (SE) is an epileptic seizure of greater than five minutes or more than one seizure within a five-minute period without the person returning to normal between them. Other previous definitions used a 30-minute time limit. Benzodiazepines are some of the most effective drugs in the treatment of acute seizures and status epilepticus. The benzodiazepines most commonly used to treat status epilepticus include diazepam (Valium), lorazepam (Ativan), or midazolam (Versed). The pharmaceutically active components in a pharmaceutical composition (e.g. pharmaceutical composition film) can be a treatment or adjunctive treatment for Angelman syndrome (AS), Benign rolandic epilepsy of childhood (BREC) and benign rolandic epilepsy with centro-temporal spikes (BECS), CDKL5 disorder, Childhood absence epilepsy (CAE), Myoclonic-astatic epilepsy or Doose Syndrome, Dravet syndrome, Early Myoclonic Encephalopathy (EME), Epilepsy with generalized tonic-clonic seizures alone (EGTCS) or epilepsy with tonic-clonic seizures on awakening, Epilepsy with Myoclonic-

Absences Frontal lobe epilepsy, Glut1 Deficiency Syndrome, Hypothalamic hamartoma (HH), Infantile spasms (also called IS) or West syndrome, Juvenile absence epilepsy (JAE), Juvenile myoclonic epilepsy (JME), Lafora progressive myoclonus epilepsy (Lafora disease), Landau-Kleffner syndrome, Lennox-Gastaut Syndrome (LGS), Ohtahara Syndrome (OS),
 5 Panayiotopoulos Syndrome (PS), PCDH19 Epilepsy, Progressive myoclonic epilepsies, Rasmussen's syndrome Ring chromosome 20 syndrome (RC20), Reflex epilepsies, TBCK-related intellectual disability syndrome, Temporal lobe epilepsy and Neurocutaneous syndromes that can be associated with seizures including Incontinentia pigmenti, Neurofibromatosis Type 1, Sturge Weber Syndrome (Encephalotrigeminal Angiomatosis), and Tuberous Sclerosis Complex.

10 A film and/or its components can be water-soluble, water swellable 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
 15 but not limited to water. A solvent can include water, or alternatively can include other solvents (preferably, polar solvents) by themselves or in combination with water.

The composition can include a polymeric matrix. Any desired polymeric matrix may be used, provided that it is orally dissolvable or erodible. The dosage should have enough bioadhesion to not be easily removed and it should form a gel like structure when administered.
 20 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.

Branched Polymers

25 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
 30 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
5 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.

10 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,
15 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 or polyether polyols such as polyglycerols.

20 A film can be produced by a combination of at least one polymer and a solvent, optionally including other components. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, or any combination thereof. In some embodiments, the solvent may be a non-polar organic solvent, such as methylene chloride. The film may be prepared by utilizing a selected casting or deposition method and a controlled drying
25 process. For example, the film may be prepared through a controlled drying processes, which include application of heat and/or radiation energy to the wet film matrix to form a visco-elastic structure, thereby controlling the uniformity of content of the film. 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
30 contacting more than one surface at the same time or at different times during the drying process. 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-swella-
5 ble, water-insoluble, or a combination of one or more either water-soluble, water-swella-
ble 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,
10 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
15 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-
20 ble polymers. The materials useful with the present invention may be water-soluble or water-swella-
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,
25 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),
30 poly(lactic acid) (PLA), polydioxanes, polyoxalates, poly(alpha-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates,

polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy)propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol
 5 copolymers, copolymers of polyurethane and (poly(lactic acid)), , 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, four or more components.

Although a variety of different polymers may be used, it is desired to select polymers that
 10 provide mucoadhesive properties to the film, as well as a desired dissolution and/or disintegration rate. In particular, the time period for which it is desired to maintain the film in contact with the mucosal tissue depends on the type of pharmaceutically active component contained in the composition. Some pharmaceutically active components may only require a few minutes for delivery through the mucosal tissue, whereas other pharmaceutically active
 15 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
 20 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.

Desirably, an individual film dosage of the pharmaceutical film can have a suitable
 25 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, or 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,
 30 about 3 inches, less than 3 inches, less than 2 inches, less than 1 inch, less than 0.5 inch, or 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 at a moderate rate, most desirably dispersing within about 1 minute and dissolving within about 3 minutes. In some embodiments, the film dosage may be capable of dispersing and dissolving at a rate of between about 1 to about 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 rates may be shorter than buccal dispersion rates.

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

Additives may be included in the films. Examples of classes of additives include preservatives, antimicrobials, excipients, lubricants, buffering agents, stabilizers, blowing agents,

pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers, anti-tacking agents, anti-static agents and mixtures thereof. These additives may be added with the pharmaceutically active component(s).

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, and UV stabilizers as discussed above and in more detail below.

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, acorbyl 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.

pH modifiers 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), 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 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 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, 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, 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 chloride, bromide or monoalkyl sulfate, N—(C₁₂-C₁₈)-alkyl-polyoxyaminoformylmethylpyridinium chloride, N—(C₁₂-C₁₈)-alkyl-N-methylmorpholinium
 5 chloride, bromide or monoalkyl sulfate, N—(C₁₂-C₁₈)-alkyl-N-ethylmorpholinium chloride, bromide or monoalkyl sulfate, (C₁₆-C₁₈)-alkyl-pentaoxethylammonium chloride, diisobutylphenoxyethoxyethyldimethylbenzylammonium chloride, salts of N,N-diethylaminoethylstearylamine and -oleylamine with hydrochloric acid, acetic acid, lactic acid, citric acid, phosphoric acid, N-acylaminoethyl-N,N-diethyl-N-methylammonium chloride,
 10 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.

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
 15 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 tocopherol, butylated hydroxytoluene, butylated hydroxyanisole, cysteine HCl, citric acid, ethylenediamine tetra acetic acid (EDTA), methionine, sodium citrate, sodium ascorbate, sodium
 20 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 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-
 25 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, feline, S-allyl cysteine, S-aminoethyl-L-cysteine), phenolic compounds (e.g., 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
 30 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 guanidium 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, 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, or 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.

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 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%.

- 5 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 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-propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sugar
15 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 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 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 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
25 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 polyvinylalcohols.

Further potential additives include solubility enhancing agents, such as substances that
30 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 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 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: 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-1-1-1,2,3-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 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 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 contains a buffer so as to control the pH of the film composition. Any desired level of buffer may be incorporated into the film composition so as to provide the desired pH level encountered as the pharmaceutically active component is released from the composition. The buffer is preferably provided in an amount sufficient to control the release from the film and/or the absorption into the body of the pharmaceutically active component. In some embodiments, the buffer may include sodium citrate, citric acid, bitartrate 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

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.

5 The pharmaceutical composition can adhere to a mucosal surface. The present invention finds particular use in the localized treatment of body tissues, diseases, or wounds which may have moist surfaces and which are susceptible to bodily fluids, such as the mouth, the vagina, organs, or other types of mucosal surfaces. The composition carries a pharmaceutical, and upon application and adherence to the mucosal surface, offers a layer of protection and delivers the
10 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 erodable
15 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
20 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
25 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
30 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 erodable bandage. Lipophilic agents can be designed to slow down erodability to decrease
5 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,
10 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.

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,
15 stearate, or oleate esters of sorbitol and sorbitol anhydrides, polyoxyethylene derivatives including monooleate, monostearate, monopalmitate, monolaurate, fatty alcohols, alkyl phenols, allyl ethers, alkyl aryl ethers, sorbitan monostearate, sorbitan monooleate and/or sorbitan monopalmitate.

The amount of pharmaceutically active component to be used depends on the desired
20 treatment strength and the composition of the layers, although preferably, the pharmaceutical component comprises from about 0.001% to about 99%, more preferably from about 0.003 to about 75%, and most preferably from about 0.005% to about 50% by weight of the composition, 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%,
25 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 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.

30 The thickness of the film may vary, depending on the thickness of each of the layers and the number of layers. As stated above, both the thickness and amount of layers may be adjusted

in order to vary the erosion kinetics. Preferably, if the 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 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 mm 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, and vaginal mucosal tissue, as well as, the skin. If the skin is to be employed as the treatment site, then usually larger areas of the skin wherein movement will not disrupt the adhesion of the 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.

5 A Franz diffusion cell is an in vitro skin permeation assay used in formulation development. The Franz diffusion cell apparatus (**Figure 1A**) consists of two chambers separated by a membrane of, for example, animal or human tissue. The test product is applied to the membrane via the top chamber. The bottom chamber contains fluid from which samples are taken at regular intervals for analysis to determine the amount of active that has permeated the membrane. Referring to **Figure 1A**, a Franz diffusion cell 100 includes a donor compound 101,
10 a donor chamber 102, a membrane 103, sampling port 104, receptor chamber 105, stir bar 106, and a heater/circulator 107.

Referring to **Figure 1B**, a pharmaceutical composition is a film 100 comprising a polymeric matrix 200, the pharmaceutically active component 300 being contained in the polymeric matrix. The film can include a permeation enhancer 400.

15 Referring to **Figures 2A** and **2B**, the graphs show the permeation of an active material from a composition. The graph shows that for the Epinephrine Base – solubilized in-situ vs. the inherently soluble Epinephrine Bitartrate, no meaningful differences were observed. Epinephrine Bitartrate was selected for further development based on ease of processing. Flux is derived as slope of the amount permeated as a function of time. Steady state flux is taken from
20 the plateau of flux vs time curve multiplied by the volume of receiver media and normalized for permeation area.

Referring to **Figure 2A**, this graph shows average amount of active material permeated vs. time, with 8.00 mg/mL epinephrine bitartrate and 4.4 mg/mL epinephrine base solubilized.

Referring to **Figure 2B**, this graph shows average flux vs. time, with 8.00 mg/mL
25 epinephrine bitartrate and 4.4 mg/mL epinephrine base solubilized.

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

30 Referring to **Figure 4**, this graph shows permeation of epinephrine bitartrate as a function of solution pH. Acidic conditions explored to promote stability. The results compared

Epinephrine Bitartrate pH 3 buffer and Epinephrine Bitartrate pH 5 buffer, and found that the Epinephrine Bitartrate pH 5 buffer was slightly favorable.

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

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

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

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

Referring to **Figure 9**, this graph shows the impact of Enhancer A (Labrasol) on the concentration profiles of a 40 mg Epinephrine film vs, a 0.3 mg Epipen. Referring to **Figure 10**, this graph shows the impact of Enhancer L (clove oil) on the concentration profiles of two 40 mg Epinephrine films (10-1-1) and (11-1-1) vs. a 0.3 mg Epipen.

Referring to **Figure 11**, This graph shows the impact of Enhancer L(clove oil) and film dimension (10-1-1 thinner bigger film and 11-1-1 thicker smaller film) on the concentration profiles of 40 mg Epinephrine films vs. a 0.3 mg Epipen.

Referring to **Figure 12**, this graph shows the concentration profiles for varying doses of Epinephrine films in a constant matrix for Enhancer L (clove oil) vs. a 0.3 mg Epipen.

Referring to **Figure 13**, the graph shows the concentration profiles for varying doses of Epinephrine films in a constant matrix for Enhancer L (clove oil) vs. a 0.3 mg Epipen.

Referring to **Figure 14**, the graph shows the concentration profiles for varying doses of Epinephrine films in a constant matrix for Enhancer A (Labrasol) vs. a 0.3 mg Epipen.

Referring to **Figure 15**, this graph shows the influence of enhancers on permeation of diazepam, indicated as amount permeated as a function of time.

Referring to **Figure 16**, this graph shows the average flux as a function of time (diazepam + enhancers).

Referring to **Figure 17**, this graph shows the impact of Farnesol and Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen.

Referring to **Figure 18**, this graph shows the impact of Farnesol and Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen.

Referring to **Figure 19**, this graph shows the impact of Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen.

Referring to **Figure 20**, this graph shows the impact of Farnesol and Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen.

The following examples are provided to illustrate pharmaceutical compositions, as well as, methods of making and using, pharmaceutical compositions and devices described herein.

