IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Prior Appl. No.: 14/738,255

Prior Appl. Filing Date: 6/12/2015

Examiner: Unassigned

Art Unit: Unassigned

CONTINUING PATENT APPLICATION TRANSMITTAL LETTER

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

Commissioner:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is a:

[**X**] Continuation [ ] Division [ ] Continuation-In-Part (CIP)

of the above-identified copending prior application in which no patenting, abandonment, or termination of proceedings has occurred. Priority to the above-identified prior application is hereby claimed under 35 U.S.C. § 120 for this continuing application. The entire disclosure of the above-identified prior application is considered as being part of the disclosure of the accompanying continuing application and is hereby incorporated by reference therein.

Enclosed are:

[**X**] Application Data Sheet (37 CFR 1.76).

[**X**] Description, Claim(s), and Abstract (27 pages).

[**X**] Drawing (1 sheet, Figure 1).

[**X**] Declaration

The adjustment to the number of sheets for EFS-Web filing follows:

Number of Sheets		**EFS-Web Adjustment**	**Number of Sheets for EFS-Web**
28	x	75%	21

The filing fee is calculated below at the large entity rate:

	Number Filed		**Included in Basic Fee**		**Extra**		Rate		Fee Totals
Basic Filing Fee							$280.00	=	$280.00
Search Fee							$600.00		$600.00
Examination Fee							$720.00		$720.00
Size Fee	21	-	100	=	0	x	$400.00		$0.00
Total Claims:	20	-	20	=	0	x	$80.00	=	$0.00
Independents:	4	-	3	=	1	x	$420.00	=	$420.00
If any Multiple Dependent Claim(s) present:						+	$780.00	=	$0.00
Surcharge under 37 CFR 1.16(e) for late filing of Executed Declaration and late payment of filing fee						+	$140.00	=	$0.00
Prioritized Examination fee (Track I) under 37 C.F.R. § 1.17 (c)									$0.00
Processing Fee (Track I) under 37 C.F.R. § 1.17 (i)									$0.00
TOTAL FILING FEE:								=	$2020.00

The above-identified fees of $2020.00 are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date Sep 30, 2015

By

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PTO/AIA/14 (07-14)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	041457-1160
	Application Number	
Title of Invention	Transdermal Estrogen Device and Delivery	

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
	Juan		Mantelle	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

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Postal Code	33176	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	22428		
Email Address	IPDocketing@foley.com	Add Email	Remove Email

Application Information:

Title of the Invention	Transdermal Estrogen Device and Delivery		
Attorney Docket Number	041457-1160	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	1	Suggested Figure for Publication (if any)	1

Filing By Reference :

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Title of Invention	Transdermal Estrogen Device and Delivery	

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

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

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

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

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

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	22428		

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 this 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 blank.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	14/738255	2015-06-12
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14/738255	Continuation of	14/024985	2013-09-12
Prior Application Status			Remove

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	041457-1160
	Application Number	
Title of Invention	Transdermal Estrogen Device and Delivery	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14/024985	Continuation of	13/553972	2012-07-20
Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/553972	Continuation of	12/216811	2008-07-10

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

Foreign Priority Information:

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

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

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

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

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

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	Application Number	
Title of Invention	Transdermal Estrogen Device and Delivery	

If 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 World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date o f filing this Authorization.

Applicant Information:

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

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◯ Assignee	◯ Legal Representative under 35 U.S.C. 117	◯ Joint Inventor
◯ Person to whom the inventor is obligated to assign.	◯ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	041457-1160
	Application Number	
Title of Invention	Transdermal Estrogen Device and Delivery	

Mailing Address Information For Applicant:			
Address 1			
Address 2			
City		**State/Province**	
Country		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

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Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	NOVEN PHARMACEUTICALS, INC.

Mailing Address Information For Assignee including Non-Applicant Assignee:			
Address 1	11960 Southwest 144th Street		
Address 2			
City	Miami	**State/Province**	FL
Country	US	Postal Code	33186
Phone Number		Fax Number	
Email Address			

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

Signature:

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

Signature	Cathy C	Date (YYYY-MM-DD)	20150930

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	041457-1160
	Application Number	
Title of Invention	Transdermal Estrogen Device and Delivery	

First Name	Courtenay C.	Last Name	Brinckerhoff	Registration Number	37288

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This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

FIELD OF THE INVENTION

[0001] Described herein are compositions and methods for the transdermal delivery of estrogen.

BACKGROUND

[0002] This invention relates generally to transdermal drug delivery systems, and more particularly, to transdermal drug delivery systems for the delivery of estrogen. The use of a transdermal system, for example, a patch comprising a pressure-sensitive adhesive containing a drug, as a means of delivering drug through the skin is well known. However, there remains a need for transdermal drug delivery systems designed for the delivery of specific drugs, such as estrogen, and there remains a particular need for smaller transdermal drug delivery systems that exhibit desired pharmacokinetic properties.

[0003] Transdermal delivery systems (adhesive patches) as dosage forms have been the subject of a vast number of patent applications over the last 25 years, yielding many patents but few commercial products in comparison. To those working in the field, the relatively small number of commercial products is not surprising. Although regulatory, economic, and market hurdles play a role in limiting the number of products on the market, the task of developing a transdermal delivery system that achieves desired physical and pharmacokinetic parameters to satisfy physician and patient demand is more daunting. Parameters to be considered during commercial product development may include drug solubility, drug stability (e.g., as may arise from interaction with other component materials and/or the environment), delivery of a therapeutic amount of drug at a desired delivery rate over the intended duration of use, adequate adhesion at the anatomical site of application, integrity (e.g., minimal curling, wrinkling, delaminating and slippage) with minimal discomfort, irritation and sensitization both during use and during and after removal, and minimal residual adhesive (or other components) after removal. Size also may be important from a manufacturing and patient viewpoint, and appearance may be important from a patient viewpoint. The physical manufacturing and production aspects of commercial product development (e.g., the identity and costs of materials, equipment, and labor)

and supporting analytical methods required for regulatory compliance also can be significant.

[0004] Of the physical parameters that are considered when developing a commercial transdermal drug delivery system, size, e.g., surface area at the site of application, is often dictated and limited by other physical and pharmacokin tic requirements, such as desired drug delivery rates and daily dosages. In general, it is easier to develop a relatively "large" transdermal drug delivery system that will achieve drug delivery at target therapeutic levels over an intended duration of therapy, than it is to develop a smaller transdermal drug delivery system that still exhibits acceptable pharmacokinetic properties. Still, because size directly impacts costs (e.g., costs of component materials, costs of packaging materials, costs for production and manufacturing equipment, labor costs relative to product yield per run time, etc.) and patients generally prefer smaller systems to larger ones (both for aesthetic reasons and comfort, since a smaller surface may permit the use of less aggressive adhesives), there is a need for smaller transdermal drug delivery systems.

SUMMARY

[0005] In accordance with one embodiment, there is provided a transdermal drug delivery system comprising a drug containing layer defining an active surface area and comprising a polymer matrix comprising estradiol, wherein the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux that is greater than 0.01 mg/cm^2/day, based on the active surface area. In some embodiments, the polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble PVP. In some embodiments, the polymer matrix comprises about 2-25% by weight acrylic adhesive, about 45-70% by weight silicone adhesive, about 2-25% by weight soluble PVP, about 5-15% penetration enhancer, and about 0.1-10% by weight estradiol, all based on the total dry weight of the polymer matrix. In some embodiments, the polymer matrix comprises about 20% by weight acrylic adhesive, about 56.9% by weight silicone adhesive, about 7.5% by weight soluble PVP, about 6.0% by weight oleyl alcohol, about 8.0% by weight dipropylene glycol, and about 1.6 % by weight estradiol. In some embodiments, the acrylic adhesive and silicone adhesive are present in a ratio of from about 1:2 to about 1:6, based on the total weight of the acrylic and silicone adhesives.

[0006] In some embodiments, the penetration enhancer comprises oleyl alchol or dipropylene glycol, or both.

[0007] In some embodiments, the polymer matrix comprises an amount of estradiol effective to deliver a therapeutically effective amount of estradiol over a period of time selected from the group consisting of at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days and at least 7 days. In some embodiments, the polymer matrix comprises an amount of estradiol effective to deliver an amount of estradiol selected from the group consisting of about 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day.

[0008] In some embodiments, the polymer matrix has a coat weight of greater than about 10 mg/cm^2. In some embodiments, the polymer matrix has a coat weight selected from the group consisting of about 12.5 and about 15 mg/ cm^2.

[0009] In accordance with some embodiments, there is provided a transdermal drug delivery system comprising a polymer matrix comprising estradiol, wherein the system has an active surface area that is about 60% of a size selected from the group consisting of 2.5, 3.75, 5.0, 7.5 and 10.0 cm^2 and is effective to deliver an amount of estradiol per day of about 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day, respectively.

[0010] In accordance with some embodiments, there is provided a method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a transdermal drug delivery system comprising a drug-containing layer defining an active surface area and comprising a polymer matrix comprising estradiol, wherein the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux that is greater than 0.01 mg/cm^2/day, based on the active surface area. In some embodiments, the system has an active surface area that is about 60% of a size selected from the group consisting of 2.5, 3.75, 5.0, 7.5 and 10.0 cm^2 and is effective to deliver an amount of estradiol per day of about 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day, respectively.

[0011] In accordance with some embodiments, there is provided a method of making a transdermal drug delivery system for administering estrogen, comprising forming a polymer matrix comprising estrogen and a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble PVP, and applying the polymer matrix to a support layer such that the system includes greater than 0.156 mg/cm^2

estradiol. In some embodiments, the system has an active surface area that is about 60% of a size selected from the group consisting of 2.5, 3.75, 5.0, 7.5 and 10.0 cm^2. In some embodiments, the polymer matrix comprises about 20% by weight acrylic adhesive, about 56.9% by weight silicone adhesive, about 7.5% by weight soluble PVP, about 6.0% by weight oleyl alcohol, about 8.0% by weight dipropylene glycol, and about 1.6% by weight estradiol. In some embodiments, the polymer matrix is applied to the support layer at a coat weight of greater than about 10 mg/cm^2. In some embodiments, the polymer matrix coat weight is selected from the group consisting of about 12.5 and about 15 mg/cm^2.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 illustrates the estradiol flux ($\mu g/cm^2/hr$) over time (0-81 hours) from transdermal delivery systems according to the invention (▲ & •), as compared to Vivelle-Dot® (♦).

DETAILED DESCRIPTION

[0013] The field of transdermal delivery systems suffers from the problem of needing to balance many different competing factors to develop a commercial product that exhibits, for example both clinical efficacy and satisfactory wear properties while remaining acceptable to patients. For example, when selecting the size of a transdermal delivery system, it is necessary to balance factors that favor a smaller size (such as lower cost , better adhesive performance and improved aesthetics) against factors that favor a larger size (such as the target delivery rate (flux) and daily dose). The Vivelle-Dot® transdermal estradiol product (manufactured by Noven Pharmaceutcials Inc.) is available in five different active surface areas (2.5, 3.75, 5.0, 7.5 and 10.0 cm^2) which each deliver different amounts of drug per day (0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day, respectively). Each of the Vivelle-Dot® products include 0.156 mg/cm^2 estradiol.

[0014] In accordance with some embodiments, the present invention provides transdermal drug delivery systems for the transdermal delivery of estrogen that have a smaller active surface area than Vivelle-Dot® but achieve daily dosages that are about equal to or greater than the Vivelle-Dot® products. For example, the present

invention includes transdermal drug delivery systems that achieve daily dosages that are about equal to a Vivelle-Dot® product, in a smaller sized system. The ability to provide a smaller system without sacrificing daily dosage represents a significant advance.

[0015] Applicant surprisingly discovered that increasing the coat weight of the drug-containing adhesive layer resulted in an increased flux per unit area, and thus permitted the development of smaller transdermal drug delivery systems that achieve comparable daily dosages. This result was surprising because coat weight is typically selected to control the duration of delivery, but is not generally understood to impact delivery rate. Thus, while it is known in the art to increase coat weight to provide delivery over a longer period of time, it was not known that increasing coat weight could increase delivery rate or flux, and thus permit the development of a smaller system while maintaining daily dosage.

[0016] In accordance with some aspects, there are provided transdermal drug delivery systems and methods for the transdermal delivery of estrogen. In specific embodiments, the systems exhibit increased flux than other known estrogen devices (such as Vivelle-Dot®, manufactured by Noven Pharmaceutcials Inc.) and, therefore, exhibit increased drug delivery per unit area. For example, in some embodiments, the systems exhibit a flux greater than the 0.01 $mg/cm^2/day$ exhibited by the Vivelle-Dot® products, such as a flux that is about 1.25, 1.33, 1.5, 1.67, 1.75, 2, 3, 4, or 5 times the flux of the Vivelle-Dot® products. In some embodiments, the systems have a greater coat weight than other known estrogen devices. For example, in some embodiments, the systems have a coat weight such that the amount of estradiol per unit area is greater than the 0.156 mg/cm^2 estradiol of the Vivelle-Dot® products, such as a coat weight that is about 1.25, 1.33, 1.5, 1.67, 1.75, 2, or 3 times the coat weight of the Vivelle-Dot® products, or greater. Thus, in accordance with some aspects, the invention permits the use of smaller devices to achieve comparable drug delivery.

DEFINITIONS

[0017] Technical and scientific terms used herein have the meanings commonly understood by one of ordinary skill in the art to which the present invention pertains, unless otherwise defined. Reference is made herein to various methodologies known

to those of ordinary skill in the art. Publications and other materials setting forth such known methodologies to which reference is made are incorporated herein by reference in their entireties as though set forth in full. Any suitable materials and/or methods known to those of ordinary skill in the art can be utilized in carrying out the present invention. However, specific materials and methods are described. Materials, reagents and the like to which reference is made in the following description and examples are obtainable from commercial sources, unless otherwise noted.

[0018] As used herein, the singular forms "a," "an," and "the" designate both the singular and the plural, unless expressly stated to designate the singular only.

[0019] The term "about" and the use of ranges in general, whether or not qualified by the term about, means that the number comprehended is not limited to the exact number set forth herein, and is intended to refer to ranges substantially within the quoted range while not departing from the scope of the invention. As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

[0020] The phrase "substantially free" as used herein generally means that the described composition (e.g., transdermal drug delivery system, polymer matrix, etc.) comprises less than about 5%, less than about 3%, or less than about 1% by weight, based on the total weight of the composition at issue, of the excluded component.

[0021] As used herein "subject" denotes any animal in need of drug therapy, including humans. For example, a subject may be suffering from or at risk of developing a condition that can be treated or prevented with estrogen, or may be taking estrogen for health maintenance purposes.

[0022] As used herein, the phrases "therapeutically effective amount" and "therapeutic level" mean that drug dosage or plasma concentration in a subject, respectively, that provides the specific pharmacological response for which the drug is administered in a subject in need of such treatment. It is emphasized that a therapeutically effective amount or therapeutic level of a drug will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

For convenience only, exemplary dosages, drug delivery amounts, therapeutically effective amounts and therapeutic levels are provided below with reference to adult human subjects. Those skilled in the art can adjust such amounts in accordance with standard practices as needed to treat a specific subject and/or condition/disease.

[0023] As used herein, "active surface area" means the surface area of the drug-containing layer of the transdermal drug delivery system.

[0024] As used herein, "coat weight" refers to the weight of the drug-containing layer per unit area of the active surface area of the transdermal drug delivery system.

[0025] As used herein, "estrogen" includes estrogenic steroids such as estradiol (17-β-estradiol), estradiol benzoate, estradiol 17β-cypionate, estropipate, equilenin, equilin, estriol, estrone, ethinyl estradiol, conjugated estrogens, esterified estrogens, and mixtures thereof.

[0026] As used herein, "flux" (also called "permeation rate") is defined as the absorption of a drug through skin or mucosal tissue, and is described by Fick's first law of diffusion:

$$J = -D\ (dCm/dx)$$

where J is the flux in $g/cm^2/sec$, D is the diffusion coefficient of the drug through the skin or mucosa in cm^2/sec and dCm/dx is the concentration gradient of the drug across the skin or mucosa.

[0027] As used herein, the term "transdermal" refers to delivery, administration or application of a drug by means of direct contact with skin or mucosa. Such delivery, administration or application is also known as dermal, percutaneous, transmucosal and buccal. As used herein, "dermal" includes skin and mucosa, which includes oral, buccal, nasal, rectal and vaginal mucosa.

[0028] As used herein, "transdermal drug delivery system" refers to a system (e.g., a device) comprising a composition that releases estrogen upon application to the skin (or any other surface noted above). A transdermal drug delivery system may comprise a backing layer, a drug-containing layer, and a release liner layer. In some embodiments, the transdermal drug delivery system is a substantially non-aqueous, solid form, capable of conforming to the surface with which it comes into contact, and capable of maintaining such contact so as to facilitate topical application without

adverse physiological response, and without being appreciably decomposed by aqueous contact during topical application to a subject. Many such systems are known in the art and commercially available, such as transdermal drug delivery patches. As described below, in one embodiment, the transdermal drug delivery system comprises a drug-containing polymer matrix that comprises a pressure-sensitive adhesive or bioadhesive, and is adopted for direct application to a user's (e.g., a subject's) skin. In other embodiments, the polymer matrix is non-adhesive and may be provided with separate adhesion means (such as a separate adhesive layer) for application and adherence to the user's skin.