EXAMPLES

Example 1

Permeation Enhancers - Epinephrine

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

Donor Solution (16.00mg/mL Epinephrine Bitartrate + enhancer)	Average Steady State Flux (ug/cm ² *min)	% Flux enhancement	Permeability
			Coefficient (cm/s)
Epinephrine Bitartrate ,no enhancer	1.3173	N/A	1.37E-06
3% Clove Oil	8.2704	527.84	8.61E-06
3% Clove Oil Repeat	5.3776	308.24	5.60E-06
3% Eugenol	7.1311	441.35	7.43E-06
3% Eugenyl Acetate	1.8945	43.82	1.97E-06
3% B-Caryophyllene	3.5200	167.22	3.67E-06
0.3% Eugenol*	3.9735	201.65	4.14E-06
100% Eugenol ¹	36.8432	2696.92	3.84E-05
0.3% Clove Oil*	3.6806	179.41	3.83E-06
100% Clove Oil ¹	52.5304	3887.81	5.47E-05
3% Phenol	4.5790	247.61	4.77E-06
3% Phenol Repeat	4.1753	216.97	4.35E-06
3% Linoleic Acid	2.1788	65.40	2.27E-06
50%Clove Oil	2.5673	94.89	2.67E-06
0.3% Labrasol	3.5221	167.38	3.67E-06
3% Vanillyl Alcohol+ 6% Ethanol	1.10243	-16.31	1.15E-06
3% Saffrole	2.60634	97.86	2.71E-06
3% Oleic Acid	2.06597	56.84	2.15E-06
3% Oleic Acid + 1% PEG200	2.73655	107.74	2.85E-06
3% Benzyl Alcohol	1.38455	5.11	1.44E-06

¹ steady state flux reached at much earlier time point

* 0.3% Eugenol vs 0.3% Clove -similar flux rates to one another

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

Example 2

Diazepam Solubility and Permeability

Diazepam was applied in the buccal area (cheek) to diffuse through the oral mucosa and enter directly into the bloodstream. Solubility of diazepam was also studied using various excipients. **Figure 15** shows the influence of enhancers on permeation of diazepam, indicated as amount permeated indicated as ug as a function of time. **Figure 16** shows the average flux

indicated as $\mu\text{g}/\text{cm}^2 \cdot \text{min}$, as a function of time in minutes in a solution of diazepam and certain selected enhancers.

The following excipients have also been studied to improve solubility.

EXCIPIENTS	HLB	Water Solubility	Melting Point °C	API Solubility mg/gm total mix
RD-0073-10 SERIES				
PEG 400		S	Liquid	90
Caprylic/Capric Triglyceride		I	Liquid	< 50
Propylene Glycol		S	Liquid	< 30
Glycerol Monooleate	1	I	24	71
Polysorbate 80	15	S	Liquid	83
PEG 4000		S	53-59	125
PEG 32 Glyceryl Palmitostearate	11	D	50	125
Mix: PEG 400, PEG 4000, PEO N80		S		118
Poloxamer 407	18 to 23	S	52-57	110-140
Polyoxyl 50 Stearate	11 to 12	S	30-35	200
RD-0073-19 series				
Benzyl Alcohol		S	Liquid	400
Polyoxyl 40 Hyd Castor Oil	14 to 16	S	16-26	167
Poloxamer 124	12 to 18	S	16	127
RD-0073-20 series				
Clove Oil		I	Liquid	394
Castor Oil		I	Liquid	<50
Light Mineral Oil		I	Liquid	<50
Oleic Acid		I	Liquid	<50
Polyoxyl 40 Stearate	17	S	38	83
Maisine 35-1 (GMLinO)	1	I	Liquid	45
Labrasol Caprylocaproyl polyoxyl-8 glycerides	12	D	Liquid	83
RD-0073-27 series				
Soybean Oil		I	Liquid	<50
RD-0073-38 series				
Clove Oil FCC		I	Liquid	370

The following excipients can also be applied for similar enhancement properties: cinnamon leaf, basil, bay leaf, nutmeg, Kolliphor® TP GS, Vit E PEG Succinate, Kolliphor® EL, Polyoxyl 35 Castor Oil USP/NF, Menthol, N-Methyl-2-pyrrolidone, SLS (SDS), SDBS, Dimethyl Phthalate, Sucrose Palmitate (Sisterna PS750-C), Sucrose Stearate (Sisterna SP70-C), CHAPS, Octyl glucoside, Triton X 100 (Octoxynol-9), Ethyl Maltol (flavorant powder), Brij 58 (Ceteth-20), Vitamin E tocopherol, tocopherol acetate or tocopherol succinate, sterols, phytoextracts, essential oils or Cod Liver Oil.

The following results were obtained in a solution of Diazepam having a concentration of 8.00 mg/mL.

Donor Solution (8.00mg/mL Diazepam + enhancer)	Average Steady State Flux (ug/cm ² *min)	Permeability
		Coefficient (cm/s)
100% Clove Oil	0.0008	1.63E-09
100% Benzyl Alcohol	0.0058	1.22E-08
3% Eugenyl Acetate	0.1037	2.16E-07
3% β -Caryophyllene	0.0798	1.66E-07
3% Phenol	0.2752	5.73E-07
3% Cinnamaldehyde	0.1306	2.72E-07
3% Clove Oil	0.0990	2.06E-07
3% Benzyl Alcohol	0.1438	3.00E-07
3% Labrasol	0.1251	2.61E-07
100% Cinnamaldehyde	0.0057	1.19E-08

Example 3

General Permeation Procedure – Ex vivo Permeation Study Protocol

In one example, a permeation procedure is conducted as follows. A temperature bath is set to 37° 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.

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

For solution studies, one can perform the following steps: (1) using a micropipette, dispense 500 μ L of the solution into each donor cell, start the timers; (2) sample 200 μ L at the following time points (time = 0 min, 20 min, 40 min, 60 min, 120 min, 180 min, 240 min, 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 materials properly.

Example 4

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.
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 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.

Example 5**Transbuccal delivery of doxepin**

The following is an exemplary permeation study on the transbuccal delivery of doxepin.

5 The studies were conducted under a protocol approved by the Animal Experimentation Ethics Committee of the University of Barcelona (Spain) and the Committee of Animal Experimentation of the regional autonomous government of Catalonia (Spain). Female pigs 3–4-months-old were used. The porcine buccal mucosa from the cheek region was excised immediately after the pigs were sacrificed in the animal facility at Bellvitge Campus (University
10 of Barcelona, Spain) using an overdose of sodium thiopental anesthesia. The fresh buccal tissues were transferred from the hospital to the laboratory in containers filled with Hank's solution. The remaining tissue specimens were stored at -80°C in containers with a PBS mixture containing 4% albumin and 10% DMSO as cryoprotective agents.

For the permeation studies, the porcine buccal mucosa was cut to $500 \pm 50\ \mu\text{m}$ thick
15 sheets, which contributes to the diffusional barrier (Buccal bioadhesive drug delivery — A promising option for orally less efficient drugs Sudhakar et al., *Journal of Controlled Release* 114 (2006) 15–40), using an electric dermatome (GA 630, Aesculap, Tuttlingen, Germany) and trimmed with surgical scissors in adequate pieces. The majority of the underlying connective tissue was removed with a scalpel.

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

Infinite dose conditions were ensured by applying 100 μL as donor solution of a saturated doxepin solution into the receptor chamber and sealed by Parafilm immediately to prevent water evaporation. Prior to conducting the experiments, the diffusion cells were incubated for 1 h in a water bath to equalize the temperature in all cells ($37^{\circ} \pm 0^{\circ}\text{C}$). Each cell contained a small
30 Teflon1 coated magnetic stir bar which was used to ensure that the fluid in the receptor compartment remained homogenous during the experiments.

Sink conditions were ensured in all experiments by initial testing of doxepin saturation concentration in the receptor medium. Samples (300 μ L) were drawn via syringe from the center of the receptor compartment at pre-selected time intervals (0.1, 0.2, 0.3, 0.7, 1, 2, 3, 4, 5 and 6 h) for 6 h. The removed sample volume was immediately replaced with the same volume of fresh receptor medium (PBS; pH 7.4) with great care to avoid trapping air beneath the membrane.

Additional details can be found in A. Gimemo, et al. Transbuccal delivery of doxepin: Studies on permeation and histological evaluation, *International Journal of Pharmaceutics* 477 (2014), 650-654, which is incorporated by reference herein.

Example 6

Oral transmucosal delivery

Porcine oral mucosal tissue has similar histological characteristics to human oral mucosal tissue (Heaney TG, Jones RS, Histological investigation of the influence of adult porcine alveolar mucosal connective tissues on epithelial differentiation. *Arch Oral Biol* 23 (1978) 713–717; Squier CA, and Collins P, The relationship between soft tissue attachment, epithelial downgrowth and surface porosity. *Journal of Periodontal Research* 16 (1981) 434-440). Lesch et al. (The Permeability of Human Oral Mucosa and Skin to Water, *J Dent Res* 68 (9), 1345-1349, 1989) reported that the water permeability of porcine buccal mucosa was not significantly different from human buccal mucosa but the floor of the mouth was more permeable in human tissue than in pig tissue. Comparisons between fresh porcine tissue specimens and those stored at -80° C revealed no significant effect on permeability as a result of freezing. Porcine buccal mucosal absorption has been studied for a wide range of drug molecules both in vitro and in vivo (see, e.g., Table 1 of M. Sattar, Oral transmucosal drug delivery – current status and future prospects, *International Journal of Pharmaceutics* 471 (2014) 498-506), which is incorporated by reference herein. Typically, in vitro studies involve mounting excised porcine buccal tissue in Ussing chambers, Franz cells or similar diffusion apparatus. The in vivo studies described in the literature involve the application of the drug as a solution, gel or composition to the buccal mucosa of pigs followed by plasma sampling.

Nicolazzo et al. (The Effect of Various in Vitro Conditions on the Permeability Characteristics of the Buccal Mucosa, *Journal of Pharmaceutical Sciences* 92(12) (2002) 2399-2410) investigated the effects of various in vitro conditions on the permeability of porcine buccal tissue using caffeine and oestradiol as model hydrophilic and lipophilic molecules. Drug permeation in the buccal mucosa was studied using modified Ussing chambers. Comparative

permeation studies were performed through full thickness and epithelial tissues, fresh and frozen tissues. Tissue integrity was monitored by the absorption of the fluorescein isothiocyanate (FITC)-labeled dextran 20 kDa (FD20) and tissue viability was assessed using an MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) biochemical assay and histological evaluation. Permeability through the buccal epithelium was 1.8-fold greater for caffeine and 16.7-fold greater for oestradiol compared with full thickness buccal tissue. Flux values for both compounds were comparable for fresh and frozen buccal epithelium although histological evaluation demonstrated signs of cellular death in frozen tissue. The tissue appeared to remain viable for up to 12 h postmortem using the MTT viability assay which was also confirmed by histological evaluation.

Kulkarni et al. investigated the relative contributions of the epithelium and connective tissue to the barrier properties of porcine buccal tissue. In vitro permeation studies were conducted with antipyrine, buspirone, bupivacaine and caffeine as model permeants. The permeability of the model diffusants across buccal mucosa with thickness of 250, 400, 500, 600, and 700 μm was determined. A bilayer membrane model was developed to delineate the relative contribution to the barrier function of the epithelium and the connective tissue. The relative contribution of the connective tissue region as a permeability barrier significantly increased with increasing mucosal tissue thickness. A mucosal tissue thickness of approximately 500 μm was recommended by the authors for in vitro transbuccal permeation studies as the epithelium represented the major permeability barrier for all diffusants at this thickness. The authors also investigated the effects of a number of biological and experimental variables on the permeability of the same group of model permeants in porcine buccal mucosa (Porcine buccal mucosa as in vitro model: effect of biological and experimental variables, Kulkarni et al., *J Pharm Sci.* 2010 99(3):1265-77). Significantly, higher permeability of the permeants was observed for the thinner region behind the lip (170–220 μm) compared with the thicker cheek (250–280 μm) region. Porcine buccal mucosa retained its integrity in Krebs's bicarbonate ringer solution at 4°C for 24 h. Heat treatment to separate the epithelium from underlying connective tissue did not adversely affect its permeability and integrity characteristics compared with surgical separation.

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

Example 7**Cryopreservation of buccal mucosa**

Different areas of porcine buccal mucosa have different pattern of permeability, there is significantly higher permeability in the region behind the lips in comparison to cheek region, because in porcine buccal mucosa, the epithelium acts as a permeability barrier, and the thickness of the cheek epithelium is greater than that of the region behind the lips (Harris and Robinson, 1992). In exemplary permeation studies, the fresh or frozen porcine buccal mucosa from the same area was cut to 500 ± 50 μm thick sheets, which contributes to the diffusional barrier (Sudhakar et al., 2006), were obtained using an electric dermatome (model GA 630, Aesculap, Tuttlingen, Germany) and trimmed with surgical scissors in adequate pieces. All devices utilized were previously sterilized. The majority of the underlying connective tissue was removed with a scalpel. Membranes were then mounted in specially designed membrane holders with a permeation orifice diameter of 9 mm (diffusion area 0.63 cm^2). Using the membrane holder, each porcine buccal membrane was mounted between the donor (1.5 mL) and the receptor (6 mL) compartments with the epithelium facing the donor chamber and the connective tissue region facing the receiver of static Franz-type diffusion cells (Vidra Foc, Barcelona, Spain) avoiding bubbles formation. Experiments were performed using PP, which has lipophilic characteristics ($\log P = 1.16$; n-octanol/PBS, pH 7.4), ionisable ($\text{pK}_a = 9.50$) and a MW= 259.3 g/mol, as a model drug (Modamio et al., 2000).

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

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

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

plotted versus time (h). The diffusion experiments were carried out 27 times for the fresh and 22 times for the frozen buccal mucosa.

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

Example 8

Permeation of quinine across sublingual mucosa sections

Since porcine and human oral membranes are similar in composition, structure and permeability measurements, porcine oral mucosa is a suitable model for human oral mucosa.

Permeability across the porcine oral mucosa is not metabolically linked therefore it is not important for the tissue to be viable.

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

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

At 2, 4, 6, 8, 10 and 12 h, the receptor phases were withdrawn from the sampling ports and aliquots of 1 mL samples were transferred to HPLC autosampler vials, before being replaced with fresh PBS stored at 37°C . Apart from the studies involving Q/2-HP- β -CD saturated

solutions (where an infinite dose was applied at the start of the experiments), 5 μ L of the respective quinine solution was reapplied to the donor phase up to 10 h. The purpose of this was to represent a hypothetical in-use finite dosing regimen based upon an interval of 2 h between doses. At least 3 replicates were carried out for each study.

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

Example 9

Ex-Vivo Initial Study – Form of the API

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

Donor Solution	Average Steady State Flux (μ g/cm ² *min)
Epinephrine Base (conc 4.4mg/mL)	0.512
Epinephrine Bitartrate (conc 8.00mg/mL)	0.466

Example 10

Concentration dependence on permeation/flux

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

Donor Solution	Average Steady State Flux (μ g/cm ² *min)
Epinephrine Bitartrate (conc 4mg/mL)	0.167
Epinephrine Bitartrate (conc 8mg/mL)	0.466
Epinephrine Bitartrate (conc 16mg/mL)*	1.317
Epinephrine Bitartrate (conc 100mg/mL)	2.942

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

Example 11

Influence of pH

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

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

Example 12

Influence of enhancers on permeation of epinephrine

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

Legend	Enhancer	Average Steady State Flux ($\mu\text{g}/\text{cm}^2 \cdot \text{min}$)	Percent Enhancement
No Enhancer	None	1.317	N/A
Enhancer A	3% Labrasol Caprylocaproyl polyoxyl-8 glycerides	5.208	395
Enhancer B	3% Propylene glycol monocaprylate	2.385	181
Enhancer C	3% Polyglyceryl-3 oleate	1.482	112
Enhancer D	3% Oleoyl polyoxyl-6 glycerides	0.281	21
Enhancer E	3% TDM	2.642	201
Enhancer F	3% SGDC	0.342	26
Enhancer G	3% Lauroyl polyoxyl-32 glycerides	1.641	125
Enhancer H	3% Ethanol	0.163	12
Enhancer I	6% Ethanol	0.254	19
Enhancer J	6% Labrasol Caprylocaproyl polyoxyl-8 glycerides	4.444	337
Enhancer K	6% Polyglyceryl-3 oleate	0.306	23
Enhancer L	3% clove oil	8.216	624

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

8.00mg/0.500mL
40mg/ strip
 no enhancer

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux ($\mu\text{g}/\text{cm}^2 \cdot \text{min}$)	std dev set 2	steady state flux average
30	0	0	0	0	
45	2.5	4.33012702	0.260416667	0.4510549	1.317274
60	5.5	7.08872344	0.3125	0.3125	
120	31.33333333	26.1549868	0.672743056	0.5050226	
180	72.66666667	58.215834	1.076388889	0.8496863	
240	112.1666667	80.1878004	1.028645833	0.5733604	
300	160.1666667	103.254943	1.25	0.6036108	
360	213.3333333	131.305306	1.384548611	0.7308311	

8.00mg/0.500mL
40mg/ strip
 Labrasol

Time (min)	set 1 (A,B,C) average amount permeated (ug)	std dev set 1 amount perm	set 1 (A, B,C) average flux ($\mu\text{g}/\text{cm}^2 \cdot \text{min}$)	std dev set 1	steady state flux average
0	0	0	0	0	
30	0.5	0.8660254	0.026041667	0.0451055	5.208333
45	2.666666667	0.28867513	0.225694444	0.0601407	
60	4	1.80277564	0.138888889	0.1674245	
120	28	16.3935963	0.625	0.3836177	
180	98	53.3291665	1.822916667	0.9701176	
240	238.1666667	93.0017921	3.650173611	1.136722	
300	421.1666667	115.153521	4.765625	0.6675003	
360	638.1666667	130.709921	5.651041667	0.4732495	

8.00mg/0.500mL
40mg/strip
 capryol 90

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

8.00mg/0.500mL
40mg/strip
 plurol oleique

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (µg/mL*min)	std dev set 2	steady state flux average
0	0.8	1.78885438	0	0	
30	10.80	13.325727	0.520833333	0.7186273	
45	20.90	22.1624683	1.052083333	0.9356173	1.481771
60	33.00	30.8058436	1.260416667	0.9319861	
120	90.70	68.1951245	1.502604167	1.005753	
180	157.00	107.373763	1.7265625	1.0427891	
240	239.80	140.586539	2.15625	1.2085059	
300	285.60	184.236397	1.192708333	1.484335	
360	353.60	221.81676	1.770833333	0.993644	

8.00mg/0.500mL
40mg/strip
 TDM

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

8.00mg/0.500mL
40mg/strip
 SGDC

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

8.00mg/0.500mL
40mg/strip
 Labrafil

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux ($\mu\text{g/mL}\cdot\text{min}$)	std dev set 2	steady state flux average
0	0.8	1.15108644	0	0	
30	1.10	1.51657509	0.015625	0.0232924	
45	1.10	1.51657509	0	0	0.28125
60	1.10	1.51657509	0	0	
120	4.00	4.89897949	0.075520833	0.0984775	
180	9.10	10.9167303	0.1328125	0.1671035	
240	15.20	18.7169709	0.158854167	0.2034753	
300	25.70	29.8487856	0.2734375	0.2910091	
360	36.80	43.3093523	0.2890625	0.3532943	

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

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

8.00mg/0.500mL
40mg/strip
 clove oil

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux ($\mu\text{g/cm}^2\cdot\text{min}$)	std dev set 2	steady state flux average
0	0	0	0	0	
20	0	0	0	0	
40	28.66666667	27.360251	2.239583333	2.1375196	8.270399
60	96.5	79.5424415	5.299479167	4.0954816	
120	389.6666667	278.072533	7.634548611	5.2070528	
180	688.6666667	451.678628	7.786458333	4.5210426	
240	1009.166667	603.252089	8.346354167	3.9590828	
300	1333.5	759.653046	8.446180556	4.1168559	
360	1644.333333	878.2762	8.094618056	3.2301203	

8.00mg/0.500mL 40mg/strip 3% Labrasol +1%TDM	Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux ($\mu\text{g/mL}\cdot\text{min}$)	std dev set 2	steady state flux average
	0	0	0	0	0	
	20	0	0	0	0	3.161892
	40	1.666666667	2.88675135	0.130208333	0.2255274	
	60	6.833333333	11.8356805	0.403645833	0.6991351	
	120	68.83333333	92.6907942	1.614583333	2.1084505	
	180	103.6666667	101.539812	0.907118056	0.3351021	
	240	180	130.184484	1.987847222	0.7476876	
	300	291.5	149.81572	2.903645833	0.5193664	
	360	422.8333333	164.032263	3.420138889	0.5530917	

Example 13**Impact of enhancers on epinephrine release**

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

10 epinephrine from the matrix.

Example 14**Accelerated stability**

The stabilizer loading variants were tested.

15

	Formulation 10	Formulation 10 with 0.25% Stabilizer	Formulation 10 with 1% Stabilizer
Time (weeks) @ 40°C/75% R.H.	EPI mg/film	EPI mg/film	EPI mg/film
0	39.3	37.9	38.3
2	35.2	36.8	34.7
4	38.2	36.8	36.2
8	37.7	35.6	35.1
12	36.1	35.4	35.1

Example 15

5 Impact of Enhancer

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

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

The impact of enhancer 3% Labrasol is shown in **Figure 9**, which shows the impact of Enhancer A (Labrasol) on the concentration profiles of a 40 mg Epinephrine film vs. a 0.3 mg Epipen. **Figure 10** shows the impact of Enhancer L (clove oil) on the concentration profiles of two 40 mg Epinephrine films (10-1-1) and (11-1-1) vs. a 0.3 mg Epipen.

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

20 Studies were performed to vary the ratio of epinephrine to an enhancer. These studies were also concentration vs. time profiles following sublingual or intramuscular epinephrine administration to male miniature swine. Varying the ratio of Epinephrine to clove oil (Enhancer L) produced the results shown in **Figure 12**. This study was carried out comparing 0.30 mg

EpiPen (n=4), a 40 mg Epinephrine Film (12-1-1) (n=5) and a 20 mg Epinephrine Film (13-1-1) (n=5).

Example 16

A varying dose was carried out in constant matrix with enhancer Labrasol (3%) and clove oil (3%) are shown in **Figures 13** and **14** respectively. The study in **Figure 13** was carried out comparing 0.30 mg EpiPen (n=4), a 40 mg Epinephrine Film (18-1-1) (n=5) and a 30 mg Epinephrine Film (20-1-1) (n=5). The study in **Figure 14** was carried out comparing 0.30 mg EpiPen (n=4), a 40 mg Epinephrine Film (19-1-1) (n=5) and a 30 mg Epinephrine Film (21-1-1) (n=5). These studies were also concentration vs. time profiles following sublingual or intramuscular epinephrine administration to male miniature swine.

Example 17

A pharmacokinetic model in the male miniature swine was studied to determine the impact of an enhancer (farnesol) on epinephrine concentration over time. The graph on **Figure 17** shows the epinephrine plasma concentration (in ng/mL) as a function of time (in minutes) following sublingual or intramuscular administration of a farnesol permeation enhancer. This study compares a 0.3 mg EpiPen (n=3), a 30 mg Epinephrine Film 31-1-1 (n=5) and a 30 mg Epinephrine Film 32-1-1 (n=5) each Epinephrine Film being formulated with a farnesol enhancer. As shown in this figure, the 31-1-1 film demonstrates enhanced stability of epinephrine concentration starting at about 30-40 minutes until approximately 130 minutes.

The graph in **Figure 18** is taken from the same study as Figure 17, but shows exclusively the data points comparing the 0.3 mg EpiPen against the 30 mg Epinephrine Film 31-1-1 (n=5).

The graph in **Figure 19** is taken from the same study as Figure 17, but shows exclusively the data points comparing the 0.3 mg EpiPen against the 30 mg Epinephrine Film 32-1-1 (n=5).

Example 18

Referring to **Figure 20**, this graph shows a pharmacokinetic model in the male miniature swine was studied to determine the impact of an enhancer (farnesol) on epinephrine concentration over time following sublingual or intramuscular administration. The epinephrine plasma concentration (in ng/mL) is shown as a function of time (in minutes) following sublingual or intramuscular administration of a farnesol permeation enhancer in Epinephrine films. The study compared data from three 0.3 mg EpiPens against five 30 mg Epinephrine films

(32-1-1). The data shows the Epinephrine films film having enhanced stability of epinephrine concentration starting at about 20-30 minutes until approximately 130 minutes.