[0029] As used herein, "polymer matrix" refers to a polymer composition which contains one or more drugs. In some embodiments, the matrix comprises a pressure-sensitive adhesive polymer or a bioadhesive polymer. In other embodiments, the matrix does not comprise a pressure-sensitive adhesive or bioadhesive. As used herein, a polymer is an "adhesive" if it has the properties of an adhesive per se, or if it functions as an adhesive by the addition of tackifiers, plasticizers, crosslinking agents or other additives. Thus, in some embodiments, the polymer matrix comprises a pressure-sensitive adhesive polymer or a bioadhesive polymer, with estrogen dissolved or dispersed therein. The polymer matrix also may comprise tackifiers, plasticizers, crosslinking agents or other additives described herein. U.S. Patent 6,024,976 describes polymer blends that are useful in accordance with the transdermal systems described herein. The entire contents of U.S. Patent 6,024,976 is incorporated herein by reference.

[0030] As used herein, the term "pressure-sensitive adhesive" refers to a viscoelastic material which adheres instantaneously to most substrates with the application of very slight pressure and remains permanently tacky. A polymer is a pressure-sensitive adhesive within the meaning of the term as used herein if it has the properties of a pressure-sensitive adhesive per se or functions as a pressure-sensitive adhesive by admixture with tackifiers, plasticizers or other additives.

[0031] The term pressure-sensitive adhesive also includes mixtures of different polymers and mixtures of polymers, such as polyisobutylenes (PIB), of different molecular weights, wherein each resultant mixture is a pressure-sensitive adhesive. In the last case, the polymers of lower molecular weight in the mixture are not

considered to be "tackifiers," said term being reserved for additives which differ other than in molecular weight from the polymers to which they are added.

[0032] In some embodiments, the polymer matrix is a pressure-sensitive adhesive at room temperature and has other desirable characteristics for adhesives used in the transdermal drug delivery art. Such characteristics include good adherence to skin, ability to be peeled or otherwise removed without substantial trauma to the skin, retention of tack with aging, etc. In some embodiments, the polymer matrix has a glass transition temperature (T_g), measured using a differential scanning calorimeter, of between about -70 °C. and 0 °C.

[0033] As used herein, the term "rubber-based pressure-sensitive adhesive" refers to a viscoelastic material which has the properties of a pressure-sensitive adhesive and which contains at least one natural or synthetic elastomeric polymer.

[0034] In some embodiments, the transdermal drug delivery system includes one or more additional layers, such as one or more additional polymer matrix layers, or one or more adhesive layers that adhere the transdermal drug delivery system to the user's skin. In other embodiments, the transdermal drug delivery system is monolithic, meaning that it comprises a single polymer matrix layer comprising a pressure-sensitive adhesive or bioadhesive with drug dissolved or dispersed therein, and no rate-controlling membrane.

[0035] The transdermal drug delivery system also may include a drug impermeable backing layer or film. In some embodiments, the backing layer is adjacent one face of the polymer matrix layer. When present, the backing layer protects the polymer matrix layer (and any other layers present) from the environment and prevents loss of the drug and/or release of other components to the environment during use. Materials suitable for use as backing layers are well-known known in the art and can comprise films of polyester, polyethylene, vinyl acetate resins, ethylene/vinyl acetate copolymers, polyvinyl chloride, polyurethane, and the like, metal foils, non-woven fabric, cloth and commercially available laminates. A typical backing material has a thickness in the range of 2 to 1000 micrometers.

[0036] The transdermal drug delivery system also may include a release liner, typically located adjacent the opposite face of the system as compared to the backing layer. When present, the release liner is removed from the system prior to use to

expose the polymer matrix layer and/or an adhesive layer prior to topical application. Materials suitable for use as release liners are well-known known in the art and include the commercially available products of Dow Corning Corporation designated Bio-Release® liner and Syl-off® 7610 and 3M's 1022 Scotch Pak.

[0037] A used herein, a "monolithic" transdermal drug delivery system may include a backing layer and/or release liner.

[0038] In accordance with some embodiments, the transdermal dug delivery system comprises a drug-containing polymer matrix layer that comprises a pressure-sensitive adhesive blend comprising an acrylic polymer, a silicone polymer, and a soluble PVP.

Acrylic Polymers

[0039] The term "acrylic polymer" is used here as in the art interchangeably with "polyacrylate," "polyacrylic polymer," and "acrylic adhesive." The acrylic-based polymers can be any of the homopolymers, copolymers, terpolymers, and the like of various acrylic acids or esters. In some embodiments, the acrylic-based polymers are adhesive polymers. In other embodiments, the acrylic-based polymers function as an adhesive by the addition of tackifiers, plasticizers, crosslinking agents or other additives.

[0040] The acrylic polymer can include copolymers, terpolymers and multipolymers. For example, the acrylic polymer can be any of the homopolymers, copolymers, terpolymers, and the like of various acrylic acids. In some embodiments, the acrylic polymer constitutes from about 2% to about 95% by weight of the polymer content of the polymer matrix, including about 3% to about 90% and about 5% to about 85%, such as 2% to 95%, 3% to 90% and 5% to 85%. In some embodiments, the amount and type of acrylic polymer is dependent on the type and amount of estrogen used.

[0041] Acrylic polymers useful in practicing the invention include polymers of one or more monomers of acrylic acids and other copolymerizable monomers. The acrylic polymers also include copolymers of alkyl acrylates and/or methacrylates and/or copolymerizable secondary monomers or monomers with functional groups. Combinations of acrylic-based polymers based on their functional groups is also contemplated. Acrylic-based polymers having functional groups include copolymers

and terpolymers which contain, in addition to nonfunctional monomer units, further monomer units having free functional groups. The monomers can be monofunctional or polyfunctional. By varying the amount of each type of monomer added, the cohesive properties of the resulting acrylic polymer can be changed as is known in the art. In some embodiments, the acrylic polymer is composed of at least 50% by weight of an acrylate or alkyl acrylate monomer, from 0 to 20% of a functional monomer copolymerizable with the acrylate, and from 0 to 40% of other monomers.

[0042] Acrylate monomers which can be used include acrylic acid and methacrylic acid and alkyl acrylic or methacrylic esters such as methyl acrylate, ethyl acrylate, propyl acrylate, amyl acrylate, butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, heptyl acrylate, octyl acrylate, nonyl acrylate, 2-ethylbutyl acrylate, 2-ethylbutyl methacrylate, isooctyl acrylate, isooctyl methacrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate, tridecyl methacrylate, glycidyl acrylate, and corresponding methacrylic esters.

[0043] Non-functional acrylic-based polymers can include any acrylic based polymer having no or substantially no free functional groups.

[0044] Functional monomers, copolymerizable with the above alkyl acrylates or methacrylates, which can be used include acrylic acid, methacrylic acid, maleic acid, maleic anhydride, hydroxyethyl acrylate, hydroxypropyl acrylate, acrylamide, dimethylacrylamide, acrylonitrile, dimethylaminoethyl acrylate, dimethylaminoethyl methacrylate, tert-butylaminoethyl acrylate, tert-butylaminoethyl methacrylate, methoxyethyl acrylate and methoxyethyl methacrylate.

[0045] As used herein, "functional monomers or groups," are monomer units typically in acrylic-based polymers which have reactive chemical groups which modify the acrylic-based polymers directly or which provide sites for further reactions. Examples of functional groups include carboxyl, epoxy, hydroxyl, sulfoxyl, and amino groups. Acrylic-based polymers having functional groups contain, in addition to the nonfunctional monomer units described above, further monomer units having free functional groups. The monomers can be monofunctional or polyfunctional. These functional groups include carboxyl groups, hydroxy groups, amino groups, amido groups, epoxy groups, etc. Typical carboxyl functional

monomers include acrylic acid, methacrylic acid, itaconic acid, maleic acid, and crotonic acid. Typical hydroxy functional monomers include 2-hydroxyethyl methacrylate, 2-hydroxyethyl acrylate, hydroxymethyl acrylate, hydroxymethyl methacrylate, hydroxyethyl acrylate, hydroxyethyl methacrylate, hydroxypropyl acrylate, hydroxypropyl methacrylate, hydroxybutyl acrylate, hydroxybutyl methacrylate, hydroxyamyl acrylate, hydroxyamyl methacrylate, hydroxyhexyl acrylate, hydroxyhexyl methacrylate. As noted above, in some embodiments, the acrylic polymer does not include such functional groups.

[0046] Further details and examples of acrylic adhesives which are suitable in the practice of the invention are described in Satas, "Acrylic Adhesives," Handbook of Pressure-Sensitive Adhesive Technology, 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989); "Acrylic and Methacrylic Ester Polymers," Polymer Science and Engineering, Vol. 1, 2nd ed., pp 234-268, John Wiley & Sons, (1984); U.S. Patent No. 4,390,520; and U.S. Patent No. 4,994,267, all of which are expressly incorporated by reference in their entireties.

[0047] Suitable acrylic polymers also include pressure-sensitive adhesives which are commercially available, such as the acrylic-based adhesives sold under the trademarks DURO-TAK® by National Starch and Chemical Corporation, Bridgewater, N.J. (such as DURO-TAK® 87-2287, -4098, -2852, -2196, -2296, -2194, -2516, -2070, -2353, -2154, -2510, -9085, -9088 and 73-9301). Other suitable acrylic adhesives include those sold under the trademark EUDRAGIT® by Roehm Pharma GmbH, Darmstadt, Germany, those sold by Cytec Surface Specialties, St. Louis, Mo., under the trademarks GELVA® Multipolymer Solution (such as GELVA® 2480, 788, 737, 263, 1430, 1753, 1151, 2450, 2495, 3067, 3071, 3087 and 3235). For example, hydroxy functional adhesives with a reactive functional OH group in the polymeric chain, can be used. Non-limiting commercial examples of this type of adhesives include both GELVA® 737, 788, and 1151, and DURO-TAK® 87-2287, -4287, -2510 and -2516.

Silicon Polymers

[0048] The term "silicone-based" polymer is used interchangeably with the terms siloxane, polysiloxane, and silicones as used herein and as known in the art. A

suitable silicone-based polymer may also be a pressure-sensitive adhesive. Thus, in some embodiments, the silicone-based polymer is an adhesive polymer. In other embodiments, the silicone-based polymer functions as an adhesive by the addition of tackifiers, plasticizers, crosslinking agents, or other additives.

[0049] Suitable polysiloxanes include silicone pressure-sensitive adhesives which are based on two major components: (i) a polymer or gum and (ii) a tackifying resin. A polysiloxane adhesive can be prepared by cross-linking a gum, typically a high molecular weight polydiorganosiloxane, with a resin, to produce a three-dimensional silicate structure, via a condensation reaction in an appropriate organic, volatilve solvent, such as ethyl acetate or heptane. The ratio of resin to polymer can be adjusted in order to modify the physical properties of polysiloxane adhesives. Sobieski, et al., "Silicone Pressure Sensitive Adhesives," Handbook of Pressure-Sensitive Adhesive Technology, 2nd ed., pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).

[0050] Exemplary silicone-based polymers are adhesives (e.g., capable of sticking to the site of topical application), including pressure-sensitive adhesives. Illustrative examples of silicone-based polymers having reduced silanol concentrations include silicone-based adhesives (and capped polysiloxane adhesives) such as those described in U.S. Pat. No. Re. 35,474 and U.S. No. 6,337,086, which are incorporated herein by reference in their entireties, and which are commercially available from Dow Corning Corporation (Dow Corning Corporation, Medical Products, Midland, Michigan) as BIO-PSA® 7-4100, -4200 and -4300 product series, and non-sensitizing, pressure-sensitive adhesives produced with compatible organic volatile solvents (such as ethyl acetate or heptane) and available commercially under their BIO-PSA® 7-4400 series, -4500 series and -4600 series.

[0051] Further details and examples of silicone pressure-sensitive adhesives which are useful in the polymer matrices and compositions and methods described herein are mentioned in the following U.S. Pat. Nos.: 4,591,622; 4,584,355; 4,585,836; and 4,655,767, which are all expressly incorporated by reference herein in their entireties. It should also be understood that silicone fluids are also contemplated for use in the polymer matrices and methods described herein.

[0052] In some embodiments, the polysiloxane constitutes from about 9% to about 97% of the polymer content of the polymer matrix, including about 8% to about 97% and about 14% to about 94%, such as 9% to 97%, 8% to 97%, and 14% to 94%.

Soluble PVP

[0053] In some embodiments, the polymer matrix includes soluble PVP. Soluble PVP has been found to be highly effective in preventing crystallization of drugs, such as estradiol, in adhesive-type transdermal drug delivery system. Soluble PVP also may modulate the transdermal permeation rate of the drug.

[0054] The term "PVP or "polyvinylpyrrolidone" refers to a polymer, either a homopolymer or copolymer, containing N-vinylpyrrolidone as the monomeric unit. Typical PVP polymers are homopolymeric PVPs and the copolymer vinyl acetate vinylpyrrolidone. The homopolymeric PVPs are known to the pharmaceutical industry under a variety of designations including Povidone, Polyvidone, Polyvidonum, Polyvidonum soluble, and Poly(1-vinyl-2-pyrrolidone). The copolymer vinyl acetate vinylpyrrolidone is known to the pharmaceutical industry as Copolyvidon, Copolyvidone, and Copolyvidonum. The term "soluble" when used with reference to PVP means that the polymer is soluble in water and generally is not substantially cross-linked, and has a molecular weight of less than about 2,000,000. See, generally, Buhler, KOLLIDON.RTM.: POLYVINYLPRYRROLIDONE FOR THE PHARMACEUTICAL INDUSTRY, BASF Aktiengesellschaft (1992).

[0055] The amount and type of soluble PVP used may depend on the quantity and type of estrogen present, as well as the type of adhesive, but can be readily determined through routine experimentation. Typically, the PVP is present in an amount from about 1% to about 20% by weight, preferably from about 5% to about 15% by weight, based on the total weight of the polymer matrix. However, the amount of PVP can be higher than 20% for example, up to 40%, depending on the particular drug used and on the desired properties of the blend. The soluble PVP may have a molecular weight of about 2,000 to 1,100,000, including 5,000 to 100,000, and 7,000 to 54,000. In some embodiments, the soluble PVP has a molecular weight of from about 17,000 to about 90,000, such as from about 17,000 to about 60,000, including from 17,000 to 90,000 and from 17,000 to 60,000.

[0056] In some embodiments, the polymer matrix comprises a soluble PVP with a rubber-based pressure-sensitive adhesive and a polyacrylate polymer, such as a blend of an acrylic polymer, a polysiloxane and a soluble PVP. In some embodiments, the blend is chosen to affect the rate of drug delivery. More specifically, a plurality of polymers including a soluble polyvinylpyrrolidone, which may have different solubility parameters for the drug and which may be immiscible with each other, may be selected to adjust the solubility of the drug in the polymer matrix, thereby controlling the maximum concentration of the drug in the system, and modulating drug delivery through the dermis.

[0057] The amount of acrylic-based polymer and silicone-based polymer can be adjusted so as to modify the saturation concentration of the drug in the polmer matrix in order to affect the rate of delivery of the drug from the system and through the skin. In some embodiments, the acrylic-based polymer and silicone-based polymer are used in a weight ratio of from about 2:98 to about 96:4, including about 2:98 to about 90:10 and 2:98 to about 86:14, such as 2:98 to 96:4, 2:98 to 90:10 and 2:98 to 86:14.

[0058] The concentration by weight of the estrogen in the transdermal drug delivery system is typically about 0.1 to about 50 %, including about 0.1 to about 40 % and about 0.3 to about 30 %, such as 0.1 to 50 %, 0.1 to 40 % and 0.3 to 30 %, all based on the total weight of the polymer matrix. In some embodiments, the estrogen is estradiol, and is present at an amount of from about 0.1 to 10%, including from about 0.1 to about 5 %, such as from 0.1 to 10% and 0.1 to 5%, all based on the total weight of the polymer matrix. Irrespective of whether there is high-loading or low-loading of the estrogen into the transdermal drug delivery system, the pressure-sensitive adhesive composition can be formulated to maintain acceptable shear, tack, and peel adhesive properties.

Other Components

[0059] In one embodiment, the polymer matrix comprises a penetration enhancer. A "penetration enhancer" is an agent known to accelerate the delivery of the drug through the skin. These agents also have been referred to as accelerants, adjuvants, and sorption promoters, and are collectively referred to herein as "enhancers." This class of agents includes those with diverse mechanisms of action, including those

which have the function of improving percutaneous absorption, for example, by changing the ability of the stratum corneum to retain moisture, softening the skin, improving the skin's permeability, acting as penetration assistants or hair-follicle openers or changing the state of the skin including the boundary layer.