Example 19

In one embodiment, an epinephrine pharmaceutical composition film can be made with the following formulation:

	Formulation A		
MATERIAL	WT % dry	WT % wet	mg/Strip
EPINEPHRINE bitartrate	46.40	18.56	54.56
Hydroxypropylmethyl cellulose	11.54	4.61	13.57
Polyvinyl pyrrolidone	27.92	11.17	32.84
Glycerol monooleate	0.58	0.23	0.68
Polyethylene Oxide	1.16	0.46	1.36
Polysorbate	0.58	0.23	0.68
Phytoextract	9.98	3.99	9.97
Stabilizer	0.12	0.05	0.14
Buffer	0.58	0.23	0.68
Artificial sweetener	1.16	0.46	1.36
Linoleic acid	0.0037	0.00	0.00
Farnesol			
Yellow # 5			
TOTAL	100.00	40.00	115.84

Example 20

An epinephrine pharmaceutical composition film was made with the following formulation:

	Formulation B		
MATERIAL	WT % dry	WT % wet	mg/Strip
EPINEPHRINE bitartrate	46.17	18.47	54.29
Hydroxypropylmethyl cellulose	11.48	4.59	13.50
Polyvinyl pyrrolidone	27.78	11.11	32.67
Glycerol monooleate	0.58	0.23	0.68
Polyethylene Oxide	1.15	0.46	1.35
Polysorbate	0.58	0.23	0.68
Phytoextract	9.93	3.97	9.92
Stabilizer	0.12	0.05	0.14
Buffer	0.58	0.23	0.68
Artificial sweetener	1.15	0.46	1.35
Linoleic acid	0.50	0.20	0.59
Farnesol			
Yellow # 5			
TOTAL	100.00	40.00	115.85

Example 21

In another embodiment, pharmaceutical film compositions were made with the following

5 formulation:

	Formulation C		
MATERIAL	WT % dry	WT % wet	mg/Strip
EPINEPHRINE bitartrate	46.35	18.54	54.51
Hydroxypropylmethyl cellulose	11.53	4.61	13.55
Polyvinyl pyrrolidone	27.90	11.16	32.80
Glycerol monooleate	0.58	0.23	0.68
Polyethylene oxide	1.16	0.46	1.36
Polysorbate	0.58	0.23	0.68
Phytoextract	9.97	3.99	9.96
Stabilizer	0.12	0.05	0.14
Buffer	0.58	0.23	0.68
Artificial sweetener	1.16	0.46	1.36
Linoleic acid			
Farnesol	0.10	0.04	0.06
Yellow # 5			
TOTAL	100.00	40.00	115.78

Example 22

In another embodiment, pharmaceutical film compositions were made with the following

5 formulation:

	Formulation D		
MATERIAL	WT % dry	WT % wet	mg/Strip
EPINEPHRINE bitartrate	46.07	18.43	54.52
Hydroxypropylmethyl cellulose	11.46	4.58	13.56
Polyvinyl pyrrolidone	27.73	11.09	32.81
Glycerol monooleate	0.57	0.23	0.68
Polyethylene oxide	1.15	0.46	1.36
Polysorbate	0.57	0.23	0.68
Phytoextract	9.91	3.96	9.96
Stabilizer	0.11	0.05	0.14
Buffer	0.57	0.23	0.68
Artificial sweetener	1.15	0.46	1.36
Linoleic acid	0.10	0.04	0.06
Farnesol	0.50	0.20	0.29
Yellow # 5	0.10	0.04	0.06
TOTAL	100.00	40.00	116.16

Example 23

Referring to **Figure 21**, this graph shows a pharmacokinetic model (logarithmic scale) in the male miniature swine studied to determine the impact of an enhancer (6% clove oil and 6% Labrasol) on epinephrine plasma concentration over time following sublingual or intramuscular administration. The epinephrine plasma concentration (in ng/mL) is shown as a function of time (in minutes) following sublingual or intramuscular administration of a farnesol permeation enhancer in Epinephrine films. The data shows the Epinephrine films film having enhanced stability of epinephrine concentration starting at just after the 10 minute time point through about 30 minutes, and until approximately 100 minutes.

Referring to **Figure 22**, this graph shows a pharmacokinetic model of the Epinephrine film formulation in the male miniature swine as referenced in **Figure 21** compared against the average data collected from a 0.3 mg Epipen (indicated in diamond data points). As the data indicates, the average plasma concentration for the 0.3 mg Epipen peaked between 0.5 and 1 ng/mL. By contrast, the Epinephrine film formulation peaked between 4 and 4.5 ng/mL.

Example 24

Referring to **Figure 23**, this graph shows a pharmacokinetic model in the male miniature swine studied to determine the impact of an enhancer (9% clove + 3% Labrasol) on epinephrine concentration over time following sublingual or intramuscular administration across 7 animal models. The general peak concentration was achieved between 10-30 minutes.

Alprazolam Data

Example 25

Referring to **Figure 24A**, **Figure 24B**, and **Figure 24B**, these graphs represent data from a male miniature swine study comparing alprazolam plasma concentration over time (in hours) upon sublingual administration of oral alprazolam disintegrating tablet (ODT) and alprazolam pharmaceutical composition film.

Figure 24A shows mean data from alprazolam ODT (Group 1). Peak concentration of between 7-12 ng/mL was achieved at approximately 1-8 hours.

Figure 24B shows mean data from alprazolam pharmaceutical composition film (Group 2). Peak concentration of between 5-17 ng/mL, including greater than 5 ng/mL, greater than 10 ng/mL, greater than 12 ng/mL, greater than 15 ng/mL, greater than 17 ng/mL, less than 17 ng/mL, less than 15 ng/mL, less than 12 ng/mL, less than 10 ng/mL, less than 5 ng/mL, was achieved between between 10 minutes to 4 hours, including greater than 10 minutes, greater than 20 minutes, greater than 30 minutes, greater than 45 minutes, greater than 1 hour, greater than 1.5 hours, greater than 2 hours, greater than 2.5 hours, greater than 3 hours, greater than 3.5 hours, or about 4 hours, less than 4 hours, less than 3.5 hours, less than 3 hours, less than 2.5 hours, less than 2 hours, less than 1.5 hours, less than 1 hour, less than 45 minutes, less than 30 minutes, or less than 20 minutes.

Figure 24C shows mean data from alprazolam pharmaceutical composition film from another group of male miniature swine (Group 3). Peak concentration of between 5-17 ng/mL, including greater than 5 ng/mL, greater than 10 ng/mL, greater than 12 ng/mL, greater than 15

ng/mL, greater than 17 ng/mL, less than 17 ng/mL, less than 15 ng/mL, less than 12 ng/mL, less than 10 ng/mL, less than 5 ng/mL, was achieved between 10 minutes to 4 hours, including greater than 10 minutes, greater than 20 minutes, greater than 30 minutes, greater than 45 minutes, greater than 1 hour, greater than 1.5 hours, greater than 2 hours, greater than 2.5 hours, greater than 3 hours, greater than 3.5 hours, and about 4 hours, less than 4 hours, less than 3.5 hours, less than 3 hours, less than 2.5 hours, less than 2 hours, less than 1.5 hours, less than 1 hour, less than 45 minutes, less than 30 minutes, or less than 20 minutes.

Example 26

Referring to **Figure 25 A**, this graph illustrates data from a male miniature swine study comparing alprazolam plasma concentration over time following sublingual administration (in hours) of oral alprazolam disintegrating tablet (ODT) (indicated by circle data points) and two groups with alprazolam pharmaceutical composition film (indicated by square and triangle data points).

As the graph indicates, the data from the alprazolam pharmaceutical composition film (both groups) obtained a higher alprazolam plasma concentration of up to approximately 15-25 mg/mL in a therapeutic window of about 30 minutes or less, including more than 10 minutes, more than 20 minutes, about 30 minutes, more than 30 minutes, less than 30 minutes, less than 20 minutes less than 15 minutes, or less than 10 minutes.

Referring to **Figure 25B**, this graph indicates the individual data points from the studies referenced in **Figure 25A**.

Referring to **Figure 25C**, this graph indicates the individual data points from the studies referenced in **Figure 25A** from 0-1 hour.

Referring to **Figure 26A**, this graph indicates the individual data points for the alprazolam ODT referenced in **Figure 25C**.

Referring to **Figure 26B**, this graph indicates the individual data points for the alprazolam pharmaceutical film referenced in **Figure 25C**.

Referring to **Figure 26C**, this graph indicates the individual data points for the alprazolam pharmaceutical film (second group) referenced in **Figure 25C**.

The data from the graphs referenced above is also summarized in the following table:

Pharmaceutical	Tmax (hrs)	Cmax (ng/mL)	AUC ng*hr/mL
Alprazolam 2 mg (ODT)	4.25	16.18 ± 2.90	120.61 ± 29.63
Alprazolam 2 mg film 12-1-1	0.5	27± 6.0	154.46 ± 41.29
Alprazolam 2 mg Film 13-1-1	1.5	20.52 ± 11.01	103.74 ± 35.57
Alprazolam 2 mg Film 6-1-1	2.5	11.5 ± 4.7	86.0 ± 35.5
Alprazolam 2 mg Film 1-1-2	1	15.2 ± 5.7	96.6 ± 44.3

5

Example 27

Referring to **Figure 27A**, this figure illustrates mean data from a male miniature swine study comparing alprazolam plasma concentration over time following sublingual administration of oral alprazolam disintegrating tablet (ODT) (indicated by circle data points) and two groups with alprazolam pharmaceutical composition film (indicated by square and triangle data points). As the data indicates, the 0.5 mg alprazolam ODT achieved a range of peak concentration of about 5-6 ng/mL between 0-4 hours, including greater than 10 minutes, greater than 20 minutes, greater than 30 minutes, greater than 45 minutes, greater than 1 hour, greater than 1.5 hours, greater than 2 hours, greater than 2.5 hours, greater than 3 hours, greater than 3.5 hours, or about 4 hours, less than 4 hours, less than 3.5 hours, less than 3 hours, less than 2.5 hours, less than 2 hours, less than 1.5 hours, less than 1 hour, less than 45 minutes, less than 30 minutes, or less than 20 minutes. The 0.5 mg alprazolam pharmaceutical composition film achieved peak concentration of about 7-8 ng/mL and 6-7 ng/mL, respectively between 0-4 hours, including greater than 10 minutes, greater than 20 minutes, greater than 30 minutes, greater than 45 minutes, greater than 1 hour, greater than 1.5 hours, greater than 2 hours, greater than 2.5 hours, greater than 3 hours, greater than 3.5 hours, or about 4 hours, less than 4 hours, less than 3.5 hours, less than 3 hours, less than 2.5 hours, less than 2 hours, less than 1.5 hours, less than 1 hour, less than 45 minutes, less than 30 minutes, or less than 20 minutes.

Referring to **Figure 27B**, this graph illustrates mean data of alprazolam plasma concentration over time following sublingual administration of oral alprazolam disintegrating tablet (ODT) (indicated by circle data points) and two groups with alprazolam pharmaceutical composition film (indicated by square and triangle data points) between 0-2 hours. Unlike the ODT, the therapeutic window for the alprazolam pharmaceutical composition films started at 10-15 minutes, whereas the ODT started at approximately 17-20 minutes.

Referring to **Figure 27C**, this graph illustrates complete data referenced in Fig. 27B, for ODT (n=4), 0.5 mg alprazolam pharmaceutical composition film 14-1-1 (n=5), and 0.5 mg alprazolam pharmaceutical composition film 15-1-1 (n=5).

The data from the graphs referenced above is also summarized in the following table:

Pharmaceutical	Tmax (hrs)	Cmax (ng/mL)	AUC ng*hr/mL
Alprazolam 0.5 mg (ODT)	1.5	5.56± 1.41	34.01±14.74
Alprazolam 0.5 mg film 14-1-1	1	10.87±3.08	50.80±10.03
Alprazolam 0.5 mg Film 15-1-1	2	7.33±2.80	37.31±10.09

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

Other embodiments are within the scope of the following claims.

CLAIMS:

What is claimed is:

1. A pharmaceutical composition, comprising:

a polymeric matrix;

5 a pharmaceutically active component in the polymeric matrix; and
an adrenergic receptor interacter.

2. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition further includes a permeation enhancer.

10

3. The pharmaceutical composition according to claim 1, wherein the adrenergic receptor interacter includes a terpenoid, a terpene, or a sesquiterpene.

4. The pharmaceutical composition according to claim 2, wherein the permeation enhancer
15 includes farnesol or Labrasol.

5. The pharmaceutical composition according to claim 2, wherein the permeation enhancer includes linoleic acid.

20 6. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is a film further comprising a polymeric matrix, the pharmaceutically active component being contained in the polymeric matrix.

7. The pharmaceutical composition according to claim 1, wherein the adrenergic receptor
25 interacter includes a phenylpropanoid.

8. The pharmaceutical composition according to claim 7, wherein the phenylpropanoid is eugenol or eugenol acetate.

30

9. The pharmaceutical composition according to claim 7, wherein the phenylpropanoid is a cinnamic acid, cinnamic acid ester, cinnamic aldehyde or hydrocinnamic acid.

5 10. The pharmaceutical composition according to claim 7, wherein the phenylpropanoid is chavicol.

11. The pharmaceutical composition according to claim 7, wherein the phenylpropanoid is safrole.

10 12. The pharmaceutical composition according to claim 1, wherein the adrenergic receptor interacter is a phytoextract.

13. The pharmaceutical composition according to claim 12, wherein the phytoextract further includes an essential oil extract of a clove plant.

15 14. The pharmaceutical composition according to claim 12, wherein the phytoextract further includes an essential oil extract of a leaf of a clove plant.

20 15. The pharmaceutical composition according to claim 12, wherein the phytoextract further includes an essential oil extract of a flower bud of a clove plant.

16. The pharmaceutical composition according to claim 12, wherein the phytoextract further includes an essential oil extract of a stem of a clove plant.

25 17. The pharmaceutical composition according to claim 12, wherein the phytoextract is synthetic or biosynthetic.

18. The pharmaceutical composition according to claim 12, wherein the phytoextract further includes 40-95% eugenol.

30

19. The pharmaceutical composition according to claim 1, wherein the pharmaceutically active component is epinephrine, diazepam, or alprazolam.