[0060] Illustrative penetration enhancers include but are not limited to polyhydric alcohols such as dipropylene glycol, propylene glycol, and polyethylene glycol; oils such as olive oil, squalene, and lanolin; fatty ethers such as cetyl ether and oleyl ether; fatty acid esters such as isopropyl myristate; urea and urea derivatives such as allantoin which affect the ability of keratin to retain moisture; polar solvents such as dimethyidecylphosphoxide, methyloctylsulfoxide, dimethyllaurylamide, dodecylpyrrolidone, isosorbitol, dimethylacetonide, dimethylsulfoxide, decylmethylsulfoxide, and dimethylformamide which affect keratin permeability; salicylic acid which softens the keratin; amino acids which are penetration assistants; benzyl nicotinate which is a hair follicle opener; and higher molecular weight aliphatic surfactants such as lauryl sulfate salts which change the surface state of the skin and drugs administered. Other agents include oleic and linoleic acids, ascorbic acid, panthenol, butylated hydroxytoluene, tocopherol, tocopheryl acetate, tocopheryl linoleate, propyl oleate, and isopropyl palmitate.

[0061] In one embodiment, the penetration enhancer is oleyl alcohol. In another embodiment, the penetration enhancer is a glycol, such as dipropylene glycol, propylene glycol, butylene glycol or polyethylene glycol. In other embodiments, the penetration enhancer comprises a mixture of at least two penetration enhancers. For example, a penetration enhancer may comprise oleyl alcohol and one or more polyhydric alcohols, such as glycerine, dipropylene glycol, butylene glycol, propylene glycol. For instance, the penetration enhancer may include oleyl alcohol and dipropylene glycol.

[0062] In some embodiments, a penetration enhancer is used in an amount up to about 30% by dry weight of the polymer matrix, including up to 30% by weight, up to about 20% by weight, including 20% by weight, or up to about 10% by weight, up to 10% by weight, or up to 5% by weight, including up to 5% by weight, based on the dry weight of the polymer matrix. In some embodiments, a penetration enhancer is used in an amount of from about 5% to about 15%, such as from 5% to 15%. In

specific embodiments, the penetration enhancer comprises a mixture of oleyl alcohol and dipropylene glycol which together amount to about 14 % by weight of the polymer matrix. The polymer matrix may further comprise various thickeners, fillers, and other additives or components known for use in transdermal drug delivery systems.

[0063] The amount of estrogen to be incorporated in the polymer matrix varies depending on the particular drug, the desired therapeutic effect, and the time span for which the system is to provide therapy. For most drugs, the passage of the drugs through the skin will be the rate-limiting step in delivery. A minimum amount of drug in the system is selected based on the amount of drug which passes through the skin in the time span for which the system is to provide therapy. In some embodiments, a system for the transdermal delivery of estrogen is used over a period of about 1 day, about 3 days, about 7 days, or longer. Thus, in one embodiment, the systems comprise an amount of drug (e.g.,estradiol) sufficient to deliver therapeutically effective amounts of drug over a period of from 1 day to 3 days, 7 days, or longer, including for 1 day, for 2 days, for 3 days, for 4 days, for 5 days, for 6 days, for 7 days, or for longer. In some embodiments, a therapeutically effective amount of estradiol is from about 0.025-0.1 mg/day, including about 0.025 mg/day, about 0.0375 mg/day, about 0.05 mg/day, about 0.075 mg/day, or about 0.1 mg/day, such as 0.025-0.1 mg/day, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day. Thus, in some embodiments, the transdermal drug delivery system comprises an amount of estradiol effective to achieve a delivery of from at least about 0.025 mg to at least about 0.1 mg of estradiol per day. In some embodiments, the system comprises an amount of estradiol effective to achieve a delivery of from about 0.025 mg to about 0.1 mg of estradiol per day, including about 0.025 mg/day, about 0.0375 mg/day, about 0.05 mg/day, about 0.075 mg/day, or about 0.1 mg/day, such as 0.025-0.1 mg/day, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day. As noted above, in some embodiments, these rates are achieved over a duration of application of at least about 1 day, including at least about 3 days and at least about 7 days, such as at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, and at least 7 days. Thus, for example, transdermal drug delivery system may comprise from at least about 0.39 mg to at least

about 1.56 mg estradiol, including about 0.39 mg, about 0.585 mg, about 0.78 mg, about 1.17 mg, and about 1.56 mg, such as 0.39 mg, about 0.585 mg, about 0.78 mg, about 1.17 mg, and about 1.56 mg. In some embodiments, the transdermal drug delivery system comprises a smaller amount of estradiol than a Vivelle-Dot® product, but achieves comparable drug delivery . For example, in some embodiments a transdermal drug delivery system according to the invention may contain about 1.44 mg or about 1.2 mg estradiol in a 6 cm^2 device, and achieve drug delivery comparable to a Vivelle-Dot® product that contains about 1.56 mg estradiol in a 10 cm^2 device.

[0064] In some embodiments, the system comprises a polymer matrix comprising an amount of acrylic-based polymer of about 1 to about 70% by weight, including about 2 to about 25 % by weight, based on the dry weight of the polymer matrix, such as 2-25 % by weight acrylic-based polymer.

[0065] In some embodiments, the system comprises a polymer matrix comprising an amount of silicone polymer of about 5 to about 70% by weight, including about 45 to about 70% by weight, based on the dry weight of the polymer matrix, such as 45-70 % by weight silicone polymer.

[0066] In some embodiments, the system comprises a polymer matrix comprising an amount of soluble PVP of about 1 to about 30% by weight, including about 2 to about 25 % by weight, based on the dry weight of the polymer matrix, such as 2-25 % by weight soluble PVP.

[0067] In some embodiments, the system comprises a polymer matrix comprising an amount of oleyl alcohol of about 1 to about 10% by weight, including about 4 to about 8% by weight, based on the dry weight of the polymer matrix, such as 4-8% by weight oleyl alcohol.

[0068] In some embodiments, the system comprises a polymer matrix comprising an amount of dipropylene glycol of about 1 to about 10% by weight, including about 5 to about 10% by weight, based on the dry weight of the polymer matrix, such as 5-10% by weight dipropylene glycol.

[0069] In some embodiments, the polymer matrix comprises about 2-25% by weight acrylic adhesive, about 45-70% by weight silicone adhesive, about 2-25% by weight soluble PVP, about 5-15% penetration enhancer, and about 0.1-10% by weight estradiol, all based on the total dry weight of the polymer matrix. In specific

embodiments, the polymer matrix comprises about 20% by weight acrylic adhesive, about 56.9% by weight silicone adhesive, about 7.5 % by weight soluble PVP, about 6.0% by weight oleyl alcohol, about 8.0% by weight dipropylene glycol, and about 1.6% by weight estradiol.

[0070] In some embodiments, the acrylic adhesive and silicone adhesive are present in a ratio of from about 1:2 up to less than about 1:7, such as up to about 1:6, based on the weight of the acrylic and silicone adhesives. For example, in some embodiments, the acrylic adhesive and silicone adhesive are present in a ratio of about 1:2, 1:3, 1:4, 1:5 or 1:6, based on the weight of the acrylic and silicone adhesives. In specific embodiments, the acrylic adhesive and silicone adhesive are present in a ratio of 1:2.8, based on the weight of the acrylic and silicone adhesives.

[0071] As noted above, in embodiments where the polymer matrix comprises a pressure-sensitive adhesive or bioadhesive, the polymer matrix can serve as an adhesive portion of the system (e.g., a reservoir device), or can serve as one or more layers of a multi-layer system. Alternatively, a polymer matrix comprising a pressure-sensitive adhesive or bioadhesive with drug dissolved or dispersed therein can constitute a monolithic device. In embodiments where the polymer matrix does not comprise an adhesive, but instead, for example, comprises a polymeric drug reservoir, it can be used in combination with one or more adhesive layers, or with a surrounding adhesive portion, as is well known to those skilled in the art.

[0072] In some embodiments, the system consists essentially of the polymer matrix layer. By "consists essentially of the polymer matrix layer" means that the system does not contain any other layers that affect drug delivery, such as an additional rate-controlling polymer layer, rate-controlling membrane, or drug reservoir layer. It will be understood, however, that the system that consists essentially of the polymer matrix layer may comprise a backing layer and/or release liner.

[0073] As discussed above, in some embodiments, the systems have a greater flux than other known estrogen devices (such as Vivelle-Dot®, manufactured by Noven Pharmaceutcials Inc.), and, therefore, exhibit increased drug delivery per unit area of the active surface area. For example, in some embodiments, the systems exhibit a flux greater than the 0.01 $mg/cm^2/day$ exhibited by the Vivelle-Dot® products, such as a flux that is about 1.25, 1.33, 1.5, 1.67, 1.75, 2, 3, 4, or 5 times the flux of the

Vivelle-Dot® products. In specific embodiments, the systems exhibit a flux that is about 1.67 times the flux of the Vivelle-Dot® products, e.g., a flux that is about 0.0167 mg/cm^2/day.

[0074] In some embodiments, the systems have a greater coat weight than other known estrogen devices. For example, in some embodiments, the systems have a coat weight such that the amount of estradiol per unit area of the active surface area is greater than the 0.156 mg/cm^2 estradiol of the Vivelle-Dot® products, such as a coat weight that is about 1.25, 1.33, 1.5, 1.67, 1.75, 2 or 3 times the coat weight of the Vivelle-Dot® products, or greater. In specific embodiments, the systems have a coat weight that is about 1.25 times the coat weight of the Vivelle-Dot® products, e.g., a coat weight of about 12.5 mg/cm^2. In other specific embodiments, the systems have a coat weight that is about 1.5 times the coat weight of the Vivelle-Dot® products, e.g., a coat weight of about 15 mg/cm^2.

[0075] The system may be of any shape or size suitable for transdermal application. In some embodiments, the systems are smaller than the Vivelle-Dot® products, but achieve comparable daily dosages. For example, the systems may have an active surface area of 0.9, 0.8, 0.7, 0.75, 0.66, 0.6, 0.5, 0.4, 0.33, 0.3, 0.25, 0.2, or 0.1 times the active surface area of a Vivelle-Dot® product. In some embodiments, the system has an active surface area that is about 60% the size of a Vivelle-Dot® product, such as about 60% of 2.5, 3.75, 5.0, 7.5 or 10.0 cm^2, and delivers a daily dosage of estradiol comparable to that of the corresponding Vivelle-Dot® product. In one embodiment, the system has an active surface area of about 6 cm^2 and delivers a daily dosage of estradiol comparable to that of the 10 cm^2 Vivelle-Dot® product, e.g., about 0.1 mg/day.

[0076] The polymer matrices described herein may be prepared by methods known in the art. The polymer matrices can be formed into systems by methods known in the art. For example, the polymer matrix material can be applied to a backing layer and release liner by methods known in the art, and formed into sizes and shapes suitable for use.

[0077] For example, after the polymer matrix is formed, it may be brought into contact with a support layer, such a releaser liner layer or backing layer, in any

manner known to those of skill in the art. Such techniques include calender coating, hot melt coating, solution coating, etc.

[0078] For example, a polymer matrix can be prepared by blending the components of the polymer matrix, applying the matrix material to a support layer such as a backing layer or release liner, and removing any remaining solvents. The estrogen can be added at any stage. In one embodiment, all polymer matrix components, including estrogen, are blended together. In another embodiment, the polymer matrix components other than estrogen are blended together, and then the estrogen is dissolved or dispersed therein. The order of steps, amount of ingredients, and the amount and time of agitation or mixing can be determined and optimized by the skilled practitioner. An exemplary general method is as follows:

Apropriate amounts of soluble PVP, solvent(s), enhancer(s), and organic solvent(s) (for example toluene) are combined and thoroughly mixed together in a vessel.

Estrogen is then added to the mixture and agitation is carried out until the drug is uniformly mixed in.

Apropriate amounts of polysiloxane and acrylic polymer are then added to the drug mixture, and thoroughly mixed.

The formulation is then transferred to a coating operation where it is coated onto a protective release liner at a controlled specified thickness. The coated product is then passed through an oven in order to drive off all volatile processing solvents.

The dried product on the release liner is then joined to the backing material and wound into rolls for storage.

Appropriate size and shape "systems" are die-cut from the roll material and then pouched.

[0079] Other manufacturing methods are known in the art that are suitable for making the systems described herein.

[0080] In some embodiments, there is provided a method of effecting transdermal drug delivery of estrogen, such as estradiol, by applying a system as described herein to the skin or mucosa of a subject in need thereof. In some embodiments, the system comprises estradiol, and the system is applied over a period of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at

least about 6 days, or at least about 7 days, such as for 1, 2, 3, 4, 5, 6 or 7 days. In some embodiments, the method is effective to achieve therapeutic levels of estrogen in the subject during the application period. As noted above, a typical dosage ranges from at least about 0.025 mg to at least about 0.1 mg of estradiol per day, such as from about 0.025 mg to about 0.1 mg of estradiol per day, including about 0.025 mg/day, about 0.0375 mg/day, about 0.05 mg/day, about 0.075 mg/day, or about 0.1 mg/day, such as 0.025-0.1 mg/day, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day.

[0081] The following specific examples are included as illustrative of the transdermal drug delivery systems and polymer matrices described herein. These example are in no way intended to limit the scope of the invention. Other aspects of the invention will be apparent to those skilled in the art to which the invention pertains.

EXAMPLE 1

[0082] A polymer matrix with the following composition is prepared:

Acrylic Adhesive	20%
Silicone Adhesive	56.9%
Povidone (PVP)	7.5%
Oleyl Alcohol	6.0%
Dipropylene Glycol, USP	8.0%
Estradiol	1.6%

(all % are % by weight based on the dry weight of the total polymer matrix)

[0083] The polymer matrix is applied to a release liner at a coat weight of 12.5 (●) or 15 (▲) mg/cm^2.

[0084] Human cadaver skin permeation studies were performed to quantitatively determine the effective permeation through the stratum corneum. The stratum corneum was obtained from split thickness, cryo-preserved cadaver skin by the heat separation technique. Samples of 5/16" diameter were cut from the laminate, in quadruplicate, and mounted onto 1/2" cut pieces of the stratum corneum. These samples were then placed on modified Franz diffusion cells. The receptor was filled

with 7.5 mL of 0.9% NaCl and 0.01% NaN_3 in deionized water. The cells were maintained at a constant 32°C and were magnetically stirred at approximately 300 rpm. At specified time points, samples of the receptor phase were taken with complete replacement of the receptor phase. These samples were quantified by high-performance liquid chromatography (HPLC) utilizing Waters HPLC instrumentation. C-8 (15 cm x 4.6 mm) 5 µm particle size columns (HYPERSIL made by MetaChem Technologies, Inc., Torrance, Calif.) were used at 50 °C. (column temperature).

[0085] Figure 1 illustrates the estradiol flux ($\mu g/cm^2/hr$) over time (0-81 hours) from transdermal delivery systems according to the invention (▲ & ●), as compared to Vivelle-Dot® (♦).

[0086] The results show that the systems according to the invention have a greater flux than the Vivelle-Dot® product and are able to achieve therapeutic daily dosages despite their significantly smaller size.

What is claimed is:

1. A transdermal drug delivery system comprising a drug containing layer defining an active surface area and comprising a polymer matrix comprising estradiol, wherein the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux that is greater than 0.01 mg/cm^2/day, based on the active surface area.

2. The transdermal drug delivery system of claim 1, wherein the polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble PVP.

3. The transdermal drug delivery system of claim 1, wherein the polymer matrix comprises about 2-25% by weight acrylic adhesive, about 45-70% by weight silicone adhesive, about 2-25% by weight soluble PVP, about 5-15% penetration enhancer, and about 0.1-10% by weight estradiol, all based on the total dry weight of the polymer matrix.

4. The transdermal drug delivery system of claim 3, wherein the penetration enhancer comprises oleyl alchol.

5. The transdermal drug delivery system of claim 3, wherein the penetration enhancer comprises dipropylene glycol.

6. The transdermal drug delivery system of claim 3, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

7. The transdermal drug delivery system of claim 3, wherein the acrylic adhesive and silicone adhesive are present in a ratio of from about 1:2 to about 1:6, based on the total weight of the acrylic and silicone adhesives.

8. The transdermal drug delivery system of claim 1, wherein the polymer matrix comprises an amount of estradiol effective to deliver a therapeutically effective

amount of estradiol over a period of time selected from the group consisting of at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days and at least 7 days.

9. The transdermal drug delivery system of claim 1, wherein the polymer matrix comprises an amount of estradiol effective to deliver an amount of estradiol selected from the group consisting of about 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day.

10. The transdermal drug delivery system of claim 3, wherein the polymer matrix comprises about 20% by weight acrylic adhesive, about 56.9% by weight silicone adhesive, about 7.5% by weight soluble PVP, about 6.0% by weight oleyl alcohol, about 8.0% by weight dipropylene glycol, and about 1.6 % by weight estradiol.

11. The transdermal drug delivery system of claim 3, wherein the polymer matrix has a coat weight of greater than about 10 mg/cm^2.

12. The transdermal drug delivery system of claim 11, wherein the polymer matrix has a coat weight selected from the group consisting of about 12.5 and about 15 mg/ cm^2.

13. A transdermal drug delivery system comprising a polymer matrix comprising estradiol, wherein the system has an active surface area that is about 60% of a size selected from the group consisting of 2.5, 3.75, 5.0, 7.5 and 10.0 cm^2 and is effective to deliver an amount of estradiol per day of about 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day, respectively.

14. A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a transdermal drug delivery system comprising a drug-containing layer defining an active surface area and comprising a polymer matrix comprising estradiol, wherein the system includes greater than 0.156 mg/cm^2

estradiol and achieves an estradiol flux that is greater than 0.01 mg/cm^2/day, based on the active surface area.