20. The pharmaceutical composition according to claim 1, wherein the polymer matrix includes a polymer.

21. The pharmaceutical composition according to claim 20, wherein the polymer includes a water soluble polymer.

22. The pharmaceutical composition according to claim 20, wherein the polymer includes a cellulosic polymer selected from the group of: hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and carboxymethyl cellulose.

23. The pharmaceutical composition according to claim 20, wherein the pharmaceutical composition is a chewable or gelatin based dosage form, spray, gum, gel, cream, tablet, liquid or film.

24. The pharmaceutical composition according to claim 20, wherein the polymeric matrix comprises a polyethylene oxide, cellulosic polymer, polyethylene oxide and polyvinyl pyrrolidone, polyethylene oxide and a polysaccharide, polyethylene oxide, hydroxypropyl methylcellulose and a polysaccharide, or polyethylene oxide, hydroxypropyl methylcellulose, polysaccharide and polyvinylpyrrolidone.

25. The pharmaceutical composition according to claim 20, wherein the polymeric matrix comprises at least one polymer selected from the group of: pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, ethylene oxide, propylene oxide co-polymers, collagen, albumin, poly-amino acids, polyphosphazenes, polysaccharides, chitin, chitosan, and derivatives thereof.

26. The pharmaceutical composition according to claim 1, further comprising a stabilizer.

27. The pharmaceutical composition according to claim 1, wherein the polymeric matrix comprises a dendritic polymer or a hyperbranched polymer.

5

28. A method of making a pharmaceutical composition comprising:

combining an adrenergic receptor interacter with a pharmaceutically active component and

forming a pharmaceutical composition including the adrenergic receptor interacter and
10 the pharmaceutically active component.

29. A device comprising

a housing that holds an amount of a pharmaceutical composition, comprising:

a polymeric matrix;
15 a pharmaceutically active component in the polymeric matrix and
an adrenergic receptor interacter; and
an opening that dispenses a predetermined amount of the pharmaceutical composition.

30. A pharmaceutical composition, comprising:

20 a polymeric matrix;
a pharmaceutically active component in the polymeric matrix; and
an aporphine alkaloid interacter.

31. A pharmaceutical composition, comprising:

a polymeric matrix;
25 a pharmaceutically active component in the polymeric matrix; and
a vasodilator interacter.

32. A pharmaceutical composition, comprising:

a polymeric matrix;
a pharmaceutically active component in the polymeric matrix; and

an interacter that creates increased blood flow or enables a flushing of the tissue to modify transmucosal uptake of the pharmaceutically active component.

33. A pharmaceutical composition, comprising:

a polymeric matrix;

5 a pharmaceutically active component in the polymeric matrix; and

an interacter that has a positive or negative heat of solution which are used as aids to modify transmucosal uptake.

34. A pharmaceutical composition, comprising:

a polymeric matrix;

10 a pharmaceutically active component in the polymeric matrix; and

an interacter, the composition contained in a multilayer film having at least one side where the edges are coterminous.

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	First Named Inventor	Alexander Mark Schobel	
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	Examiner Name	Michael P. BARKER	
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Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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19	3189174		1965-06-15	J. A. Cormack	

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21	3242959		1966-03-29	H.P. Glass	
22	3249109		1966-05-03	H. Maeth et al	
23	3324754		1967-06-13	A. Peavy	
24	3370497		1968-02-27	C.E. Busse	
25	3419137		1968-12-31	G.A. Walck III	
26	3444858		1969-05-20	H. S. Russell	
27	3536809		1970-10-27	Applezwig	
28	3539605		1970-11-10	Oberhofer	
29	3551556		1970-12-29	Kliment et al	
30	3598122		1971-08-10	Zaffaroni	

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31	3610248		1971-10-05	Davidson	
32	4365423		1982-12-28	Arter et al	
33	3632740		1972-01-04	Robinson et al	
34	3640741		1972-02-08	Etes	
35	3641237		1972-02-08	F.E. Gould et al	
36	3677866		1972-07-18	C.G. Pickett et al	
37	3731683		1973-05-08	Zaffaroni	
38	3753732		1973-08-21	Boroshok	
39	3755558		1973-08-28	Scribner	
40	3768725		1973-10-30	Pilaro	
41	3795527		1974-03-05	Stone et al	

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42	3809220		1974-05-07	Arcudi	
43	3814095		1974-06-04	Lubens	
44	3825014		1974-07-23	Wroten	
45	3835995		1974-09-17	Haines	
46	3840657		1974-10-08	Norfleet	
47	3892905		1975-07-01	Albert	
48	3911099		1975-10-07	DeFoney et al	
49	3972995		1976-08-03	Tsuk et al	
50	3996934		1976-12-14	Zaffaroni	
51	3998215		1976-12-21	Anderson et al	
52	4015023		1977-03-29	Lamberti et al	

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53	4022924		1977-05-10	Mitchell et al	
54	4029757		1977-06-14	Mlodozeniec et al	
55	4029758		1977-06-14	Mlodozeniec et al	
56	4031200		1977-06-21	Reif	
57	4049848		1977-09-20	Goodale et al	
58	4123592		1978-10-31	Rainer et al	
59	4128445		1978-12-05	Sturzenegger et al	
60	4136145		1979-01-23	Fuchs et al	
61	4136162		1979-01-23	Fuchs et al	
62	4139627		1979-02-13	Lane et al	
63	4202966		1980-05-13	Misaki et al	

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64	4226848		1980-10-07	Nagai et al	
65	4251400		1981-02-17	Columbus	
66	4292299		1981-09-29	Suzuki et al	
67	4294820		1981-10-13	Keith et al	
68	4302465		1981-11-24	AF Ekenstam et al	
69	4307075		1981-12-22	Martin	
70	4307117		1981-12-22	Leshik	
71	4325855		1982-04-20	Dickmann et al	
72	4341563		1982-07-27	Kurihara et al	
73	4373036		1983-02-08	Chang et al	
74	4390450		1983-06-28	Gibson et al	

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75	4406708		1983-09-27	Hesselgren	
76	4432975		1984-02-21	Libby	
77	4438258		1984-03-20	Graham	
78	4460532		1984-07-17	Cornell	
79	4460562		1984-07-17	Keith et al	
80	4466973		1984-08-21	Rennie	
81	4478658		1984-10-23	Wittwer	
82	4503070		1985-03-05	Eby, III	
83	4511592		1985-04-16	Percel et al	
84	4515162		1985-05-07	Yamamoto et al	
85	4517173		1985-05-14	Kizawa et al	

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86	4529301		1985-07-16	Rountree	
87	4529601		1985-07-16	Broberg et al	
88	4529748		1985-07-16	Wienecke	
89	4562020		1985-12-31	Hijiya et al	
90	4569837		1986-02-11	Suzuki et al	
91	4572832		1986-02-25	Kigasawa et al	
92	4582835		1986-04-15	Lewis et al	
93	4593053		1986-06-03	Jevne et al	
94	4598089		1986-07-01	Hadvary et al	
95	4608249		1986-08-26	Otsuka et al	
96	4613497		1986-09-23	Chavkin	

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97	4615697		1986-10-07	Robinson	
98	4619701		1986-10-28	Angrick et al	
99	4621482		1986-11-11	Crevasse et al	
100	4623394		1986-11-18	Nakamura et al	
101	4631837		1986-12-30	Magoon	
102	4639367		1987-01-27	Mackles	
103	4562020		1985-12-31	Hijiya et al	
104	4659714		1987-04-21	Watt-Smith	
105	4661359		1987-04-28	Seaborne et al	
106	4675009		1987-06-23	Hymes et al	
107	4695465		1987-09-22	Kigasawa et al	

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108	4704119	1987-11-03	Shaw et al
109	4713239	1987-12-15	Babaian et al
110	4713243	1987-12-15	Schiraldi et al
111	4713251	1987-12-15	Seighman
112	4722761	1988-02-02	Cartmell et al
113	4727064	1988-02-23	Pitha
114	4740365	1988-04-26	Yukimatsu et al
115	4748022	1988-05-31	Busciglio
116	4752465	1988-06-21	Mackles
117	4762230	1988-08-09	Croce
118	4765983	1988-08-23	Takayanagi et al

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119	4772470	1988-09-20	Inoue et al
120	4777046	1988-10-11	Iwakura et al
121	4780309	1988-10-25	Geria et al
122	4781294	1988-11-01	Croce
123	4789667	1988-12-06	Makino et al
124	4802924	1989-02-07	Woznicki et al
125	4828841	1989-05-09	Porter et al
126	4849246	1989-07-18	Schmidt
127	4851394	1989-07-25	Kubodera
128	4860754	1989-08-29	Sharik et al
129	4872270	1989-10-10	Fronheiser et al

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130	4876092	1989-10-24	Mizobuchi et al
131	4876970	1989-10-31	Bolduc
132	4880416	1989-11-14	Horiuchi et al
133	4888354	1989-12-19	Chang et al
134	4894232	1990-01-16	Reul et al
135	4900552	1990-02-13	Sanvordeker et al
136	4900554	1990-02-13	Yangibashi et al
137	4900556	1990-02-13	Wheatley et al
138	4910247	1990-03-20	Haldar et al
139	4915950	1990-04-10	Miranda et al
140	4925670	1990-05-15	Schmidt

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141	4927634		1990-05-22	Sorrentino et al	
142	4927636		1990-05-22	Hijiya et al	
143	4937078		1990-06-26	Mezei et al	
144	4940587		1990-07-10	Jenkins et al	
145	4948580		1990-08-14	Browning	
146	4958580		1990-09-25	Asaba et al	
147	4978531		1990-12-18	Yamazaki et al	
148	4980169		1990-12-25	Oppenheimer et al	
149	4981693		1991-01-01	Higashi et al	
150	4981875		1991-01-01	Leusner et al	
151	4993586		1991-02-19	Taulbee, deceased et al	

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152	5023082		1991-06-11	Friedman et al	
153	5024701		1991-06-18	Desmarais	
154	5028632		1991-07-02	Fuisz	
155	5044761		1991-09-03	Yuhki et al	
156	5045445		1991-09-03	Schultz	
157	5047244		1991-09-10	Sanvordeker et al	
158	5056584		1991-10-15	Seaton	
159	5064717		1991-11-12	Suzuki et al	
160	5072842		1991-12-17	White	
161	5078734		1992-01-07	Noble	
162	5089307		1992-02-18	Ninomiya et al	

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163	5107734		1992-04-28	Armbruster	
164	5116140		1992-05-26	Hirashima	
165	5118508		1992-06-02	Kikuchi et al	
166	5126160		1992-06-30	Giddey et al	
167	5137729		1992-08-11	Kuroya et al	
168	5158825		1992-10-27	Altwirth	
169	5166233		1992-11-24	Kuroya et al	
170	5176705		1993-01-05	Noble	
171	5186938		1993-02-16	Sablotsky et al	
172	5196436		1993-03-23	Smith	
173	5229164		1993-07-20	Pins et al	

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174	5234957		1993-08-10	Mantelle	
175	5264024		1993-11-23	Bosvot et al	
176	5271940		1993-12-21	Cleary et al	
177	5272191		1993-12-21	Ibrahim et al	
178	5316717		1994-05-31	Koepff et al	
179	5325968		1994-07-05	Sowden	
180	5328942		1994-07-12	Akhtar et al	
181	5346701		1994-09-13	Heiber et al	
182	5354551		1994-10-11	Schmidt	
183	5369131		1994-11-29	Poli et al	
184	5375930		1994-12-27	Tani	

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185	5380529		1995-01-10	Heusser et al	
186	5393528		1995-02-28	Staab	
187	5405637		1995-04-11	Martinez et al	
188	5411945		1995-05-02	Ozaki et al	
189	5413792		1995-05-09	Ninomiya et al	
190	5422127		1995-06-06	Dube et al	
191	5433960		1995-07-18	Meyers	
192	5451419		1995-09-19	Schwab et al	
193	5455043		1995-10-03	Fischel-Ghodsian	
194	5458884		1995-10-17	Britton et al	
195	5462749		1995-10-31	Rencher	

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196	5472704		1995-12-05	Santus et al	
197	5479408		1995-12-26	Will	
198	5506046		1996-04-09	Andersen et al	
199	5518902		1996-05-21	Ozaki et al	
200	5529782		1996-06-25	Staab	
201	5530861		1996-06-25	Diamant et al	
202	5550178		1996-08-27	Desai et al	
203	5551033		1996-08-27	Foster et al	
204	5567431		1996-10-22	Vert et al	
205	5587175		1996-12-24	Viegas et al	
206	5588009		1996-12-24	Will	

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207	5589357		1996-12-31	Martinez et al	
208	5593697		1997-01-14	Barr et al	
209	5601605		1997-02-11	Crowe et al	
210	5605696		1997-02-25	Eury et al	
211	5605698		1997-02-25	Ueno	
212	5613779		1997-03-25	Niwa	
213	5620757		1997-04-15	Ninomiya et al	
214	5629003		1997-05-13	Horstmann et al	
215	5641093		1997-06-24	Dolin et al	
216	5641536		1997-06-24	Lech et al	
217	5647431		1997-07-15	Takeshita et al	

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218	5653993		1997-08-05	Ghanta et al	
219	5656296		1997-08-12	Khan et al	
220	5656297		1997-08-12	Bernstein et al	
221	5670168		1997-09-23	Baichwal et al	
222	5679145		1997-10-21	Andersen et al	
223	5681873		1997-10-28	Norton et al	
224	5689550		1997-11-18	Garson et al	
225	5698181		1997-12-16	Luo	
226	5700478		1997-12-23	Biegajski et al	
227	5700479		1997-12-23	Lundgren	
228	5725648		1998-03-10	Brown et al	

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229	5733575		1998-03-31	Mehra et al	
230	5742905		1998-04-21	Pepe et al	
231	5750145		1998-05-12	Patell	
232	5750157		1998-05-12	Grosswald et al	
233	5750585		1998-05-12	Park et al	
234	5759599		1998-06-02	Wampler et al	
235	5764639		1998-06-09	Staples et al	
236	5764899		1998-06-09	Eggleston et al	
237	5765004		1998-06-09	Foster et al	
238	5766525		1998-06-16	Andersen et al	
239	5766620		1998-06-16	Heiber et al	

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240	5766839		1998-06-16	Johnson et al	
241	5771353		1998-06-23	Eggleston et al	
242	5785180		1998-07-28	Dressel et al	
243	5792494		1998-08-11	Kanca et al	
244	5800832		1998-09-01	Tapolsky et al	
245	5806284		1998-09-15	Gifford	
246	5822526		1998-10-13	Waskiewicz	
247	5830437		1998-11-03	Ascione et al	
248	5830884		1998-11-03	Kasica et al	
249	5846557		1998-12-08	Eisenstadt et al	
250	5847023		1998-12-08	Viegas et al	

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251	5862915		1999-01-26	Plezia et al	
252	5864684		1999-01-26	Nielsen	
253	5881476		1999-03-16	Strobush et al	
254	5891461		1999-04-06	Jona et al	
255	5894930		1999-04-20	Faughey et al	
256	5906742		1999-05-25	Wang et al	
257	5937161		1999-08-10	Mulligan et al	
258	5941393		1999-08-24	Wilfong, Jr.	
259	5948430		1999-09-07	Zerbe et al	
260	5948430		1999-09-07	Zerbe et al	
261	5980554		1999-11-09	Lenker et al	

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262	5995597		1999-11-30	Woltz et al	
263	6004996		1999-12-21	Shah et al	
264	6030616		2000-02-29	Waters et al	
265	6031895		2000-02-29	Cohn et al	
266	6036016		2000-03-14	Arnold	
267	6047484		2000-04-11	Bolland et al	
268	6051253		2000-04-18	Zettler et al	
269	6054119		2000-04-25	Hurme et al	
270	6064990		2000-05-16	Goldsmith	
271	6077558		2000-06-20	Euber	
272	6072100		2000-06-06	Mooney et al	

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273	6090401		2000-07-18	Gowan, Jr. et al	
274	6099871		2000-08-08	Martinez	
275	6103266		2000-08-15	Tapolsky et al	
276	6143276		2000-11-07	Unger	
277	6148708		2000-11-21	Pfeiffer	
278	6152007		2000-11-28	Sato	
279	6153210		2000-11-28	Roberts et al	
280	6159498		2000-12-12	Tapolsky et al	
281	6161129		2000-12-12	Rochkind	
282	6177066	B1	2001-01-23	Pataut et al	
283	6177092	B1	2001-01-23	Lentini et al	

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284	6177096	B1	2001-01-23	Zerbe et al	
285	6183808	B1	2001-02-06	Grillo et al	
286	6203566	B1	2001-03-20	Alanen et al	
287	6219694	B1	2001-04-17	Lazaridis et al	
288	6230894	B1	2001-05-15	Danville	
289	6231957	B1	2001-05-15	Zerbe et al	
290	6238700	B1	2001-05-29	Dohner et al	
291	6264981	B1	2001-07-24	Zhang et al	
292	6267808	B1	2001-07-31	Grillo et al	
293	6268048	B1	2001-07-31	Topolkaraev et al	
294	6284264	B1	2001-09-04	Zerbe et al	

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Filing Date	2017-10-03
First Named Inventor	Alexander Mark Schobel
Art Unit	1655
Examiner Name	Michael P. BARKER
Attorney Docket Number	18460.0028

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Application Number		15724234
Filing Date		2017-10-03
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Art Unit	1655	
Examiner Name	Michael P. BARKER	
Attorney Docket Number	18460.0028	

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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

OR

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See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Harold H. Fox, Reg.# 41498/	Date (YYYY-MM-DD)	2018-08-04
Name/Print	Harold H. Fox	Registration Number	41,498

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

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	First Named Inventor	Alexander Mark Schobel
	Art Unit	1655
	Examiner Name	Michael P. BARKER
	Attorney Docket Number	18460.0028

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22	0514691	EP	A2	1992-04-29	Euroresearch S.r.L		
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24	0598606	EP	A1	1994-05-25	Johnson & Johnson Consumer Products, Inc.		
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26	0949925	EP	B1	2004-01-07	LTS Lohmann Therapie-Systeme AG	English Abstract	
27	1110546	EP	A1	2001-06-27	Johnson & Johnson Consumer Companies, Inc.		

**INFORMATION DISCLOSURE
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Application Number		15724234
Filing Date		2017-10-03
First Named Inventor	Alexander Mark Schobel	
Art Unit	1655	
Examiner Name	Michael P. BARKER	
Attorney Docket Number	18460.0028	

28	1243523	EP	A1	2002-09-25	Amcor Flexibles France		
29	1267829	EP	B1	2006-05-03	Warner-Lambert Co. LLC		
30	1504765	EP	A1	2005-02-09	Kyukyu Pharmaceutical Co., LTD		
31	1591106	EP	B1	2009-07-22	Shin-Etsu Chemical Co., Ltd		
32	1852041	EP	A2	2007-11-07	Baldan, Ferdinando		
33	2716098	FR	A1	1995-08-18	Socoplan (S.A.)		
34	1061557	GB		1967-03-15	Ashe Chemical Limited		
35	1154317	GB		1969-06-04	Higham Stanley Russell		
36	1510999	GB		1978-05-17	Schering Aktiengesellschaft		
37	56100714	JP	A	1981-08-12			
38	62126950	JP	A	1987-06-09	Unie Colloid KK	English Abstract	

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39	2265444	JP	A	1990-10-30	Fuji Oil Co LTD	English Abstract	
40	473268	JP	A	1992-03-09			
41	5147140	JP	A	1993-06-15	Mitsubishi Rayon Co	English Abstract	
42	7322812	JP	A	1995-12-12	Osaka Kagaku Gokin KK	English Abstract	
43	11255247	JP	A	1999-09-21			
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48	2008011194	JP	A	2008-01-17	Fujifilm Corp	English Abstract	
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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Harold H. Fox, Reg.# 41498/	Date (YYYY-MM-DD)	2018-08-04
Name/Print	Harold H. Fox	Registration Number	41,498

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

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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.
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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.
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15724234
	Filing Date	2018-10-03
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1655
	Examiner Name	Michael P. BARKER
	Attorney Docket Number	18460.0028

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	1	4251561		1981-02-17	Gajewski	
	2	4716802		1988-01-05	O'Connor et al	
	3	5633006		1997-05-27	Catania et al	
	4	5815398		1998-09-29	Dighe et al	
	5	7115507		2006-10-03	Kawase	

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	1	20040102867	A1	2004-05-27	Palanisamy et al	

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2	20050055123	A1	2005-03-10	Franz	
3	20050222781	A1	2005-10-06	Yue et al	
4	20060198885		2006-09-07	Dharmadhikari et al	
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12	20090146336	A1	2009-06-11	Masi	

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	1	9215289	WO	A1	1992-09-17	Noven Pharmaceuticals, Inc.		
	2	9505416	WO	A2	1995-02-23	Cygnus Therapeutic Systems		
	3	9518046	WO	A1	1995-07-06	Frank, Richard, D.		
	4	9530601	WO	A1	1995-11-16	Sales S.P.A.		
	5	9615903	WO	A1	1996-05-30	W.R. Grace & Co.		
	6	9731621	WO	A1	1997-09-04	Warner-Lambert Co.		
	7	9810993	WO	A1	1998-03-19	Unfill International A/G		
	8	9817251	WO	A1	1998-04-30	Virotex Co.		
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10	0018365	WO	A2	2000-04-06	Warner-Lambert Co.		
11	0024647	WO	A1	2000-05-04	Novartis AG		
12	0042992	WO	A2	2000-07-27	Lavipharm Laboratories, Inc.		
13	0130288	WO	A1	2001-05-03	Anesta Co.		
14	0156904	WO	A1	2001-08-09	JR Crompton Limited		
15	0168452	WO	A1	2001-09-20	Stanelco Fibre Optics Ltd		
16	0170194	WO	A1	2001-09-27	Warner-Lambert Co.		
17	0170197	WO	A2	2001-09-27	Collaborative Technologies, Inc.		
18	0191721	WO	A2	2001-12-06	A.E. Staley Manufacturing Co.		
19	0205789	WO	A2	2002-01-24	SCS Skin Care Systems GmbH		
20	0243657	WO	A2	2002-06-06	WM. Wrigley Jr. Co.		

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21	02062315	WO	A1	2002-08-15	Pharmacia Co.		
22	02074238	WO	A2	2002-09-26	Lavipharm Laboratories Inc.		
23	02091965	WO	A1	2002-11-21	Chalmers, Susanna, Elizabeth		
24	03011259	WO	A1	2003-02-13	WM. Wrigley Jr. Co.		
25	03015749	WO	A1	2003-02-27	Colgate-Palmolive Co.		
26	03030881	WO	A1	2003-04-17	Kosmos Pharma		
27	03030882	WO	A1	2003-04-17	Kosmos Pharma		
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29	03043659	WO	A1	2003-05-30	Givaudan SA		
30	2004009445	WO	A2	2004-01-29	Kosmos Pharma		
31	2004035407	WO	A1	2004-04-29	Toppan Printing Co., LTD		

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32	2004043165	WO	A1	2004-05-27	Givaudan SA		
33	2004045305	WO	A2	2004-06-03	WM. Wrigley Jr. Co		
34	2004045537	WO	A2	2004-06-03	Zengen, Inc.		
35	2004052335	WO	A1	2004-06-24	MonoSol Rx LLC		
36	2004060298	WO	A2	2004-07-22	Sarnoff Co.		
37	2004087084	WO	A1	2004-10-14	The Procter & Gamble Co.		
38	2005035776	WO	A2	2005-04-21	MonoSol Rx, LLC		
39	2005039499	WO	A2	2005-05-06	Adhesives Research, Inc.		
40	2005074867	WO	A1	2005-08-18	L-Oreal	English Abstract	
41	2005102287	WO	A2	2005-11-03	Duocort AB		
42	2005123074	WO	A1	2005-12-29	Boots Healthcare International Limited		

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43	2006004480	WO	A1	2006-01-12	Radi Medical Systems AB		
44	2006017462	WO	A2	2002-02-16	R.P. Scherer Technologies, Inc.		
45	2006031209	WO	A1	2006-03-23	MonoSol Rx, LLC		
46	2006039264	WO	A1	2006-04-13	MonoSol Rx, LLC		
47	2006085210	WO	A1	2006-08-17	Warner-Lamber Co. LLC		
48	2006133948	WO	A2	2006-12-21	Novartis Pharma GmbH		
49	2007067494	WO	A1	2007-06-14	MonoSol Rx, LLC		
50	2007070632	WO	A2	2007-06-21	Biodelivery Sciences International, Inc.		

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EXAMINER SIGNATURE

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Signature	/Harold H. Fox, Reg.# 41498/	Date (YYYY-MM-DD)	2018-08-04
Name/Print	Harold H. Fox	Registration Number	41,498

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	1	5023271		1991-06-11	Vigne et al	
	2	5049322		1991-09-17	Devissaguet et al	
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9	5573783		1996-11-12	Desieno et al	
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Examiner Name	Michael P. BARKER
Attorney Docket Number	18460.0028

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Attorney Docket Number	18460.0028

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

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

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See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Harold H. Fox, Reg.# 41498/	Date (YYYY-MM-DD)	2018-08-04
Name/Print	Harold H. Fox	Registration Number	41,498

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	Art Unit	1655	
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Filing Date	2017-10-03
First Named Inventor	Alexander Mark Schobel
Art Unit	1655
Examiner Name	Michael P. BARKER
Attorney Docket Number	18460.0028

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☒ A certification statement is not submitted herewith.