15. The method of claim 14, wherein the system has an active surface area that is about 60% of a size selected from the group consisting of 2.5, 3.75, 5.0, 7.5 and 10.0 cm^2 and is effective to deliver an amount of estradiol per day of about 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day, respectively.

16. A method of making a transdermal drug delivery system for administering estrogen, comprising forming a polymer matrix comprising estrogen and a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble PVP, and applying the polymer matrix to a support layer such that the system includes greater than 0.156 mg/cm^2 estradiol.

17. The method of claim 16, wherein the system has an active surface area that is about 60% of a size selected from the group consisting of 2.5, 3.75, 5.0, 7.5 and 10.0 cm^2.

18. The method of claim 16, wherein the polymer matrix comprises about 20% by weight acrylic adhesive, about 56.9% by weight silicone adhesive, about 7.5% by weight soluble PVP, about 6.0% by weight oleyl alcohol, about 8.0% by weight dipropylene glycol, and about 1.6% by weight estradiol.

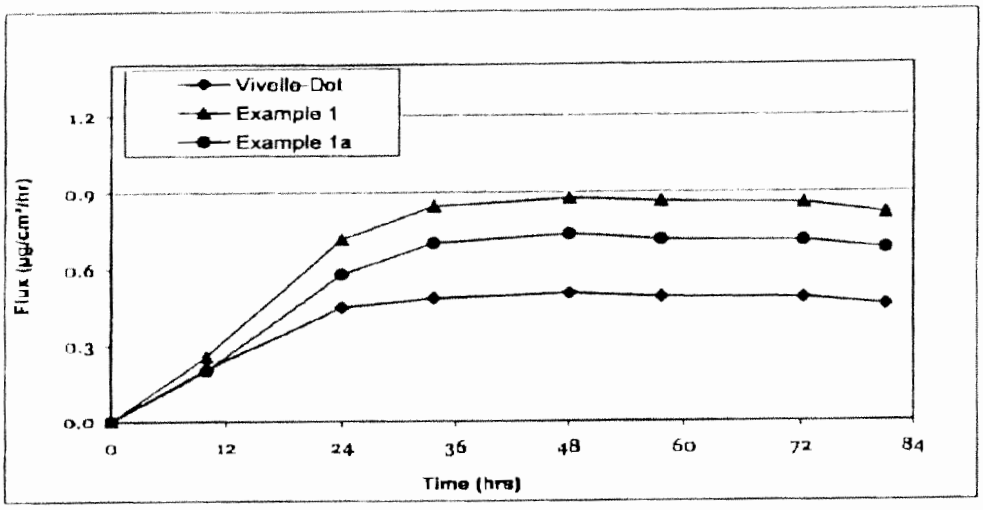
19. The method of claim 16, wherein the polymer matrix is applied to the support layer at a coat weight of greater than about 10 mg/cm^2.

20. The method of claim 19, wherein the polymer matrix coat weight is selected from the group consisting of about 12.5 and about 15 mg/ cm^2.

ABSTRACT OF THE DISCLOSURE

Described are transdermal drug delivery systems for the transdermal administration of estrogen, comprising a polymer matrix and estrogen. Methods of making and using such systems also are described.

Figure 1


Vivelle-Dot
Example 1
Example 1a
Flux (µg/cm²/hr)
1.2
0.9
0.6
0.3
0.0
0
12
24
36
48
60
72
84
Time (hrs)

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-1160

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Independent claims in excess of 3	1201	1	420	420
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2020**

Electronic Acknowledgement Receipt

EFS ID:	23646952
Application Number:	14870574
International Application Number:	
Confirmation Number:	5148
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Customer Number:	22428
Filer:	Courtenay C. Brinckerhoff
Filer Authorized By:	
Attorney Docket Number:	041457-1160
Receipt Date:	30-SEP-2015
Filing Date:	
Time Stamp:	14:17:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$2020
RAM confirmation Number	3508
Deposit Account	
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	decl.pdf	242457 5d0521374b8472a58af9f85e88226e3231df5041	no	3
Warnings:					
Information:					
2		contapp.pdf	1284857 75117ef90ce4d97e96e4d5a00a580cc338a6e363	yes	37

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal of New Application	1	3
Application Data Sheet	4	9
Specification	10	32
Claims	33	35
Abstract	36	36
Drawings-only black and white line drawings	37	37

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	36801 f16a8e5f9c636888fd322a7dff68f7285832d0b0	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1564115	

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New International Application Filed with the USPTO as a Receiving Office

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DECLARATION

As a below named inventor, I HEREBY DECLARE:

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Transdermal Estrogen Device and Delivery

(Attorney Docket No. 041457-1016)

the application of which (check one)

__ is attached hereto.

_X_ was filed on _09/12/2013_ as United States Application Number or PCT International Application Number _14/024,985_ and was amended on _____ (if applicable).

THAT the above-identified application was made or authorized to be made by me.

THAT I do not know and do not believe that the same invention was ever known or used by others in the United States of America, or was patented or described in any printed publication in any country, before I (we) invented it;

THAT I do not know and do not believe that the same invention was patented or described in any printed publication in any country, or in public use or on sale in the United States of America, for more than one year prior to the filing date of this United States application;

THAT I do not know and do not believe that the same invention was first patented or made the subject of an inventor's certificate that issued in any country foreign to the United States of America before the filing date of this United States application if the foreign application was filed by me (us), or by my (our) legal representatives or assigns, more than twelve months (six months for design patents) prior to the filing date of this United States application;

THAT I have reviewed and understand the contents of the above-identified application, including the claim(s), as amended by any amendment specifically referred to above;

THAT I believe that the above-identified application contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and sets forth the best mode contemplated by me of carrying out the invention; and

THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number	Country	Foreign Filing Date	Priority Claimed?	Certified Copy Attached?

I HEREBY CLAIM the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

U.S. Provisional Application Number	Filing Date

I HEREBY CLAIM the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of

Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number
12/216,811		7/10/2008	
13/553,972		7/20/2012	

I FURTHER DECLARE THAT all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment of not more than five (5) years, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Name of first inventor	Juan Mantelle
Residence	Miami, Florida
Citizenship Country	U.S.A.
Post Office Address	9827 S.W. 106th Terrace Miami, Florida 33176
Inventor's signature	
Date	12/18/13

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/870,574

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 420 =	420
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2020

APPLICATION AS AMENDED - PART II

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

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/870,574	09/30/2015	1615	2020	041457-1160	20	4

CONFIRMATION NO. 5148

FILING RECEIPT

22428
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

OC000000078044615

Date Mailed: 10/16/2015

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Juan Mantelle, Miami, FL;

Applicant(s)

Juan Mantelle, Miami, FL;

Assignment For Published Patent Application

NOVEN PHARMACEUTICALS, INC., Miami, FL

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 14/738,255 06/12/2015
which is a CON of 14/024,985 09/12/2013
which is a CON of 13/553,972 07/20/2012
which is a CON of 12/216,811 07/10/2008 PAT 8231906

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 10/14/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/870,574**

Projected Publication Date: 01/21/2016

Non-Publication Request: No

Early Publication Request: No

Title

TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

Preliminary Class

424

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

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/870,574	09/30/2015	Juan Mantelle	041457-1160

CONFIRMATION NO. 5148

22428
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PUBLICATION NOTICE

Title:TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

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NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: April 22, 2016

(use as many sheets as necessary)

Sheet 1 of 6

Complete if Known	
Application Number	14/870,574
Filing Date	09/30/2015
First Named Inventor	Juan Mantelle
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	041457-1160

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2015/0272905	10/01/2015	MANTELLE	
	A2	2014/0200530	07/17/2014	MANTELLE	
	A3	2013/0156815	06/20/2013	MANTELLE	
	A4	8,231,906	07/31/2012	MANTELLE	
	A5	8,343,538	04/13/2006	KANIOS ET AL.	
	A6	5,446,070	08/29/1995	MANTELLE	
	A7	4,915,950	04/1990	MIRANDA ET AL.	
	A8	6,562,363	05/13/2003	MANTELLE ET AL.	
	A9	6,221,383	04/24/2001	MIRANDA ET AL.	
	A10	6,235,306	05/22/2001	MIRANDA ET AL.	
	A11	2005/0169977 A1	08/04/2005	KANIOS	
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	A13	2006/0240087 A1	10/26/2006	HOUZE ET AL.	
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	A16	4,994,278	02/19/1991	SABOLTSKY ET AL.	
	A17	4,494,278	2/19/1991	SABLOTSKY ET AL.	
	A18	5,300,291	4/5/1994	SABLOTSKY ET AL.	
	A19	5,958,446	9/28/1999	MIRANDA ET AL.	
	A20	5,474,783	12/12/1995	MIRANDA ET AL.	
	A21	4,814,168	3/21/1989	SABLOTSKY ET AL.	
	A22	4,994,267	2/19/1991	SABLOTSKY	
	A23	5,656,286	8/12/1997	MIRANDA ET AL.	
	A24	6,024,976	2/15/2000	MIRANDA ET AL.	
	A25	6,337,086	1/8/2002	KANIOS ET AL.	
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	A30	2005/2022073	09/15/2005	JACKSON ET AL.	
	A31	2003/099695	05/29/2003	MUELLER	
	A32	4,591,622	5/27/1986	BLIZZARD ET AL.	
	A33	5,584,355	4/22/1986	BLIZZARD ET AL.	
	A34	4,585,836	4/29/1986	HOMAN ET AL.	
	A35	4,390,520	6/28/1983	NAGAI ET AL.	
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	A37	2003/0228354	12/2003	MURAOKA ET AL.	
	A38	5,730,999	03/24/1998	LEHMANN ET AL.	
	A39	5,505,956	04/09/1996	KIM ET AL.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: April 22, 2016

(use as many sheets as necessary)

Sheet 2 of 6

Complete if Known	
Application Number	14/870,574
Filing Date	09/30/2015
First Named Inventor	Juan Mantelle
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	041457-1160

U.S. PATENT DOCUMENTS

Examiner	Cite No.[1]	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant
	A40	5,350,581	09/27/1994	KOCHINKE	
	A41	4,983,395	01/08/1991	CHANG ET AL.	
	A42	4,559,222	12/17/1985	ENSCORE ET AL.	
	A43	5,762,952	06/09/1998	BARNHART ET AL.	
	A44	4,591,622	05/27/1986	BLIZZARD ET AL.	
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	A47	2002/0100185 A1	08/01/2002	SITZ ET AL.	
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	A55	4,911,707	03/27/1990	HEIBER ET AL.	
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	A57	5,904,931	05/1999	LIPP ET AL.	
	A58	4,938,759	07/1990	ENSCORE ET AL.	
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	A62	6,156,335	12/2000	ROVATI ET AL.	
	A63	2009/0041831	02/2009	MILLER ET AL.	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	A64	EP 0 887 075 A2	12/30/1998	BERTEK, INC.		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/870,574
Date Submitted: April 22, 2016				**Filing Date**	09/30/2015
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	3	of	6	Attorney Docket Number	041457-1160

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A65	VAUGHAN, "Using Solubility Parameters in Cosmetics Formulation," *J. Soc. Cosmet. Chem.*, Vol. 36, pp. 319-333 (1985).	
	A66	SOBIESKI ET AL., "Silicone Pressure Sensitive Adhesives," *Handbook of Pressure-Sensitive Adhesive Technology*. 2nd ed., pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).	
	A67	"Acrylic Adhesives," *Handbook of Pressure-Sensitive Adhesive Technology*, 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, N.Y. (1989)	
	A68	NAGAI ET AL., "New Drug Delivery Systems," Kurashiki Printing Co. Ltd., Academic Document 2009-00984-005, published January 31, 2000.	
	A69	SEKINE ET AL., "New Cosmetic Handbook," Nikko Chemical Co. Ltd., et al., Academic Documents 2008-02180-001, published October 30, 2006.	
	A70	NOVARTIS PHARMACEUTICALS CORPORATION, "Vivelle-Dot® (estradiol transdermal system)," prescription labeling, August 2004.	
	A71	BENSON, "Transdermal Drug Delivery: Penetration Enhancement Techniques," Current Drug Delivery, Vol. 2, pp. 23-33, 2005.	
	A72	FELDMANN ET AL., "Percutaneous Penetration of Steroids in Man," The Journal of Investigative Dermatology, Vol. 52, No. 1, pp. 89-94, 1969.	
	A73	SCHAEFER ET AL., "Contraception via Topical Application? A Review," Contraception, Vol. 20, No. 3, pp. 225- 236, September 1979.	
	A74	International Preliminary Report on Patentability and Written Opinion issued April, 19, 2007.	
	A75	International Search Report issued on 04/06/2005 in application number PCT/US2004/029789.	
	A76	International Search Report issued on 02/24/2011 in application number PCT/US2009/050069.	
	A77	"Acrylic and Methacrylic Ester Polymers," *Polymer Science and Engineering*, Vol. 1, 2nd ed., pp. 234-269, John Wiley & Sons (1984).	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO				***Complete if Known***	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/870,574
Date Submitted: April 22, 2016				**Filing Date**	09/30/2015
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	4	of	6	Attorney Docket Number	041457-1160

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A78	Office Action issued on 09/09/2010 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A79	Office Action issued on 01/20/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A80	Office Action issued on 06/30/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A81	Office Action issued on 09/13/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A82	Office Action issued on 11/08/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A83	Office Action issued on 05/29/2012 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A84	Notice of Allowance issued on 06/19/2012 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A85	Office Action issued on 12/29/2010 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A86	Office Action issued on 04/14/2010 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A87	Office Action issued on 06/10/2009 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A88	Office Action issued on 10/26/2011 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A89	Office Action issued on 05/13/2011 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A90	Office Action issued on 06/13/2012 by the Examiner in application number 11/245,084 (US 8,343,538)	

Examiner Signature		Date Considered	

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Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/870,574
Date Submitted: April 22, 2016				**Filing Date**	09/30/2015
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	5	of	6	Attorney Docket Number	041457-1160

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A91	Notice of Allowance issued on 08/22/2012 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A92	Office Action issued on 04/12/2013 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A93	Office Action issued on 09/04/2013 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A94	Office Action issued on 03/05/2014 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A95	Office Action issued on 05/05/2015 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A96	Notice of Allowance issued on 10/02/2015 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A97	Office Action issued on 05/20/2015 by the Examiner in application number 14/024,985 (US 2014/0200530)	
	A98	Notice of Allowance issued on 10/02/2015 by the Examiner in application number 14/024,985 (US 2014/0200530)	
	A99	Office Action issued on 08/12/2015 by the Examiner in application 14/738,255 (US 2015/0272905)	
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	A101	RIETSCHEL ET AL., "Effects of harvesting techniques on hydration dynamics: gravimetric studies of stratum corneum," J. Soc. Cosmet. Chem., Vol. 29, pp. 777-782, December 1978.	
	A102	FELDSTEIN ET AL., "Modeling of percutaneous drug transport in vitro using skin-imitating Carbosil membrane," Journal of Controlled Release, Vol. 52, pp. 25-40, 1998.	
	A103	PFISTER, "Transdermal and Dermal Therapeutic Systems: Current Status," Transdermal and Topical Drug Delivery Systems, Ghosh et al., eds., Chapter 2, pp. 33-112, 1997.	

Examiner Signature		Date Considered	

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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/870,574
Date Submitted: April 22, 2016				**Filing Date**	09/30/2015
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	6	of	6	Attorney Docket Number	041457-1160

NON PATENT LITERATURE DOCUMENTS

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	A104	Dow Corning, :"Dow Corning® BIO-PSA Standard Silicone Adhesives," Product Information, 07/28/2008.	
	A105	JANISCH ET AL., Email correspondence, March 10, 2016.	
	A106	MANNGOLD, 04/28/2004 letter to Angela Nwaneri re: Duro-Tak® 87-4287 and 87-2287.	
	A107	Noven Pharmaceuticals, Inc., Response filed in European application number 09790211.8 on 12/19/2014.	

Examiner Signature		Date Considered	

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	14/870,574
Filing Date:	9/30/2015
Examiner:	Unassigned
Art Unit:	Unassigned
Confirmation Number:	5148

TRANSMITTAL OF SECOND APPLICATION DATA SHEET AND REQUEST FOR CORRECTED FILING RECEIPT

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

Commissioner:

Attached is a Second Application Data Sheet for the captioned application.

The Second Application Data Sheet is being submitted in compliance with 37 CFR 1.76 to update the name of the Applicant to the Assignee: NOVEN PHARMACEUTICALS, INC. This update has been marked by underlining on the Second Application Data Sheet.

Applicant respectfully requests that a Corrected Filing Receipt be issued to reflect the updated Applicant information.

Although Applicant believes no fee is due, the Commissioner is authorized to charge deposit account number 19-0741 for any required fees.