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

Signature	/Harold H. Fox, Reg.# 41498/	Date (YYYY-MM-DD)	2018-08-04
Name/Print	Harold H. Fox	Registration Number	41,498

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Art Unit	1655
Examiner Name	Michael P. BARKER
Attorney Docket Number	18460.0028

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	2	5293699		1994-03-15	Faust et al.	
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	1	2746414	DE	A1	1979-04-26	Detert et al.		×
	2	0014253	EP	A2	1980-08-20	Rider		☐
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	Filing Date	2017-10-03
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1655
	Examiner Name	Michael P. BARKER
	Attorney Docket Number	18460.0028

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Name/Print	Harold H. Fox	Registration Number	41,498

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15724234
Filing Date	2017-10-03
First Named Inventor	Alexander Mark Schobel
Art Unit	1655
Examiner Name	Michael P. BARKER
Attorney Docket Number	18460.0028

1	Index of Image File Wrapper and Transaction History for Ex Parte Reexamination Control No. 90/012,098, current as of .
2	Index of Documents for Inter Partes Review Case No. IPR2013-00316, current as of August 29, 2017.
3	Index of Image File Wrapper and Transaction History for Ex Parte Reexamination Control No. 90/012,097, current as of August 29, 2017.
4	Index of Documents for Inter Partes Review Case No. IPR2013-00315, current as of August 29, 2017.
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8	Index of Documents for Inter Partes Review Case No. IPR2014-00794, current as of August 29, 2017.
9	Index of Documents for Inter Partes Review Case No. IPR2015-00165, current as of August 29, 2017.
10	Index of Documents for Inter Partes Review Case No. IPR2015-00167, current as of August 29, 2017.
11	Index of Documents for Inter Partes Review Case No. IPR2015-00168, current as of August 29, 2017.

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12	Index of Documents for Inter Partes Review Case No. IPR2015-00169, current as of August 29, 2017.
13	Index of Documents for Inter Partes Review Case No. IPR2016-00281, current as of August 29, 2017.
14	Index of Documents for Inter Partes Review Case No. IPR2016-00282, current as of August 29, 2017.
15	Index of Documents for Inter Partes Review Case No. IPR2016-01111, current as of August 29, 2017.
16	Index of Documents for Inter Partes Review Case No. IPR2016-01112, current as of August 29, 2017.
17	Index of Documents for Inter Partes Review Case No. IPR2017-00200, current as of August 29, 2017.
18	Index of Documents for Inter Partes Review Case No. IPR2017-01557, current as of August 29, 2017.
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OR

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

See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Harold H. Fox, Reg.# 41498/	Date (YYYY-MM-DD)	2018-08-04
Name/Print	Harold H. Fox	Registration Number	41,498

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15724234
	Filing Date	2017-10-03
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1655
	Examiner Name	Michael P. BARKER
	Attorney Docket Number	18460.0028

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	1	20110257096		2011-10-20	Maggio	
	2	20130267585		2013-10-10	LJUSBERG-WAHREN	
	3	20070202163		2007-08-30	RAWAS-QALAJI	
	4	20050042271		2005-02-24	Xiong	

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First Named Inventor	Alexander Mark Schobel
Art Unit	1655
Examiner Name	Michael P. BARKER
Attorney Docket Number	18460.0028

1	2193891	GB	1998-02-24	Sandoz
2	2017/192921	WO	2017-11-09	MONOSOL RX LLC
3	2017/192923	WO	2017-11-09	MONOSOL RX LLC

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	1	International Search Report and Written Opinion for PCT/US2018/052927, mailed December 19, 2018.	
	2	Ho, N.F.H. , et al., "(D) Routes of delivery: Case studies," Advanced Drug Delivery Reviews, Vol. 8, No. 2-3 (March 1, 1992) pages 197-236.	
	3	Merkle, H.P., et al., "Buccal delivery for peptide drugs," Journal of Controlled Release, Vol. 21 No. 1-3 (1992).	
	4	Wolany, Gregor, "Zur bukkalen Applikation und Absorption des Oktapeptids Octreotid," (January 1, 1990).	
	5	International Search Report and Written Opinion for PCT/US2018/053042, mailed December 11, 2018.	
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EXAMINER SIGNATURE

Examiner Signature		Date Considered	
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See attached certification statement.

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Signature	/Harold H. Fox, Reg.# 41498/	Date (YYYY-MM-DD)	2019-01-11
Name/Print	Harold H. Fox	Registration Number	41,498

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/724,234	10/03/2017	Alexander Mark Schobel	18460.0028	2978
27890	7590	08/17/2020		
STEPTOE & JOHNSON LLP 1330 CONNECTICUT AVENUE, N.W. WASHINGTON, DC 20036			EXAMINER BARKER, MICHAEL P	
			ART UNIT	PAPER NUMBER
			1655	
			NOTIFICATION DATE	DELIVERY MODE
			08/17/2020	ELECTRONIC

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

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

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ipdocketing@steptoe.com
lfielding@steptoe.com

DETAILED ACTION

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

In the 03/13/2020 Non-Final Office Action, claims 1-34 were pending. Claims 1-27 were rejected, while claims 28-34 were withdrawn.

In Applicant's 06/02/2020 Reply, claim 1 was amended.

Claims 1-34 remain pending.

Remarks and Amendments

Claims 1-27 were rejected under 35 U.S.C. 103 as being unpatentable over US20070293581A1 (published 12/20/2007); US20120058158A1 (published 03/08/2012):

US20070293581A1 describes buccal, lingual, and sublingual dosage forms ([0002],[0010],[0016],[0019],[0026],[0030],[0037],[0041],[0048],[0052],[0059],[0063],[0083]-[0092], claims 1-44) in the form of tablets or films ([0016],[026],[0037],[0048],[0059],[0076]-[0078],[0084],[0086],[0093]-[0097],[0101],[0102],[0116]) comprising a pharmaceutically active component, epinephrine (Abstract, [0002],[0009],[0015],[0019],[0025],[0030],[0036],[0041]-[0044],[0052]-[0058], claims 1-44). The buccal, lingual, and sublingual dosage forms may be formulated as a polymeric matrix ([0089],[0104]), which may include polymers, e.g., polyethylene glycol which encompasses hyperbranched polymers, hydroxypropylmethyl cellulose, polyvinylpyrrolidone (a water soluble polymer) ([0089],[0104]), polysaccharides, chitosan (a polysaccharide) ([0095],[0089]), methylmethacrylate copolymers, stabilizers, polyethylene oxides, and carboxyvinyl polymers ([0104]), which encompass water soluble carbomers. Accordingly, US20070293581A1 describes a pharmaceutical composition comprising a polymeric matrix and pharmaceutically active component. Accordingly, US20070293581A1 describes a pharmaceutical composition comprising a polymeric matrix and pharmaceutically active component but fails to teach inclusion of an adrenergic receptor interacter.

US20120058158A1 also teaches pharmaceutical compositions in a sublingual dosage form comprising, inter alia, oil-based excipients and oil-soluble drugs leading to greater permeability ([0043]), such as clove oil ([0024],[0039]), an adrenergic receptor interacter, by acting as penetration enhancers, increasing solubility of medicaments, and providing a flavor component giving organoleptic feedback to the user ([0024]).

The cited references render obvious claims 1, 2, 5, 6, 12, 13, and 19-27, because it would be obvious to incorporate the adrenergic interacter clove oil into the pharmaceutical composition described in US20070293581A1 to increase the composition's permeability, enhance its penetration and solubility, and provide a flavor component to give organoleptic feedback to the user. This combination provides a composition that contains a phytoextract as the interacter, which is derived from a clove plant, and contains epinephrine, a polymeric matrix encompassing a water soluble polymer, polyethylene oxide, hydroxypropylmethyl cellulose, polysaccharide, polyvinylpyrrolidone, and stabilizing agents. Regarding claim 5, which requires the permeation enhancer of claim 2 to include linoleic acid. Linoleic acid is a well-known permeation enhancer, which would be obvious to add to the composition of the cited references for its intended purpose.

Claim 3 requires that the adrenergic receptor interacter comprise a terpenoid, terpene, or sesquiterpene. Claim 4 requires the permeation enhancer of claim 2 include farnesol or Labrasol.

Claim 7 requires that the adrenergic receptor interacter comprise a phenylpropanoid.

Claim 8 requires the composition of claim 7, wherein the phenylpropanoid is eugenol or eugenol acetate.

Claim 9 requires the pharmaceutical composition of claim 7, wherein the phenylpropanoid is cinnamic acid, cinnamic acid ester, cinnamic aldehyde, or hydrocinnamic acid.

Claim 10 requires the composition of claim 7 wherein the phenylpropanoid is chavicol.

Claim 11 requires the composition of claim 7 wherein the phenylpropanoid is safrole.

Claims 14-16 require the composition of claim 12, wherein the clove oil derives from a bud, leaf, or flower of clove.

Claim 17 requires that the phytoextract of claim 12 is synthetic or biosynthetic.

Claim 18 requires that the phytoextract further includes 40-95% eugenol.

Regarding claims 3, 4, 7, 8-11, and 14-18, the cited references teach these features and render obvious these claims, because as an evidentiary matter, clove oil extracted from clove buds, leaves, and stems is known to contain eugenol (72.08% to 96.65%), β -caryophyllene (a sesquiterpene), chavicol (a phenylpropanoid), α -copaene (a sesquiterpene), methyl eugenol, iso-eugenol (a phenylpropanoid), eugenol acetate (a phenylpropanoid), α -humulene (a sesquiterpene), and caryophyllene oxide (a sesquiterpene metabolite) (Razafimamonjison, et al., International Journal of Basic and Applied Sciences, 3:224 (2014), Abstract; p. 226, Table 2), as well as farnesol (a permeation enhancer) (Gopalakrishnan, et al., J. Sci. Food Agric., 50:111 (1990), p. 114, Tables 1, 2; p. 115, Table 3; p. 116, Tables 4, 5), cinnamic aldehyde, and safrol (Juglal, et al., J. Food Prot., 65:683 (2002), p. 64, Figure 1).

Regarding present claim 27, the combination of cited references do not specifically require a dendritic or hyperbranched polymer. However, Cheng teaches that dendrimers are hyperbranched and monodisperse polymers, wherein the dendrimers are suitable for drug delivery through the mucosa (Cheng, et al., J. Pharm. Sci., 97:123 (2008), p. 123, 138). Tülü et al. teach that cationic dendrimers may have intrinsic mucoadhesive properties for use in the oral cavity, as mucin is negatively charged, thus creating an electrostatic attraction between mucus and dendrimer wherein an encapsulated active may be slowly released into the oral cavity (Tülü, et al., A Search for Antibacterial Agents: Chapter 6: Dendrimers as Antibacterial Agents (2012), p. 97). It would have been obvious to prepare the buccal, lingual or sublingual dosage forms according to the cited references, wherein the compositions comprise a dendritic polymer or hyperbranched polymer, because dendrimers are suitable for drug delivery through the mucosa and have an intrinsic mucoadhesive properties in the oral cavity for slow release an encapsulated active agent.

Applicant amended claim 1 to require the pharmaceutically active component to include a benzodiazepine in the polymeric matrix. The rejection does not address this limitation and is, therefore, withdrawn.

Claim 20 was rejected under 35 U.S.C. 112(d) as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends:

Claim 20 recites the pharmaceutical composition of claim 1, "wherein the polymeric matrix includes a polymer" [sic], however, a polymeric matrix includes a polymer by definition. Thus claim 20 fails to further limit claim 1.

Applicant may cancel the claim, amend the claim to place the claim in proper dependent form, rewrite the claim in independent form, or present a sufficient showing that the dependent claim complies with the statutory requirements.

Applicant amended claim 20 to recite "wherein the polymeric matrix includes a polymer," however, this amendment does not substantively alter the basis of the rejection. A polymeric matrix includes a polymer by definition, thus, claim 20 fails to further limit claim 1. This rejection is maintained.

Claims 1-27 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, and 4-31 of copending Application No. 15/587364 (filed 05/04/2017).

Claims 1-3, 6, 13-16, and 18-20 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-16, 19, 29, and 33 of copending Application No. 15/791249 (filed 10/23/2017).

Claims 1, 6, 19, and 20 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29 and 35-43 of copending Application No. 16/143678 (filed 09/27/2018).

Claims 1-27 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 of copending Application No. 16/143821 (filed 09/27/2018).

Applicant amended claim 1 to require the pharmaceutically active component to include a benzodiazepine in the polymeric matrix. These rejections do not address this limitation and are, therefore, withdrawn.

Claims 1-27 were provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-27 of copending Application No. 16/143678 (filed 09/27/2018).

Applicant amended claim 1 to require the pharmaceutically active component to include a benzodiazepine in the polymeric matrix. The rejection does not address this limitation and is, therefore, withdrawn.

Claim 20 was objected to for depending from claim 1 and reciting "wherein the polymer matrix includes a polymer," however, claim 1 recites a "polymeric matrix."