Respectfully submitted,

Date April 26, 2016

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288

PTO/AIA/14 (07-14)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	041457-1160
	Application Number	
Title of Invention	Transdermal Estrogen Device and Delivery	

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
	Juan		Mantelle	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Miami	State/Province	FL	Country of Residence	US

Mailing Address of Inventor:

Address 1	9827 S.W. 106th Terrace		
Address 2			
City	Miami	State/Province	FL
Postal Code	33176	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	22428		
Email Address	IPDocketing@foley.com	Add Email	Remove Email

Application Information:

Title of the Invention	Transdermal Estrogen Device and Delivery		
Attorney Docket Number	041457-1160	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	1	Suggested Figure for Publication (if any)	1

Filing By Reference :

PTO/AIA/14 (07-14)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	041457-1160
	Application Number	
Title of Invention	Transdermal Estrogen Device and Delivery	

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

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

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

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

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

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	22428		

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 this 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 blank.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	14/738255	2015-06-12
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14/738255	Continuation of	14/024985	2013-09-12
Prior Application Status			Remove

PTO/AIA/14 (07-14)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	041457-1160
	Application Number	
Title of Invention	Transdermal Estrogen Device and Delivery	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14/024985	Continuation of	13/553972	2012-07-20
Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/553972	Continuation of	12/216811	2008-07-10

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

Foreign Priority Information:

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

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Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

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

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

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

PTO/AIA/14 (07-14)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	041457-1160
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If 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 World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date o f filing this Authorization.

Applicant Information:

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

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

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Address 2			
City	Miami	**State/Province**	FL
Country	US	Postal Code	33186
Phone Number		Fax Number	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	041457-1160
	Application Number	
Title of Invention	Transdermal Estrogen Device and Delivery	

Email Address	

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Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	NOVEN PHARMACEUTICALS, INC.

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	11960 Southwest 144th Street		
Address 2			
City	Miami	**State/Province**	FL
Country i	US	Postal Code	33186
Phone Number		Fax Number	
Email Address			

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

Signature:

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

Signature	Courtenay C Brinckerhoff			Date (YYYY-MM-DD)	2016 04 26
First Name	Courtenay C.	Last Name	Brinckerhoff	Registration Number	37288

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	041457-1160
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Title of Invention	Transdermal Estrogen Device and Delivery	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Juan Mantelle

Application No./Patent No.: 14/870,574 Filed/Issue Date: 9/30/2015

Titled: Transdermal Estrogen Device and Delivery

NOVEN PHARMACEUTICALS, INC., a Corporation

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

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [✓] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [✓] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 021510, Frame 0897, or for which a copy thereof is attached.

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

1. From: _____ To: _____

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

   Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

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

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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

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4. From: _____ To: _____

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

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

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

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

Courtney C. Brinckerhoff — Signature

April 26, 2016 — Date

Courtenay C. Brinckerhoff — Printed or Typed Name

37,288 — Title or Registration Number

PTO/SB/80 (12-03)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

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

I hereby appoint:

☒ Practitioners associated with the Customer Number: 22428

OR

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

Name	Registration Number	Name	Registration Number

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

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

☒ The address associated with Customer Number: 22428

OR

☐ Firm or Individual Name

Address

City State Zip

Country

Telephone Fax

Assignee Name and Address:
Noven Pharmaceuticals, Inc.
11960 Southwest 144th Street
Miami, FL 33186

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

SIGNATURE of Assignee of Record

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

Company Name	NOVEN PHARMACEUTICALS, INC.		
Name	Jeff Mihm		
Signature		Date	11-11-10
Title	Vice-President, CAO & Gen. Counsel	Telephone	(305) 253-5099

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to 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 3 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.**

DECLARATION

As a below named inventor, I HEREBY DECLARE:

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Transdermal Estrogen Device and Delivery

(Attorney Docket No. 041457-1016)

the application of which (check one)

__ is attached hereto.

_X_ was filed on 09/12/2013 as United States Application Number or PCT International Application Number 14/024,985 and was amended on _____ (if applicable).

THAT the above-identified application was made or authorized to be made by me.

THAT I do not know and do not believe that the same invention was ever known or used by others in the United States of America, or was patented or described in any printed publication in any country, before I (we) invented it;

THAT I do not know and do not believe that the same invention was patented or described in any printed publication in any country, or in public use or on sale in the United States of America, for more than one year prior to the filing date of this United States application;

THAT I do not know and do not believe that the same invention was first patented or made the subject of an inventor's certificate that issued in any country foreign to the United States of America before the filing date of this United States application if the foreign application was filed by me (us), or by my (our) legal representatives or assigns, more than twelve months (six months for design patents) prior to the filing date of this United States application;

THAT I have reviewed and understand the contents of the above-identified application, including the claim(s), as amended by any amendment specifically referred to above;

THAT I believe that the above-identified application contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and sets forth the best mode contemplated by me of carrying out the invention; and

THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number	Country	Foreign Filing Date	Priority Claimed?	Certified Copy Attached?

I HEREBY CLAIM the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

U.S. Provisional Application Number	Filing Date

I HEREBY CLAIM the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of

Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number
12/216,811		7/10/2008	
13/553,972		7/20/2012	

I FURTHER DECLARE THAT all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment of not more than five (5) years, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Inventor's signature	
Date	12/18/13

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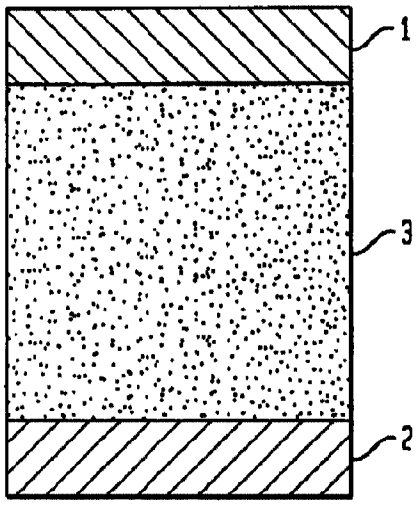
(54) Adhesive mixture for transdermal delivery of highly plasticizing drugs

(57) Transdermal drug delivery patches and methods of their production are described. The patches can be made such that the accommodate highly plasticizing drugs such as selegiline and/or the use of protonated forms of various drugs.

FIG. 1



EP 0 887 075 A2

Description

FIELD OF THE INVENTION

The present invention relates to the field of pharmaceutical delivery devices and dosage forms and in particular, transdermal delivery vehicles as well as methods of malting same.

BACKGROUND OF THE INVENTION

Most pharmaceutical formulations are available in salt forms. In fact, many formulations are only available in the form of a pharmaceutically acceptable salt. Salts have long been considered advantageous because of their high stability, ease of handling and formulation and generally high water solubility. Unfortunately, salt formulations do not tend to be useful in transdermal drug delivery systems. Because of the growing acceptance of such drug delivery systems by the general public, the inability to conveniently produce transdermal patches utilizing various pharmaceutical formulations is a great disadvantage.

There are many possible explanations for the general incompatibility of salt forms of drugs and transdermal performance. For example, protonated pharmaceutically active compounds (basic salts) are generally relatively high in polarity. It is known, however, that non-polar drugs, in general, are transmitted through the skin easily because of a high degree of compatibility with lipophillic layers of the skin. Highly polar substances such as salt forms of drugs and indeed some free forms of drugs, by virtue of their incompatibility with such lipophillic layers, are generally very slow in permeating skin.

One approach to forming a transdermal patch to overcome such problems was suggested in *Yoshida et al.*, U.S. Patent No. 4,738,848 and *Nakano et al.*, U.S. Patent No. 4,740,374. According to these patents, compounds such as diclofenac sodium and non-steroidal anti-inflammatory analgesic agents, when present in their salt forms, are difficult to dissolve into a pressure sensitive adhesive material having relatively high lipophillic properties. It is also difficult to maintain the active ingredient therein. If large amounts of drugs are added to the adhesive, in some cases, the drug cannot be dissolved or crystallization of the drug may occur. This makes it impossible to deliver a sufficient amount of the drug into the skin.

According to *Yoshida et al.* and *Nakano et al.*, these difficulties can be overcome by concurrently using an organic acid during the formulation of the adhesive material. The organic acid apparently increases the solubility of the active ingredient in the pressure sensitive adhesive material and also increases the percutaneous absorption properties thereof. These references express their belief that the reason for the increased absorption properties is that the drug is converted to its free form having a higher oleophilicity (lipophilicity) resulting in the higher solubility of the drug.

Another approach was taken in *Heiber et al.*, U.S. Patent No. 4,917,676, which relates to a user-activated transdermal therapeutic system. The transdermal drug delivery system described therein includes separate compartments for various formulations in "pre-activated states". Just prior to use, the patient or other person applying the system allows the partitioned ingredients to commingle, thus activating the system. The user generally bursts a burstable barrier separating the two reservoirs. Then the therapeutic agent, usually in the form which must be altered for the desired transdermal delivery, and the activating substance combine and transform the therapeutic agent to a suitable species.

Inactive forms of therapeutic agents in accordance with *Heiber et al.* can include, for example, an acidic drug which, as an ionized species, penetrates skin to a slight degree, but in a free acid form, permeates freely through the skin. Activating substances may include pH regulators such as buffers, acids or bases.

Such transdermal systems, however, suffer from several disadvantages. First, they require a rather complex arrangement of two or more compartments separated by, for example, a burstable but otherwise nonpermeable material. In addition to the complexity of such a structure and the potential difficulties in separately filling and maintaining discretely the individual compartments, there is also the problem of premature bursting of the burstable layer and the premature intermingling of the vanous components. Clearly, the ability to manufacture a transdermal device wherein all of the necessary ingredients can be intermixed and intermingled from the start and added together to each and every cavity in a transdermal patch would be a great advantage. Finally, the *Heiber et al.* patent considers the complexities of forming a patch where the therapeutic and activity agents are mixed and maintained together at the time of manufacture or the subsequent storage stability problems attendant such a mixture.

Moreover, resolving the question of the physical state of a drug does not resolve all of the issues surrounding the production of transdermal patches from certain highly plasticizing drugs. In fact, providing these drugs in a free base form could actually raise additional problems. It comes as no surprise that a drug or solvent loaded into an adhesive system will have an effect on the adhesive properties of the resulting mixtures. In certain cases, with certain drugs, the effect on the hardness and tackiness of the resulting adhesive mixture is minimal. However, in certain other instances, drugs such as, for example, nitroglycerin or nicotine may act as plasticizers for many conventional adhesive systems. Plasticizing drugs such as these, can have a significant deleterious effect on the physical properties of the resulting

adhesive matrix depending upon the type of drug, and the amount used. Generally, plasticizing drugs act to soften or disturb the structural integrity of the adhesive making it more fluid like and can, in certain cases, negatively effect the degree of adhesivity.

A number of companies have introduced either high molecular weight or highly crosslinked adhesive systems. It is known that these systems can generally be used almost interchangeably with plasticizing drugs. Typical examples of such adhesives include, without limitation, GELVA 737, GELVA 2655, and GELVA 1753 self crosslinkable acrylic adhesives from Monsanto's Chemical Group, 730 Worcester Street, Springfield, Mass. 01151 and DUROTAK 87-2516, DUROTAK 87-2194 and DUROTAK 87-2852 self crosslinkable acrylic adhesives available from National Starch and Chemical Company, 10 Finderne Ave., P.O. Box 6500, Bridgewater, NJ 08807-0500. All of these crosslinked adhesives find wide spread use in the pharmaceutical industry in the formulation of transdermal drug delivery systems. When liquid, lipophillic drugs are added to these adhesives at amounts of between 30 and about 40% the resulting material would generally not suffer deterioration in physical properties so as to render many of these acrylic based adhesives unusable. While many of these adhesives are virtually interchangeable, of course, some combinations of a specific drug and a specific adhesive may provide marginally better properties.

When the inventors attempted to construct a transdermal delivery vehicle for selegiline, a particularly highly plasticizing drug, they too expected that selegiline patches produced with any of the foregoing class of adhesives could be accomplished without a problem. This was particularly true as loading levels were anticipated at only between about 10 and about 20%; not particularly challenging for these adhesives.

As illustrated in Table 1, when mixtures of selegiline (15 wt %) and various adhesive materials were tested using conventional performance tests, they all demonstrated comparable and generally acceptable results.

TABLE 1

POLKEN TACK OF VARIOUS TRANSDERMAL ADHESIVES WITH 15% SELEGILINE	
ADHESIVE	POLKEN TACK
GELVA 1753	346
DUROTAK 87-2194	453
GELVA 737	333
DUROTAK 87-2516	286

Yet when these formulations were tried on skin, the results were quite surprising. While some of the formulations worked, others unexplainably exhibited significant cohesive failure whereby adhesive remained on the skin after a transdermal patch was peeled-away. The disparity in the results obtained between conventional "bench-top" testing and actual field application was truly discouraging. It essentially placed a whole host of established tests in a highly compromised state.

The inventors were also taken aback by the degree of disparity observed. When they formulated a selegiline containing transdermal patch with, for example, DUROTAK 87-2194, those patches exhibited cohesive failure and adhesive transfer. Formulations made with GELVA 2655 exhibited total adhesive failure. Neither result could have been predicted based on results such at that reported in Table 1. This problem was only amplified by the use of other traditional tests such as a measure of shear strength. As shown in Table 1A, a number of formulations including selegiline were measured in terms of shear strength.

TABLE 1A

SHEAR STRENGTH OF DIFFERENT ADHESIVE SYSTEMS WITH SELEGILINE BASE		
ADHESIVE	SHEAR (MIN)	SELEGILINE
GELVA 737	4.31	13%
GELVA 788	3.1	13%
DUROTAK 87-2516	1174	13%

TABLE 1A (continued)

SHEAR STRENGTH OF DIFFERENT ADHESIVE SYSTEMS WITH SELEGILINE BASE		
ADHESIVE	SHEAR (MIN)	SELEGILINE
DUROTAK 87-2194	36	13%
GELVA 1753	1440	4%
GELVA 1753	1440	8%
GELVA 1753	1440	13%

Typically, shear values of greater than about a half an hour to one hour would be considered acceptable adhesive systems. As one can see from Table 1A, GELVA 1753 produced relatively high shear rates, which should indicate an acceptable adhesive system. However, DUROTAK 87-2516 also exhibited acceptable shear, and the formulations made from this adhesive were totally unacceptable when applied to skin. In addition, selegiline with 10% propylene glycol as a solvent, provided shear values of greater than 800 minutes when formulated with GELVA 1753. However, while such results are generally indicative of good adhesion characteristics, this particular formulation exhibited very poor adhesion.

Much to their dismay, the inventors discovered that with a certain class of particularly highly plasticising drugs, only selected adhesives would work. They also found that, based on the state of the art, they could not predict which adhesives would work and which would not.

SUMMARY OF THE INVENTION

One aspect of the present invention is the creation of a free base material in an adhesive and or in a transdermal patch, or just prior to mixing with the adhesive. The result is the creation of a transdermal patch including the converted free base of the drug material. Another aspect of the present invention involves the creation of certain transdermal formulations which include a highly plasticizing drug, in free base form, whether the free base was created *in situ* or not.

Therefore, in accordance with one aspect of the present invention, a method of producing an adhesive formulation for a therapeutic drug delivery patch adapted for the percutaneous or transdermal delivery of a drug is provided. The method includes the step of providing a pharmaceutically active agent in protonated form, whose corresponding free base has a given pK_b which ranges from between about 4.75 and about 11. Then, the protonated pharmaceutically active agent is dissolved in a nonaqueous solvent, the nonaqueous solvent being capable of dissolving the pharmaceutically active agent in both a protonated and unprotonated forms.

The dissolved pharmaceutically active agent is reacted with a biocompatible deprotonating agent which can substantially deprotonate the pharmaceutically active agent without causing irritation upon prolonged exposure to the skin. The deprotonated agent will have a pK_b which is at least about 0.75 lower than the pK_b of the pharmaceutically active agent. The deprotonated agent thereby becomes protonated. The deprotonating agent may be selected and apportioned such that some excess of unreacted deprotonating agent remains. Finally, the deprotonated pharmaceutically active agent is incorporated into an adhesive material. In a particularly preferred embodiment, these methods also include the steps of separating at least a portion of the now protonated deprotonating agent from the mixture of deprotonated pharmaceutically active agent, solvent and protonated deprotonating agent prior to incorporating the pharmaceutically active agent into the adhesive material. The now protonated deprotonating agent can also be removed alter it has been added to an adhesive as well.

In addition, in accordance with another aspect of the present invention, it is possible to actually undertake the deprotonation of the protonated pharmaceutically active agent, *in situ*, within the adhesive material. Moreover, in accordance with still another aspect of the present invention, it is possible to construct a patch in such a way that the protonated pharmaceutically active agent and the deprotonating agent are disposed in discrete but adjacent dry layers. Over time, the deprotonation reaction occurs *in situ* such that the resulting patch includes a deprotonated pharmaceutically active agent or drug which is capable of enhanced skin penetration.

Of course, the designing of an acceptable adhesive formulation for incorporation into a transdermal patch, one which allows for the conversion of a protonated drug to its free form and can accommodate the presence of deprotonating agent, can be extremely demanding. For example, many polymer based adhesive systems are fairly incompatible with the drug in its salt form. Finding a way of introducing the salt to the adhesive must therefore be developed. In doing so, however, it must be realized that alter conversion the resulting free form of the drug must also be compatible with the adhesive. Similarly, a patch in accordance with the present invention or an adhesive formulation in accordance herewith would require the incorporation of some agent which would convert the protonated form of the drug, such as

a protonated amine form, to its free form. This deprotonating agent, like the therapeutic pharmaceutically active agent itself, will undergo transformation. It is important, therefore, to ensure that both the deprotonating agent, and that agent in its later protonated form, are also compatible with the adhesive base in terms of stability. This means finding a system where either the protonated deprotonating agent will remain dissolved in the solvent/adhesive material system, or the crystallized protonated deprotonating agent will not have an adverse effect on the transdermal device or the patient.