Applicant amended claim 20 to recite "polymeric matrix," therefore, this objection is withdrawn.

Rejections

35 U.S.C. 103: A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-27 are rejected under 35 U.S.C. 103 as being unpatentable over US20070293581A1 (published 12/20/2007); US20120058158A1 (published 03/08/2012).

US20070293581A1 describes buccal, lingual, and sublingual dosage forms ([0002],[0010]-[0016],[0019]-[0026],[0030]-[0037],[0041]-[0048],[0052]-[0059],[0063],[0083]-[0092]; claims 1-44) in the form of tablets or films ([0016],[026],[0037],[0048],[0059],[0076]-[0078],[0084],[0086],[0093]-[0097],[0101],[0102],[0116]) comprising a pharmaceutically active component, epinephrine (Abstract; [0002],[0009]-[0015],[0019]-[0025],[0030]-[0036],[0041]-[00448],[0052]-[0058]; claims 1-44). The buccal, lingual, and sublingual dosage forms may be formulated as a polymeric matrix ([0089],[0104]), which may include polymers, e.g., polyethylene glycol which encompasses hyperbranched polymers, hydroxypropylmethyl cellulose, polyvinylpyrrolidone (a water soluble polymer) ([0089],[0104]), polysaccharides, chitosan (a polysaccharide) ([0095],[0089]), methylmethacrylate copolymers, stabilizers, polyethylene oxides, and carboxyvinyl polymers ([0104]), which encompass water soluble carbomers. While US20070293581A1 teaches a drug delivery system comprising epinephrine as the pharmaceutically active component, it would be obvious to replace epinephrine with other lipophilic pharmaceutical components, e.g., benzodiazepines, in order to improve their delivery into or through mucosa, providing rapid effect to the patient in need thereof.

Accordingly, US20070293581A1 describes a pharmaceutical composition comprising a polymeric matrix and pharmaceutically active component as claimed but fails to teach inclusion of an adrenergic receptor interacter.

US20120058158A1 also teaches pharmaceutical compositions in a sublingual dosage form comprising, inter alia, oil-based excipients and oil-soluble drugs leading to greater permeability ([0043]), such as clove oil ([0024],[0039]), an adrenergic receptor interacter, by acting as penetration enhancers, increasing solubility of medicaments, and providing a flavor component giving organoleptic feedback to the user ([0024]).

The cited references render obvious claims 1, 2, 5, 6, 12, 13, and 19-27, because it would be obvious to incorporate the adrenergic interacter clove oil into the pharmaceutical composition described in US20070293581A1 to increase the composition's permeability, enhance its penetration and solubility, and provide a flavor component to give organoleptic feedback to the user. This combination provides a composition that contains a phytoextract as the interacter, which is derived from a clove plant, and contains epinephrine, a polymeric matrix encompassing a water soluble polymer, polyethylene oxide, hydroxypropylmethyl cellulose, polysaccharide, polyvinylpyrrolidone, and stabilizing agents, where epinephrine represents a lipophilic pharmaceutical component that would be obvious to substitute with other lipophilic pharmaceutical components such as benzodiazepines in order to improve mucosal delivery. Regarding claim 5, which requires the permeation enhancer of claim 2 to include linoleic acid. Linoleic acid is a well-known permeation enhancer, which would be obvious to add to the composition of the cited references for its intended purpose.

Claim 3 requires that the adrenergic receptor interacter comprise a terpenoid, terpene, or sesquiterpene. Claim 4 requires the permeation enhancer of claim 2 include farnesol or Labrasol.

Claim 7 requires that the adrenergic receptor interacter comprise a phenylpropanoid.

Claim 8 requires the composition of claim 7, wherein the phenylpropanoid is eugenol or eugenol acetate.

Claim 9 requires the pharmaceutical composition of claim 7, wherein the phenylpropanoid is cinnamic acid, cinnamic acid ester, cinnamic aldehyde, or hydorcinnamic acid.

Claim 10 requires the composition of claim 7 wherein the phenylpropanoid is chavicol.

Claim 11 requires the composition of claim 7 wherein the phenylpropanoid is safrole.

Claims 14-16 require the composition of claim 12, wherein the clove oil derives from a bud, leaf, or flower of clove.

Claim 17 requires that the phytoextract of claim 12 is synthetic or biosynthetic.

Claim 18 requires that the phytoextract further includes 40-95% eugenol.

Regarding claims 3, 4, 7, 8-11, and 14-18, the cited references teach these features and render obvious these claims, because as an evidentiary matter, clove oil extracted from clove buds, leaves, and stems is known to contain eugenol (72.08% to 96.65%), β -caryophyllene (a sesquiterpene), chavicol (a phenylpropanoid), α -copaene (a sesquiterpene), methyl eugenol, iso-eugenol (a phenylpropanoid), eugenol acetate (a phenylpropanoid), α -humulene (a sesquiterpene), and caryophyllene oxide (a sesquiterpene metabolite) (Razafimamonjison, et al., International Journal of Basic and Applied Sciences, 3:224 (2014), Abstract; p. 226, Table 2), as well as farnesol (a permeation enhancer) (Gopalakrishnan, et al., J. Sci. Food Agric., 50:111 (1990), p. 114, Tables 1, 2; p. 115, Table 3; p. 116, Tables 4, 5), cinnamic aldehyde, and safrol (Juglal, et al., J. Food Prot., 65:683 (2002), p. 64, Figure 1).

Regarding present claim 27, the combination of cited references do not specifically require a dendritic or hyperbranched polymer. However, Cheng teaches that dendrimers are hyperbranched and monodisperse polymers, wherein the dendrimers are suitable for drug delivery through the mucosa (Cheng, et al., J. Pharm. Sci., 97:123 (2008), p. 123, 138). Tülü et al. teach that cationic dendrimers may have intrinsic mucoadhesive properties for use in the oral cavity, as mucin is negatively charged, thus creating an electrostatic attraction between mucus and dendrimer wherein an encapsulated active may be slowly released into the oral cavity (Tülü, et al., A Search for Antibacterial Agents: Chapter 6: Dendrimers as Antibacterial Agents (2012), p. 97). It would have been obvious to prepare the buccal, lingual or sublingual dosage forms according to the cited references, wherein the compositions comprise a dendritic polymer or hyperbranched polymer, because dendrimers are suitable for drug delivery through the mucosa and have an intrinsic mucoadhesive properties in the oral cavity for slow release an encapsulated active agent.

35 U.S.C. 112(d): REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

Claims 19 and 20 are rejected under 35 U.S.C. 112(d) as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.

Claim 19 requires the pharmaceutical composition of claim 1 and recites “wherein the pharmaceutically active component is epinephrine, diazepam, or alprazolam.” However, claim 1 indicates the pharmaceutically active component includes a benzodiazepine, which does not encompass epinephrine. Thus, claim 19 fails to further limit claim 1.

Claim 20 recites the pharmaceutical composition of claim 1, “wherein the polymeric matrix includes a polymer,” however, a polymeric matrix includes a polymer by definition. Thus claim 20 fails to further limit claim 1.

Applicant may cancel the claim, amend the claim to place the claim in proper dependent form, rewrite the claim in independent form, or present a sufficient showing that the dependent claim complies with the statutory requirements.

35 U.S.C. 112(b): The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

Claim 19 is rejected under 35 U.S.C. 112(b) as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor regards as the invention.

Claim 19 requires the pharmaceutical composition of claim 1 and recites “wherein the pharmaceutically active component is epinephrine, diazepam, or alprazolam.” However, claim 1 indicates the pharmaceutically active component includes a benzodiazepine, which does not encompass epinephrine. Thus, claim 19 lacks antecedent basis in reciting “epinephrine.”

Relevant Art

US20050266085A1 (published 12/01/2005) teaches a pharmaceutical composition comprising a benzodiazepine, alprazolam, in a polymeric matrix with an adrenergic receptor interacter, eugenol. US20050266085A1 teaches that alprazolam is a lipophilic drug ([0007]) that has greater solubility than water in eugenol (clove oil) and in labrasol. ([0020]). In addition, US20050266085A1 teaches an exemplary formulation comprising an aqueous phase and an oil phase. ([0039]). The aqueous phase is prepared by combining dissolved polyvinyl alcohol in water and Pemulen TR2 (Acrylates/C10-30 alkyl acrylate crosspolymer, emulsifying agent) in water. Id. The oil phase is prepared by dissolving alprazolam into eugenol. Id. The emulsion, once formed, may be cast onto a fabric material impregnated with sodium borate, which acts to gel the aqueous phase by crosslinking with the polyvinyl alcohol, solidifying the formulation into a soft solid that can be applied to the skin for delivery of alprazolam, such as in a matrix dermal delivery patch. Id.

While the general idea of a pharmaceutical composition comprising a benzodiazepine in a polymeric matrix together with a component that improves solubility and permeation is known, Applicant may find a path to allowability through the inclusion of more specific limitations defining the adrenergic receptor interacter, permeation enhancer, and dosage form.

Conclusion

Claims 1-34 remain pending.

Claims 1-27 are rejected.

Claims 28-34 are withdrawn.

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

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

Questions about this Office Action may be directed toward Examiner Michael Barker at 571.272.0303. If, however, attempts to reach Mr. Barker are not successful, the Examiner's supervisor, Terry McKelvey, may be reached at 571.272.0775.

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

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

/MICHAEL BARKER/
Primary Examiner, Art Unit 1655

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Alexander Mark Schobel Examiner: Michael P. BARKER

Serial No.: 15/724,234

Group Art Unit: 1655

Filed : October 3, 2017

Confirmation No.: 2978

For: PHARMACEUTICAL COMPOSITIONS WITH ENHANCED PERMEATION

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REPLY TO OFFICE ACTION OF NOVEMBER 5, 2021

In response to the non-final Office Action of November 5, 2021 (“Office Action”),
Applicant submits the following amendments and remarks.

REMARKS

Claims 1-18 and 21-35 are pending. Claims 1, 22 and 35 have been amended. Claims 28-34 have been cancelled without prejudice. New claims 36-68 have been added. Support for the amendments and new claims can be found throughout the specification. No new matter has been added.

Applicants thank the Examiner for indicating claim 35 is allowable and that claim 24 contains allowable subject matter. Claims 1 and 35 have been amended in a manner shared with the Examiner in interviews on November 19, 2021 and the Examiner indicated the amended claims that were presented with minor edits on November 22, 2021. Applicants thank the Examiner for the interviews.

OBJECTIONS

Claims 24 and 27 were objected to for dependence on a rejected base claim. This objection has been addressed by the amended claims. Reconsideration and withdrawal of this rejection is respectfully requested.

REJECTIONS

35 U.S.C. 102

Claims 1, 3, 7, 8, 21, 23 and 25 were rejected under 35 U.S.C. 102 over US2005/0266085. Not in acquiescence, but to advance prosecution, the claims have been amended, thereby mooting this rejection. Allowance of claims 1 and claims that depend therefrom is respectfully requested.

35 U.S.C. 103

Claims 2, 4-6 and 26 were rejected under 35 U.S.C. 103 over US2005/0266085. Claims 2, 4-6 and 26 depend from claim 1. Not in acquiescence, but to advance prosecution, the claims have been amended, thereby mooting this rejection. Allowance of claims 1 and claims that depend therefrom is respectfully requested.

35 U.S.C. 112

Claim 25 was rejected under 35 U.S.C. 112(b) as indefinite. Claim 25 has been amended, thereby mooting this rejection. Allowance of claim 25 is respectfully requested.

Applicant : Schobel, et al.
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New claims

New claims 36 – 65 depend from allowable claims 1 and 35. Accordingly, allowance of claims 36-65 is respectfully requested.

New claims 66-68 also feature allowable subject matter. Accordingly, allowance of claims 36-65 is respectfully requested.

CONCLUSION

Applicants believe that the claims are in condition for allowance. Should any further fees be required by the present Reply, the Commissioner is hereby authorized to charge Deposit Account 50-3145.

Respectfully submitted,

Date: November 22, 2021

/Harold H. Fox, Reg. # 41,498/
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		15724234
	Filing Date		2017-10-03
	First Named Inventor	Schobel, Alexander Mark	
	Art Unit	1655	
	Examiner Name	Barker, Michael P.	
	Attorney Docket Number	270712/AQU-013USC2/479666	

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	1	8617589	B2	2013-12-31	Fuisz et al.	
	2	8936825	B2	2015-01-20	Myers et al.	
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	4	5879690	A	1999-03-09	Perricone	
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CERTIFICATION STATEMENT

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

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

OR

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

See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Harold H. Fox, Reg. # 41,498/	Date (YYYY-MM-DD)	2021-11-22
Name/Print	Harold H. Fox, Ph.D	Registration Number	41,498

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ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

The Patent Term Adjustment is 410 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

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

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

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

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