When highly plasticizing drugs are being formulated into transdermal patches, the interaction of the drug and the adhesive system can become even more complex. Not only must the system be able to accommodate the various states of the drug and deprotonating agent, but they must also meet some rather unique criteria for the use of highly plasticizing drugs as well.

Surprisingly, formulations which address and balance all of the often competing requirements of converting a protonated drug to its free form, *in situ*, in a percutaneous dosage form or transdermal patch and accommodating highly plasticizing drugs have been developed. The resulting patches have long term storage stability, reliable release profiles, high levels of skin permeation and, best of all, are easy and economical to manufacture. Additionally, it has been discovered that, by the practice of the present invention, it may be possible to tailor the rate of release of the free form of the drug, and thereby its permeation through the skin, by controlling the rate of reaction of the various reactive components within the patch.

In accordance with a particularly preferred aspect of the present invention there are provided methods of producing transdermal delivery vehicles for highly plasticizing drugs. These methods involve providing between about 97% and about 65%, by weight, of a very specific class of acrylic polymeric adhesives. This acrylic polymeric adhesive includes between about 40% and about 90% by weight of a C_4-C_{12} alkyl acrylate, between about 10% and about 40% by weight of a C_1-C_4 alkyl acrylate hardening monomer; between about 1% and about 15% by weight of a functionalizing monomer which facilities crosslinking; and, in many instances, a crosslinking agent. The acrylic polymeric adhesive is mixed with a highly plasticizing drug provided in an amount of between about 3% and about 35% by weight based on the dry weight of the mixture. The therapeutic adhesive formulations and transdermal patches using same are also contemplated.

Most preferably, the highly plasticizing drug is selegiline which is provided in an amount of between about 3 and about 18% by weight, based on the dried mixture. Also preferably, the only solvents used in the production of therapeutic adhesive formulations including a highly plasticizing drug provided in a free base form are relatively high volatility solvents, such as ethanol, which will be removed upon drying as well as those solvents found in the acrylic polymeric adhesive which prevent *in situ* cross-linking and maintain the adhesive in liquid form until removed. Solvents which will remain after drying, such as propylene glycol used for deprotonation are preferably not used in these adhesive formulations.

After observing the unexpected failure of certain highly crosslinked acrylic based adhesives to maintain their advantageous properties following the incorporation of moderately low doses of selegiline, the inventors discovered that a relatively small class of acrylic based adhesive formulations can be used with particularly aggressively plasticizing drugs. The reasons why these particular acrylic based adhesives work with certain highly plasticizing drugs and why other very closely related adhesive formulations fail is not fully appreciated. However, from amongst the numerous commercially available adhesive formulations of which those of ordinary skill in the art traditionally look to solve these sorts of problems, only a few have been identified as being useful in these cases, and these adhesives do have some common properties.

In another preferred aspect of the present invention, there is provided a method of producing a therapeutic adhesive formulation for use in a transdermal patch. The method includes the step of selecting an acrylic polymeric adhesive which is suitable for use with highly plasticizing drugs. This decision is not based upon the bench-tested properties of the adhesive but rather upon it's content of between about 40% and about 90% of a C_4-C_{12} alkyl acrylate and between about 10% and about 40% by weight of a C_1-C_4 alkyl acrylate hardening monomer. Once the acrylic polymeric adhesive is selected, it is mixed with the highly plasticizing drug in an amount of between about 3% and about 35% by weight based on the weight of said mixture and on a liquid basis.

Often the selection process for the adhesive also involves consideration of the content of a functionalizing monomer which facilitates crosslinking; and/or a crosslinking agent. This method may therefore also include the step of crosslinking the acrylic polymeric adhesive to form a matrix capable of controlling the release of the highly plasticizing drug when used in a transdermal patch and applied to the skin of a patient. The proper selection and formulation of this adhesive material will result in a transdermal patch and which will not ooze, suffer from adhesive failure, fall off of a patient prematurely or be difficult to remove when necessary.

Applicants have also discovered that the traditional bench-top methods of gauging the performance of such adhesives are unreliable with particularly highly plasticizing drugs like selegiline. Therefore while tests like shear strength, peel tests from a steal plate and tack tests may eliminate certain candidates, they will not reliably identify successful candidates. Instead, it was discovered that the acrylic polymeric adhesives that worked the best in these application all have similar compositions: Generally, they include a C_4-C_{12} alkyl acrylate, a lower alkyl acrylate (C_1-C_4) hardening

monomer such as methyl acrylate and a functionalizing monomer such as acrylic acid which facilities crosslinking. A crosslinking agent is also often useful.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a side planar view of a drug delivery patch in accordance with the present invention.

Fig. 2 is a side planar view of a drug delivery patch having plural layers in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The terms pharmaceutically active agent and drug are used synonymously, and these terms include any drug or biologically active substance which is available in protonated form. These pharmaceutically active agents must be capable of transdermal application and must be susceptible to inclusion in a patch in accordance with the present invention, both in protonated and nonprotonated forms. Additionally, the drug must be compatible with the other ingredients that are components of the therapeutic adhesive formulation. Generally, the content of the formulation will be tailored around the pharmaceutically active agent. However, if the pharmaceutically active agent cannot be stored in contact with, for example, any of the biocompatible deprotonating agents in accordance with the present invention, then that drug is not a candidate for use in some of the therapeutic adhesive formulations discussed herein. That is, of course, unless the drug can be provided in a free base form without any of the deprotonating agent. In addition, the drug should not cause irritation to the skin of the patient in either protonated or deprotonated form. Similarly, the drug should be susceptible of deprotonation by an agent which itself will not cause any irritation, unless the drug will be provided as a free base. This will further limit and define the class of the drugs capable of use in accordance with the present invention.

Without limitation, pharmaceutically active agents in accordance with the present invention may include selegiline-HCl, propranolol-HCl, ketorolac-HCl, buprenorphine-HCl, scopolamine-HCl, terbutaline-HCl, clonidine-HCl, morphine-HCl, terazosin-HCl, prazosine-HCl, diliazem-HCl, verapamil-HCl and Ciprofloxacin-HCl. The amount of the pharmaceutically active agent will vary widely. Some drugs are active in dosages of a few milligrams per day while others may require thousands of milligrams per day. However, in general, the pharmaceutically active agents in accordance with the present invention are provided in an amount which ranges from between about 0.1 to about 45 percent by weight based on the total formulation. More preferably, the amount of drug ranges from between about 2 to about 20 percent by weight based on the weight of the total formulation.

The pharmaceutically active agent has a pK_b of at least about 4.5-5.0 and no more than about 11-11.5. The deprotonating agent should have a pK_b of at least about 3.5-4.0 and no more than about 10.0-10.5. References to the pK_b of the pharmaceutically active agent are always to the pK_b of the free base form of the drug. In addition, the pK_b of the deprotonating agent should be at least about 0.75, preferably 1.0 and more preferably 2.0 less than the pK_b of the drug.

The term highly plasticizing drug generally means, a pharmaceutical or biologically active agent having a low molecular weight (under 300MW), being liquid at normal process temperatures, and of an oily or lipophillic nature such that it fluidizes the adhesive and would cause viscous cold flow at adhesive during normal stage. The result would be ooziness and eventually, cohesive failure or splitting of the adhesive material. If the highly plasticizing drug can be provided as a free base, then its pK_b will not be an issue. Typically, the highly plasticizing drug in accordance with the present invention would be provided in an amount ranging from between about 3% to about 35% based on the weight of the finished adhesive and drug mixture (dry weight). More preferably, the amount of drug will range from between about 3% to about 25%. Most preferably, the amount will range from between about 3% and about 18%. Preferred particularly highly plasticizing drugs in accordance with the present invention include: selegiline, fluoxetine, Des-methyl selegiline, tetracaine and chlorpheniramine.

As used herein, a therapeutic adhesive formulation includes an adhesive formulation which can be utilized as part of a percutaneous or transdermal drug delivery patch or the like. The therapeutic adhesive formulation may be provided as one or more thin adhesive layers in a patch, can be placed in a recess or cavity within a patch as a monolithic structure or as a relatively viscous gel-like substance.

The therapeutic adhesive formulation in accordance with the present invention generally includes at least two components: at least one adhesive formulation and a pharmaceutically active agent. If the drug used is in a protonated form, then it will be necessary to include a solvent capable of dissolving the drug, in both protonated and deprotonated form. Such solvents may remain in the formulation after drying. If the drug used is a highly plasticizing drug provided in protonated form, then the amount of this type of solvent should be minimized as it may affect the adhesion characteristics of the resulting therapeutic adhesive formulation. If the highly plasticizing drug is provided as a free base, then there is most often no need for such a solvent at all. In fact, under such circumstances, it is desirable to avoid using a low-volatility solvent which will not be driven off during drying, if possible. This lowers the amount of drying required which reduces the loss of drug. It also reduces the cost of the formulations and eliminates a potential source of adhesion problems. In cases where a protonated form of the drug is used, the therapeutic adhesive formulation also includes at least

some amount of a biocompatible deprotonating agent. Each of these components, as well as any others that may be used such as dyes, permeation enhancers, crosslinkers, adhesion promoters, gelling agents, crystallization inhibitors, anti-inflammatory agents and the like are mixed together in a generally homogeneous mixture. This mixture is then formed into a film, block or where appropriate, poured into a mold, or poured directly into the cavity or recess of a patch.

While, as discussed in late passages, the adhesive formulations useful with highly plasticizing drugs are defined more restrictively, the adhesive formulation useful in accordance with the present invention may include any adhesive useful in accordance with the creation of transdermal patches. Broadly, these include acrylics, silicones, polyisoalkylenes, rubbers, vinyl acetates, polyisobutylene rubber, polybutadiene, styrene-butadiene (or isoprene)-styrene block copolymer rubber, acrylic rubber and natural rubber; vinyl-based high molecular weight materials such as polyvinyl alkyl ether, polyvinyl acetate, a partially saponified product of polyvinyl acetate, polyvinyl alcohol and polyvinyl pyrrolidone; cellulose derivatives such as methyl cellulose, carboxylmethyl cellulose and hydroxypropyl cellulose; polysaccharides such as pullulan, dextrin and agar; polyurethane elastomers; and polyester elastomers. Of course, the adhesives must be biocompatible and nonirritating. They must also allow for a patch to adhere firmly to the skin of a patient in need of treatment by a patch but not be so adhesive so as to injure the patient as the patch is removed. It is also important that the adhesive be selected such that it is compatible with the other components of the therapeutic adhesive formulation of the present invention. It has been found that, as a group, the acrylic adhesives are particularly useful and compatible in this regard and therefore, it is preferred that the adhesive used be acrylic based. More specifically, acrylic adhesives in accordance with the present invention may preferably be (meth)acrylic acid such as butyl (meth)acrylate, pentyl (meth)acrylate, hexyl (meth)acrylate, heptyl (meth)acrylate, octyl (meth)acrylate, nonyl (meth)acrylate, decyl (meth)acrylate, undecyl (meth)acrylate, dodecyl (meth)acrylate, and tridecyl (meth)acrylate, and copolymers of at least one of the above esters and other monomers copolymerizable therewith.

Examples of the copolymerizable monomer include carboxyl group-containing monomers such as (meth)acrylic acid, itaconic acid, crotonic acid, maleic acid, maleic anhydride and fumaric acid; sulfoxyl group-containing monomers such as styrenesulfonic acid, arylsulfonic acid, sulfopropyl acrylate, (meth)acryloyloxynaphthalenesulfonic acid, acrylamidomethylpropanesulfonic acid and acryloyloxybenzenesulfonic acid; hydroxyl group-containing monomers such as hydroxyethyl (meth)acrylate and hydroxypropyl (meth)acrylate; amide group-containing acrylic monomers such as (meth)acrylamide, dimethyl(meth)acrylamide, N-butylacrylamide, tetramethylbutylacrylamide and N-methylol(meth)acrylamide; alkylaminoalkyl group-containing acrylic monomers such as aminoethyl (meth)acrylate, dimethylaminoethyl (meth)acrylate, diethylaminoethyl (meth)acrylate and tertbutyl (meth)acrylate; alkyl esters of acrylic acid containing an ether bond in the molecule thereof such as methoxyethyl (meth)acrylate, ethoxyethyl (meth)acrylate, butoxyethyl (meth)acrylate, tetrahydrofurfuryl (meth)acrylate, methoxyethylene glycol (meth)acrylate, methoxydiethylene glycol (meth)acrylate, methoxypolyethylene glycol (meth)acrylate and methoxypolypropylene glycol (meth)acrylate; vinyl monomers such as N-(meth)acryloylamino acid; functional monomers such as acrylic monomers such as urethane, urea or isocyanate ester of acrylic acid; and vinyl monomers such as (meth)acrylonitrile, vinyl acetate, vinyl propionate, vinyl pyrrolidone, vinyl pyridine, vinyl pyrazine, vinyl piperadine, vinyl piperidone, vinyl pyrimidine, vinyl pyrrole, vinyl imidazole, vinyl caprolactam, vinyl oxazole, vinyl thiazole, vinyl morpholine, styrene, a-methylstyrene and bis(N,N'-dimethylaminoethyl) maleate.

The above alkyl esters of (meth)acrylic acid and copolymerizable monomers include isomers in which the alkyl portion is straight or branched, and isomers and derivatives in which the position of substituents is different.

It is desirable from a standpoint of the balance between adhesive properties to the skin and cohesion that the ratio of the alkyl ester of (meth)acrylic acid to the copolymerizable monomer in the acrylic pressure-sensitive adhesive material is 50:50 to 99:1 by weight. When alkyl esters of (meth)acrylic acid containing an ether bond in the molecule thereof are used from the standpoint of the low skin irritating properties, it is desirable that the ratio of the alkyl ester of (meth)acrylic acid/the alkyl ester of (meth)acrylic and containing an ether bond in the molecule/the other copolymerizable monomer is 40 to 80/59 to 10/1 to 40.

It is preferred that the adhesive formulations be subjected to suitable chemical crosslinking treatment (e.g., copolymerization of crosslinkable monomers and addition of a crosslinking agent) or physical crosslinking treatment (e.g., irradiation with ultraviolet rays and ionizing radiations such as electron beam).

In accordance with the present invention, the amount of adhesive generally utilized ranges from between about 30 to about 85 percent by weight based on the total weight of the resulting formulation. Preferably, the amount of adhesive used ranges from between about 45 to about 75 percent by weight based on the total weight of the formulation.

When the transdermal patch in accordance with the present invention will be used to deliver highly plasticizing drugs, a more specific group of acrylic based adhesives has been found to be useful. These are identified herein as acrylic polymeric adhesives.

Acrylic polymeric adhesives in accordance with this aspect of the present invention include between about 40% and about 90% of a C_4-C_{12} alkyl acrylate as the principal monomeric component. Any alkyl acrylate having between 4 and 12 carbons which has been used for the formulation of transdermal adhesives can be used, although, of course, other acrylates are also contemplated. Traditional C_4-C_{12} alkyl acrylates useful in accordance with the present invention

include, for example, 2-ethylhexyl acrylate, butyl acrylate, n-decyl, n-nonyl, 2 ethyoctyl, isooctyl and dodecyl-acrylate Generally, the C_4-C_{12} alkyl acrylate in accordance with the present invention will be used in a matter of between about 40 and about 90% based on the weight of the finished adhesive material. More preferably, however, the amount of the C_4-C_{12} alkyl acrylate will range from between about 60% to about 80% by weight, based on the weight of the adhesive.

The properties of the acrylic polymeric adhesive can be dramatically altered depending upon whether or not a hardening monomer is used and the type of hardening monomer used. It has been found that the use of between about 10% and about 40% by weight of a C_1-C_4 alkyl acrylate hardening monomer, in combination with the C_4-C_{12} alkyl acrylate, is the key to providing an acrylic polymeric adhesive system capable of providing desirable therapeutic delivery, as well as structural integrity, for transdermal application of highly plasticizing drugs as discussed herein. Examples of C_1-C_4 alkyl acrylate hardening monomers useful in accordance with the present invention include methyl acrylate, methyl methacrylate, ethylacrylate, ethyl methacrylate, hydroxyethyl acrylate and hydroxy propyl methacrylate. More preferably, the amount of C_1-C_4 alkyl acrylate hardening monomer useful in accordance with the present invention ranges from between about 15% to about 30% based on the weight of the adhesive.

It has been discovered that the attributes of the acrylic polymeric adhesive when used with highly plasticizing drugs are largely a function of the C_4-C_{12} alkyl acrylate and the hardening monomer selected. The compositions of various commercially available transdermal adhesives are provided below in Table 2.

TABLE 2

COMPOSITIONS OF VARIOUS TRANSDERMAL ADHESIVES						
	GELVA 788	**GELVA 737**	**DUROTAK 2194**	**GELVA 1753**	**DUROTAK 2516**	**DUROTAK 2852**
2-Ethyl Hexyl Acrylate	67	67	75	61	70	65
Methyl Acrylate				33		27.5
Vinyl Acetate	28	28	20		25	
Acrylic Acid			5	6		7.5
Hydroxy Ethylacrylate	5	5			5	
Glycidyl Methacrylate	<0.5	<0.5		<0.1	Yes	
X-Linker	No	Butyl Titinate	Aluminum Isopropoxide	Aluminum Isopropoxide	Polybutyl Titinate	Aluminum

These materials all have similar amounts of 2-ethyl hexyl acrylate (A C_4-C_{12} alkyl acrylate) and similar amounts of a functionalizing monomer which facilitates crosslinking. (Three of the formulations have between about 6 and about 7.5% acrylic acid, and the remaining formulations have about 5% hydroxy thylacrylate.) Two of the compositions, both of which have been found to be effective in accordance with the present invention, GELVA 1753 and DUROTAK 87-2852 each contain a hardening monomer which is methyl acrylate. The remaining formulations contain vinyl acetate as the hardening monomer. Vinyl acetate is a widely employed monomer for this purpose.

In accordance with the present invention, it is also desirable to use a functionalizing monomer which facilitates crosslinking. Functionalizing monomers provide functional groups for crosslinking. Such functionalizing monomers are well known in the art and include, for example, acrylic acid, hydroxy ethylacrylate, methacrylic acid, and acrylamide. It should be noted, however, that when using an acrylate hardening monomer in an acid form, it is preferred to use a functionalizing monomer, such as acrylic acid, whereas, where the hardening monomer is an alcohol, compounds such as hydroxy thylacrylate should be chosen. functionalizing monomers are generally provided in the range and between about 1% and about 20%.

It is also desirable to include a crosslinking agent. Crosslinking agents can include butyl titanate, polybutyl titanate, aluminum zinc acetate and other multivalent metals, methylol ureas and melamines Generally the crosslinking agent is provided in an amount of between about 0.005 and about 2% the adhesive.

Crosslinking can be effected in many ways depending upon a number of factors. Most importantly, crosslinking depends upon the mode of action of the crosslinking agent. Most of the acrylic polymeric adhesive formulations commercially available use crosslinking agents which will be activated upon the drying of the formulation. It is not the heat which activates these agents but rather the removal of the solvent by, for example, evaporation or drying. Drying to remove these solvents can by done under completely conventional conditions such as 100 to 140°F. It should be noted that certain formulations are commercially available without crosslinkers. For example, GELVA 1430 is identical to

GELVA 1753 except that it does not include a crosslinker. This allows one to accommodate situations where no crosslinking is needed (such as when very low concentrations of drug are used) or to custom select a crosslinker that has a different mode of action.

It should also be noted that the solvents found in the adhesives which maintain the liquid form of the adhesive and generally prevent the activation of the crosslinkers are not to be confused with the low-volatility solvents which can be added as part of the dissolution system for patches using a protonated drug. Solvents normally found in commercial adhesive formulations, solvents included merely to prevent premature crosslinking, or relatively high volatility solvents such as ethanol, used only during mixing and processing, which are evaporated during drying are generally not a problem with regard to the properties of the adhesives.

As shown in Table 3, quite unexpectedly, the properties of the resulting adhesive vary greatly with relatively minor variations and the relative amounts of the various ingredients. It is clear, therefore, that the unique combinations of monomers is primarily responsible for dictating whether or not a particular adhesive formulation will be successful with a highly plasticizing drug discussed herein.

TABLE 3

EFFECT OF SELEGILINE AND PLASTICIZER COMBINATION ON VARIOUS PHYSICAL PROPERTIES OF VARIOUS ADHESIVES				
ADHESIVE	PLASTICIZER	SELEGILINE	PEL FROM SS (gm/in)	PHYSICAL OBSERVATIONS
GELVA 1753	-0-	~18	-	No Adhesive Transfer No Oozing
	-0-	~15%	1110	
	-0-	~10%	933	
	10% PG	8%	527	
DUROTAK 87-2194	10% PG	8%	2217	Adhesive Transfer (Cohesive Failure)
GELVA 788	10% PG	8%	1267	Adhesive Transfer
DUROTAK 87-2516	10% PG	8%	960	Adhesive Transfer
GELVA 2655	-0-	18%	—	Total Adhesive Failure
DUROTAK 87-2852	-0-	12%	—	No Adhesive Transfer No Oozing
	-0-	18%	—	Somewhat Soft

Only those adhesive/drug formulations which included a C_1-C_4 alkyl acrylate hardening monomer as discussed above provided the necessary performance in terms of adhesive transfer and oozing to allow it to be useful for transdermal applications without adhesive transfer on skin.

It is interesting to note from Table 3 that GELVA 1753 provided acceptable results in terms of adhesive transfer and oozing. However, the formulation which included 10 % propylene glycol ("PG"), a relatively low-volatility solvent used in systems involving protonated drugs, also exhibited relatively poor adhesive characteristics. It has been found that the use of these types of solvent only amplifies the plasticizing effects of highly plasticizing drugs. Therefore, when a free base form of a highly plasticizing drug is used, it is desirable to reduce, if not eliminate, the use of such low-volatility solvents. Of course, this has other processing advantages, as it reduces costs, exposes a patient to fewer chemicals, reduces chemical waste and reduces process time, both in terms of preparation and in terms of drying the formulation.

Other acrylic polymeric adhesives containing the proper combination of ingredients include GELVA 2873 (similar to 1753, but without residual monomers) and DUROTAK 87-2852.

When the pharmaceutically active agent used is a protonated form, it must be converted to its free form, before, during or after being mixed with the adhesive thereby rendering it more readily permeable through the skin of a patient. Protonated forms of pharmaceutically active agents, including highly plasticizing drugs, are generally incompatible with the adhesive materials described above. However, the present inventor has found that this problem can be overcome by dissolving the usually solid salt in a nonaqueous solvent which is capable of maintaining the pharmaceutically active

agent in both its protonated and nonprotonated form. Again, there are trade-offs based on the use of this type of solvent and highly plasticizing drugs, particularly if the solvent used has a relatively low-volatility such as PG.

In accordance with the present invention, the nonaqueous solvent is preferably an alcohol. Alcohols in accordance with the present invention can include monoalcohols, such as ethanol, propanol, isopropanol, butanol, and tertbutyl alcohol. The alcohol may also be a generally low molecular weight polyols, i.e., glycols such as propylene glycol and polyalkylene glycol having an average molecular weight of less than about 400. For example, the nonaqueous solvent may be polyethylene glycol having an average molecular weight of between about 200 and about 400.

Most preferably, a nonaqueous solvent in accordance with the present invention is a normal short chain polyol of between about 2 and about 4 carbons in length. Such polyols may include 1,4 butanediol, glycerol, ethylene glycol, propylene glycol, and the like. Also useful in accordance with the present invention are acetates such as, for example, ethyl acetate, cellulose acetate, vinyl acetate and the like.

It is important that the nonaqueous solvents not only be compatible with the adhesive material and the pharmaceutically active agent, both in its protonated and nonprotonated forms, but also that it be compatible with the biocompatible deprotonating agent as well. Moreover, the nonaqueous solvent must be compatible with the biocompatible deprotonating agent in both its protonated and nonprotonated forms. The nonaqueous solvent must also be biocompatible such that it will not cause irritation or discomfort when in contact with the skin of a patient.

The amount of nonaqueous solvent used in accordance with the present invention must be sufficient to completely dissolve both the pharmaceutically active agent and the biocompatible deprotonating agent. Thus the amount may vary widely with the amount of each such ingredient used. However, in general, the therapeutic adhesive formulation in accordance with the present invention may include an amount of nonaqueous solvent ranging from between about 5 to about 30 percent by weight based on the total weight of the formulation. More preferably, the nonaqueous solvent is provided in an amount of between about 10 and about 20 percent by weight based on the weight of the total formulation.

When the pharmaceutically active agent is a highly plasticizing drug, then it may be necessary to reduce the amount of nonaqueous solvent used, particularly those which do not evaporate during drying. As previously noted, certain solvents can accentuate the highly plasticizing nature of the drug, or can reduce the adhesive characteristics of the resulting patch, if they remain. In such cases, it is preferable to use only solvents which will volatilize or evaporate during drying and to use other solvents in amounts of less than about 10% by weight. Preferably as little solvent is used as possible. The exact amount of solvent useful in accordance with this aspect of the invention, will vary considerably, depending upon the exact acrylic polymeric adhesive system selected, the specific highly plasticizing drug used and the amount of the highly plasticizing drug provided. Generally though, the more highly plasticizing the drug, and the greater the overall content, the lower the amount of non-volatile solvent which can be accommodated before yielding undesirable properties.

Of course, during the normal drying process, at temperatures ranging from 100-200°F, any solvents in the system, whether provided as part of the adhesive or added or evaporated or dried. The high-volatility solvents are driven off and lower-volatility solvents are dried. However, this process can also cause the loss of drug, particularly when using highly plasticizing drugs. Therefore, to provide a formulation or patch containing between about 3% and about 35% dry as desired, one might need to add as much as 100% (70% by weight) additional drug to the adhesive prior to drying. The amount of additional drug will vary with the drug or drugs used, the type of adhesive and the amount and types of solvents and the drying conditions. By lowering drying temperatures and eliminating additional solvents (those not found in the commercial adhesive) the amount of drug lost can be reduced. By consistent formulation and drying conditions, it is possible to determine the amount of drug lost so as to provide full compensation therefore. The result will be patches having the desired amount of drug.

Finally, the biocompatible deprotonating agent provided must be strong enough to substantially deprotonate the pharmaceutically active agent, but must not be so aggressive so as to cause irritation upon prolonged exposure to the skin. The biocompatible deprotonating agent must also be selected so that it is storage compatible with the drug and soluble, in both protonated and nonprotonated forms, in both the adhesive material and the nonaqueous solvent.

In order to be strong enough to substantially deprotonate the pharmaceutically active agent, it should be generally understood that the biocompatible deprotonating agent should have a pK_b which is at least 0.75 lower than the pK_b of the deprotonated form of the pharmaceutically active agent. More preferably, the pK_b differential is 1.0 or 2.0, or even greater. For example, if the active drug in free form has a pK_b of about 9.0, then the deprotonating agent in accordance with the present invention should have a pK_b of about 8.25 and, more preferably 8 or less. At the same time, the biocompatible deprotonating agent should not be so aggressive so as to cause irritation upon prolonged exposure to skin. Thus the pK_b of the deprotonating agent should not be under at least about 3.5-4.0 or over about 10.0-10.25. More, preferably, the pK_b of the drugs (in deprotonated form) will range from between about 5 and about 11 and the pK_b of the deprotonating agents will range from between 4 and about 10. Of course, in some cases, it may be possible to use a lower pK_b, but the risk of irritation grows accordingly.

By prolonged exposure to skin, it should be understood that certain patches may only be in contact with skin for a matter of hours, while others may be left on for a matter of days. In the context of longer term patches left in contact with

the skin for greater than about 8 hours, the meaning of the term should be readily apparent. However, as to shorter exposure patches, the term prolonged exposure to the skin contemplates irritation caused by repeated administration of a patch to the same area of skin.

The biocompatible deprotonating agent in accordance with the present invention may be any compound which is capable of deprotonating the drug, and which is compatible with the formulations in the present invention. Preferably, the biocompatible deprotonating agent can be polymeric imines, aromatic imines, alkanol imines, polymeric amines, aromatic amines, alkanolamines, alkyl-aryl amines, and the like.

Particularly preferred deprotonating agents in accordance with the present invention include alkanolamines such as, for example, triethanolamine, diethanolamine, ethanolamine, propanolamine, ammonia and the like. Other biocompatible deprotonating agents in accordance with the present invention include polymeric imines such as, for example, polyethylene imine ("PEI"), polydimethylaminoethyl methacrylate such as Eudragit E100 from Rohm Pharmacy and polyacryloamin. PEI is a particularly interesting biocompatible deprotonating agent as it tends to form a sphere or cage which may encapsulate or entrap some of the pharmaceutically active agent. The rate of reaction between the PEI and protonated drugs will depend largely upon the molecular weight of the PEI. Therefore, by tailoring the size of the PEI, it may be possible to control, at least to some degree, the rate of deprotonation.

It is also possible to use a second drug as a deprotonating agent. For example, if drug X has a pK_b of 9 and drug Y has a pK_b of at least about 8.25, drug Y could be used to deprotonate drug X. Drug X would then have an enhanced rate of penetration into the skin. This can be particularly useful where drug Y is intended to act topically, is intended to be administered over a relatively longer period of time such that the salt form created is not a problem, or where the salt form of drug Y retains a relatively high rate of skin penetration. It may also be desirable to use two drugs with a pK_b differential of less than about .75 so as to setup a competitive deprotonating reaction between them.

Again, the amount of biocompatible deprotonating agent in accordance with the present invention will vary with a number of factors. The amount will be very dependent upon the amount of pharmaceutically active agent utilized. Moreover, the strength or pK_b differential between the deprotonating agent and the pharmaceutically active agent may also play a role in determining how much deprotonating agent is necessary. The range of deprotonating agent used will also vary with the stoichiometry of the deprotonation reaction. Generally, once the amount of protonated pharmaceutically active agents are selected, a stoichiometrically corresponding amount of deprotonating agent should be used. It may be desirable to add an excess of deprotonating agent relative to the amount of deprotonated pharmaceutically active agent so as to ensure a complete reaction.

Any of the formulations discussed herein may also include a viscosity modifier such as Fumed Silica such as Cabosil, adhesive compatible acrylic polymers such as Elvacite from DuPont, and vinyl polymers such as Polyvinyl Pyrrolidone (Plazdone C-30 from ISP), Ammonium Polyacrylates (such as Acrysol G-110 from Rohm and Haas), Hydroxy Propylcellulose (such as Klucel from Aqualon). The viscosity modifier may play a role in controlling release of the drug and/or the rate of the deprotonation reaction. Cross linkers such as: Metal Alkoxides (such as Isopropoxide), Melamine-based Polyols (such as Cylink HPC resins from Cytec Industries, Inc.), Organic Titanates (such as Tyzor from DuPont Chemicals) may also be used. The composition of the present invention may further include one or more Permeation Enhancers such as: Propylene Glycol, Polyethylene Glycol, unsaturated long-chain fatty acids (such as Oleic Acid), short-chain alcohols (such as Ethanol, Isopropanol, n-Butanol), Dimethylsulfoxide, Azone, N-Methyl-2-Pyrrolidone, Decylmethylsulfoxide, Anionic Surfactants (such as Sodium Lauryl Sulfate), Nonionic Surfactants (such as Polyoxyethylene (20) Sorbitan Monoleate), Cationic Surfactants (such as N, N-Bis (2-Hydroxyethyl)-Oleylamine), Zwitteronic Surfactants (such as Dodecyl-Dimethylammoniopropane Sulfate), Terpenes. These may be particularly useful when using a drug as a deprotonating agent as the delivery profile of the later protonated drug may be significantly enhanced. Anti-irritants such as Hydrocortisone, Flurbiprofen, and Indomethecin may also be useful.

The therapeutic formulation in accordance with the present invention can be made in a number of ways. A particularly preferred method, the deprotonating agent such as, for example, TEA or PEI, is mixed with a small amount of non-aqueous solvent such as, for example, 1,2 propanediol. This solution is then mixed into the acrylic adhesive base material. Thereafter, a pharmaceutically active agent in protonated form, such as, for example, selegiline-HCl, is dissolved in a nonaqueous solvent, and, preferably, the same nonaqueous solvent used to dissolve the deprotonating agent. Thereafter, the drug-containing solution is added to the mixture of the adhesive base and the dissolved deprotonating agent. While within the acrylic adhesive base, the selegiline-HCl and the deprotonating agent, i.e., TEA, react such that TEA-HCl and free selegiline are formed. The reaction kinetics of this reaction strongly favor these end products. Of course, the order of the addition of ingredients can vary. For example, the TEA solution can be added to the selegiline-HCl solution and then the resulting mix can be added to the adhesive.

Generally, all mixing is done at room temperature. However, the deprotonating reaction may be somewhat exothermic and, therefore, it may be advantageous to cool the mixture to prevent degradation of the drug. After the mixture in accordance with the present invention has been formed and while the deprotonating reaction is taking place, the material may be directly forwarded and introduced into a transdermal patch.

A typical patch is shown in Fig. 1. It includes a baking layer 1, a release layer 2 and a therapeutic adhesive formu-

lation including both adhesive and drug in free form 3, disposed therebetween. In use, the release layer is peeled away exposing a surface of the adhesive which is then applied to the skin. The backing layer helps contain the material and prevent contamination. Any material useful in the production of transdermal patches can be used herein and almost any construction is appropriate

In accordance with another aspect of the present invention, it is possible to deprotonate the protonated pharmaceutically active agent prior to its introduction into an admixture with the adhesive material. In this case, the pharmaceutically active agent and the deprotonating agent, as previously described herein, are mixed in a solvent until the reaction between the two components is complete. Generally, a stoichiometric or slightly greater amount of deprotonating agent is used relative to the amount of pharmaceutically active agent so as to insure that the equilibrium drives the deprotonating reaction to completion. Often, the consequence of this reaction will be the formation of crystals or a precipitate of the now protonated deprotonating agent. While there is generally no adverse consequence because of the inclusion of such crystals, it is preferred to minimize or entirely eliminate such crystals if possible. Accordingly, before the mixture is mixed into the adhesive material base, the mixture is centrifuged, filtered, or otherwise processed such that the solid crystals or precipitate are removed. The remaining solution comprising mainly solvent and deprotonated pharmaceutically active agent, along with some residual liquid deprotonating agent, is then mixed into the adhesive mixture and then used in the production of transdermal patches as previously described. It is also possible to remove any crystals or other solids from the adhesive before the adhesive is used to construct a transdermal patch. This is accomplished as previously discussed.

In accordance with another aspect of the present invention, it may also be desirable to control the rate of the deprotonating reaction and, therefore, the conversion of the protonated pharmaceutically active agent to the free form thereof. By this statement, it should be understood that the present invention is nonetheless different than the *Heiber et al.* patent previously discussed. In *Heiber et al.*, a physical barrier is provided to stop substantially any reaction between the therapeutic agent and an activating agent therefor until just prior to use. The materials must be maintained completely separately starting from manufacture and continuing through storage up until the moment of use. In the present invention, even if steps are taken to control the rate of reaction, nonetheless, some reaction between the protonated form of the pharmaceutically active agent and the biocompatible deprotonating agent will take place during manufacture or not long thereafter. Additional conversion will take place during storage prior to use.

One method of controlling the rate of reaction was described previously and involves the use of PEI. Other cage-like deprotonating agents may also be used. Similarly, it may be possible to place either the pharmaceutically active agent or the biocompatible deprotonating agent inside of a microcapsule, microsphere, or matrix microparticle which somewhat restricts but does not completely eliminate the interaction of the two reactive species. The degree of permeability or the degree of dissolution of the microcapsule material will, at least in part, be rate controlling. Alternatively, the viscosity and/or degree of crosslinking of the adhesive material and/or the totality of the formulation can be increased or decreased. The greater the viscosity and/or molecular weight of the adhesive mixture, the greater the diffusion time for the various ingredients and the slower the time of reaction. Patches in accordance with the present invention can also be stored at generally lower temperatures which can also control the reaction of kinetics.

Another interesting method in accordance with the present invention involves separate formation of two or more layers of adhesive material in accordance with the present invention. One of the adhesive layers would include mixed therein the protonated form of the pharmaceutically active agent dissolved in a nonaqueous solvent. A second layer (adhesive or not) would include the biocompatible deprotonating agent dissolved in a nonaqueous solvent. These two layers could then be superimposed or placed in intimate contact with one another. Some reaction between the deprotonating agent in one layer and the pharmaceutically active agent in the adjacent layer will take place substantially immediately or shortly after contact. However, depending upon the design, the ratio of continued reaction may depend upon diffusion through the various layers. Eventually, the entirety of the pharmaceutically active agent will be deprotonated.

As shown in Fig. 2, a transdermal patch of this type includes a baking layer 1, a release layer 2 a first adhesive layer 3 adjacent the release layer and a second layer 4 disposed between the adhesive layer 3 and the backing layer 1. Second layer 4 may be an adhesive layer, but it need not be adhesive. The protonated drug is initially disposed in either layer 3 or layer 4 and the deprotonating agent is disposed in the other layer. Over time, as the drug is converted to free form, the distribution of the drug may vary within the layers. In use, the release layer 2 is peeled away exposing a surface of the first adhesive layer 3 which is then applied to the skin. The backing layer 1 helps contain the material and prevent contamination. Any material useful in the production of transdermal patches can be used herein and almost any construction is appropriate

This later arrangement has additional benefits. Specifically, during the manufacture of an adhesive patch as described herein, after the adhesive mixture including the pharmaceutically active agent have been introduced into the patch or formed into a mold, the material is dried. During that drying, it is not uncommon for some of the pharmaceutically active agent to evaporate. This can cause the dosage form to be underweight in terms of the amount of therapeutic material delivered, or may force a manufacturer to incur additional costs by producing a wet mixture containing an

excess of pharmaceutically active agent with the expectation that a percentage thereof will evaporate away. In accordance with one aspect of the present invention, however, the deprotonating agent and the pharmaceutically active agent are dissolved into two different layers, each of which is separately dried. Neither the deprotonating agent nor the protonated drug are as sensitive to the heat used in drying as the deprotonated pharmaceutically active agent. After drying, the individual layers can be brought into intimate contact with each other such that the deprotonating reaction can begin.

Finally, when the drug used is a highly plasticizing drug as defined herein, it may be added to the adhesive as either a free base form or as a protonated drug. In the case of the former, deprotonating agents, and possibly solvents, will not be necessary. In the case of the latter, as with any other protonated pharmaceutically active agent as defined herein both solvent and deprotonating agent may be necessary.

Formulating patches including highly plasticizing drugs in free form tends to be a far simpler operation. The drug is merely mixed with an acrylic polymeric adhesive, as well as any other additional excipients, and then treated as any other material, using methods conventional in the manufacturing of transdermal patches. the material can be made into a film, dried into a block poured into a mold and the like.

EXAMPLES

EXAMPLE 1

Three formulations were produced in accordance with the present invention. The formulations are shown in Table 4 below.

TABLE 4

INGREDIENTS	WET BASIS	DRY BASIS*
Selegiline Base	3.5	5
GELVA 1753	119	85
Selegiline Base	6.74	10
GELVA 1753	134.4	80
Selegiline Base	9.45	15
GELVA 1753	105	15

*parts

Each formulation was prepared with the same protocol. An amount of liquid drug as indicated in Table 4 was weighed out. The indicated amount of dry adhesive was also weighed. The drug was slowly added to the adhesive while agitation continued moderately to create a homogenous blend. A thin film of the drug/adhesive blend was produced in a controlled thickness of between 70-95 mg/ 10 cm^2 to a thickness of onto a release-coated plastic/paper substrate using a knife-over-roll technique. The coating was then dried in an oven at between 110° and 140°F to remove the solvents. The dry drug-polymer film was then laminated to a backing material made of PET/PE and die-cut into patches.

EXAMPLE 2 - ANALYTICAL STUDY OF CONVERSION OF SELEGILINE-HCl TO SELEGILINE FREE BASE.

Selegiline-HCl and one of the following deprotonating agents were added to water and analyzed for turbidity using standard protocols. The results are reported below in Table 5.

TABLE 5

Deprotonating Agent	pK_b	Turbidity
Diethylamine	3.07	Yes
Triethylamine	3.28	Yes
Ethanolamine	4.5	Yes

TABLE 5 (continued)

Deprotonating Agent	pK_b	Turbidity
Ammonia	4.75	Yes
Triethanolamine	6.2	Yes
Imidazole	7.05	Yes
Pyridine	8.77	Yes - Slight
Aniline	9.34	No

Selegiline free base, i.e., in its deprotonated form is only sparingly soluble in water. For this reason it is important that the solvent used in accordance with the present invention be a nonaqueous solvent. Visual observations of the resulting mixtures indicated turbidity in most of the tested cases. Turbidity is attributable to the conversion of the selegiline-HCl which is readily soluble in water to the free base form which is not.

Selegiline free form or free base has a pK_b value of approximately 9.0. As will be apparent from Table 5, pyridine having a pK_b of 8.77 produced some slight turbidity indicating some level of conversion of the selegiline-HCl to selegiline free base. However, aniline having a pK_b higher than selegiline, produced no turbidity indicating no conversion to the free base form. Imidazole having a pK_b of 7.05 produced strong turbidity indicating significant conversion.

Diethylamine and triethylamine also produced significant turbidity indicating conversion of the selegiline-HCl to the free base form. However, because of their low pK_b, and their resulting high pH, these deprotonating agents would generally be inappropriate for use in accordance with the present invention. Of course, it is possible that certain patch formulations which will require only brief exposure to the skin or very low concentrations of active ingredient may allow for the use of such agents.

The test was repeated using propylene glycol as the test medium. Selegiline free base concentration was measured by UV absorbency of cyclohexane extract and compared with a stoichiometric value of selegiline free base. The results are illustrated in Table 6.

TABLE 6

List	pK_b	Selegiline Free Base Conversion
Imidazole	7.05	100%
Pyridine	8.77	15%
Amiline	9.34	0%

Imidazole having a pK_b of 7.05 produced a selegiline conversion of approximately 100%. Pyridine having a pK_b of 8.77 produced a selegiline free base conversion of 15%. Aniline having a pK_b of 9.34 produced no conversion. This data strongly supports the visual observances of turbidity described above.

EXAMPLE 3 - ADDITIONAL ANALYTICAL TESTING

Additional testing was undertaken by dissolving various pharmaceutically active agents in a 25% solution of propylene glycol and analyzing them as described in Example 2. Triethylamine having a pK_b of approximately 3.28 was capable of converting phenylpropranolol-HCl and propranolol-HCl (the free base forms having a pK_b of 4 and 5 respectively). UV testing indicated that conversions were substantially complete. This shows that a pK_b differential of about 0.75 (in the case of phenylpropranolol, a differential of .72) is necessary for complete conversion from the hydrochloride salt to the free base form.

Of course, triethylamine had a measured pH of approximately 11.7 and a calculated pH of approximately 13.7. Such material would generally be too caustic for use in accordance with the present invention, especially of the calculated pH value, except under specialized circumstances. An actual pH of 11.7 is acceptable, an actual pH of 13.7 is not. Similarly, phenylpropranolol-HCl generally requires the use of a deprotonating agent having a pK_b which is so low that it may cause irritation. In addition, the free base form of this pharmaceutical itself has a pH of approximately 13 which is generally too caustic for use in accordance with the present invention.

Ammonia having a pK_b of 4.75 was able to completely deprotonate verapamil-HCl (free base having a pK_b of 6) and, partially deprotonate propanol (free base form having a pK_b of 5). This also demonstrates that the pK_b differential

between the drug and the deprotonating agent needs to be approximately 0.75 or greater is useful to insure a complete reaction. Triethanolamine having a pK_b of 6 was fully able to convert scopolamine-HCl and clonidine-HCl to their respective free base forms (pK_b of 7-8 and 7 respectively).

EXAMPLE 4

0.6 kg of selegiline HCl was dissolved in 1.17 kg of 1,2 Propanediol in a 2 gallon container, under mild agitation, using an air mixer. In a separate 2 liter container, 0.407 kg of TEA was mixed with 0.4 kg of Ethanol at ambient temperature using mild agitation from air mixer. In a separate 5 gallon container, 3.55 kg of liquid adhesive GELVA 1753 was placed and 0.5 kg of Ethanol was mixed in using a high shear mixer. After all the Ethanol was dissolved, the Ethanol solution of TEA from the 2 liter container was gradually mixed into the adhesive while continuously mixing using a high shear mixer (Sharr mixer). After complete addition of TEA solution, 1.2 Propanediol solution of selegiline HCl, from a 2 gallon container, was gradually added to the continuously mixed adhesive. The mixing continued until a homogenous mixture was realized (about 30 minutes). Final adhesive mixture was coated (using knife-over-roll coating method) on a siliconized release liner and dried continuously in the 3 zone oven and "in line" laminated to a backing layer such as 1 mil Polyester. This laminate was subsequently die cut into round 10 cm^2 patches and packaged in heatsealable pouches.

EXAMPLE 5

The procedure used in example 4 was repeated. However, 3.6 kg of selegiline HCl was dissolved in 6.3 kg of 1,2 Propanediol. Accordingly, the amount of TEA was increased from 0.407 kg to 2.44 kg and mixed with 2.4 kg of Ethanol. The amount of GELVA 1753 adhesive was increased to 21.0 kg and diluted with 3.0 kg of Ethanol. The adhesive mixture was agitated using Sharr Mixer while both solutions of selegiline HCl and TEA were subsequently added into mix as described in Example 4. The coating, drying, laminating was done as described in Example 4. Die cutting of the laminate and pouching of the patches were done as described in Example 4.

EXAMPLE 6

17.773 kg of selegiline HCl was dissolved in 34.55 kg 1,2 Propanediol under mild agitation using an air mixer. In a separate container, 12.046 kg of TEA was mixed with 12.046 kg of Ethyl Alcohol and mixed using an air mixer. In a separate 10 gallon mixer, 16.05 kg of GELVA 1753 was placed and 5.7 kg of Ethanol was mixed in. While mixing 3.65 kg of the TEA solution was added to the adhesive mix and mixed very well using Sharr mixer. 7.926 kg of selegiline HCl solution was added. The mixing was continued until an homogenous mixture was obtained. The final mixture was pumped into the centrifuge and crystals of TEA HCl were separated from the clear adhesive mix at 17,000 rpm. The clear adhesive mix containing Selegiline Free Base was collected in a separate container. The clear adhesive mixture was coated, dried and laminated as described in Example 4. Die cutting of the laminate and pouching of the patches were done as described in Example 4.

EXAMPLE 7

8.82 kg of selegiline HCl was dissolved in 16.92 kg of Propanediol in a stainless steel container under mild agitation using air mixer. 5.98 kg of TEA was mixed with 5.98 kg of Ethyl Alcohol in a stainless steel container under mild agitation using air mixer at 600 rpm. The contents of the two containers were then mixed together while mixing the selegiline HCl solution, the TEA solution was added gradually for about 10 minutes and then allowed to stand for a minimum of 8 hours. The above solution containing slurries of TEA HCl crystals were pumped to a centrifuge at a low rate. The centrate was separated and collected in a 10 gallon stainless steel container. The 10.91 kg of the centrate was dispersed in 59.3 kg of GELVA 1753 in a separate container using Sharr mixer. The mixing was continued until a homogenous adhesive mixture was realized. The adhesive mixture was coated, dried and laminated as described in Example 4. Die cutting of the laminate and pouching of the patches were done as described in Example 4.

EXAMPLE 8

18 grams of selegiline HCl was dissolved in 35 grams of 1.2 Propanediol at about 40°C in a 100 ml beaker under mild agitation using a magnetic stirrer. In a separate 150 ml beaker, 48.35 grams of GELVA 1753 adhesive was mixed with 17.33 grams of 1,2 Propanediol solution of selegiline HCl. After completion of mixing the adhesive mixture containing selegiline HCl was coated on a siliconized release liner using a laboratory knife-over-roll coater, dried in the oven and laminated to 1 mil polyester film. the coat weight of adhesive was about 100 mg per 10 cm^2. This was "Part A" of

the final patch. 24.4 grams of TEA were mixed with 20 ml of 1.2 Propanediol in a 100 ml beaker. In a separate 150 ml beaker 42.9 g of GELVA 1753 adhesive was mixed with 11.1g of 1,2 Propanediol solution of TEA. After completion of mixing, the adhesive mixture containing TEA was coated on a siliconized release linear using a laboratory knife-over-roll coater, and dried in the oven. The coat weight of adhesive was 50 mg per 10 cm^2. This was "Part B" of the final patch. After removing the release liner, the adhesive layer of "Part A" was laminated to adhesive layer "Part B". This laminate was allowed to age at room temperature for 3 days. After that, 10 cm^2 round patches were die cut and extracted in cyclohexane. The resulting free base of selegiline was analyzed. the conversion rate of selegiline HCl into selegiline free base was found to be 83%.

(Examples 9 through 18 relate to the formulations described in Table 3.)

EXAMPLE 9

1.07 kg of selegiline free base was added to 10.9 kg of GELVA 1753 acrylic polymeric adhesive; both were in liquid form. The resulting therapeutic adhesive formulation was coated onto a polyester release liner using a knife-over-roll technique at 93 mg/10 cm^2 target coat weight and the result was dried. The resulting therapeutic adhesive formulation included 18 mg/10 cm^2 (dry) of selegiline and 72 mg/cm^2 (dry) of adhesive. The dried film was then laminated onto a clear PET/EVA backing material. The resulting patches exhibited acceptable drug storage stability as defined by the U.S. Food and Drug Administration for this class of transdermal patches and drug delivery profile. The resulting patches were able to remain on skin for at least 24 hours, exhibited no peeling or oozing, left no adhesive residue on the skin when removed and were removable without injury to the skin. Note that this therapeutic adhesive formulation does not include solvents other than those which are part of the commercially available adhesive and that the system is anhydrous. Substantially, all liquids in the system are removed by drying. However, some trace amounts of either liquid or solvent may still be present.

EXAMPLE 10

130.5 parts of GELVA 1753 were mixed with 7.41 parts of selegiline free base and 20 parts of ethanol. The resulting therapeutic adhesive formulation was coated onto a polyester release liner and dried at 130°F for 4 minutes. The dried film was then laminated on a PET backing. The resulting patches included approximately 15 mg/10 cm^2 (dry). The resulting patches were able to remain on skin for at least 24 hours, exhibited no peeling or oozing, left no adhesive residue on the skin when removed and were removable without injury to the skin. This therapeutic adhesive formulation was produced with ethanol as an added solvent. That solvent, as well as the solvents found in the commercial adhesive were evaporated during drying. The resulting formulation contains substantially no water or non-volatile liquids after drying. However, some trace amounts of either liquid or solvent may still be present.

EXAMPLE 11

4.91 parts of selegiline free base and 20 parts by weight of ethanol were mixed with 136.75 parts of GELVA 1753 using the process described immediately in Example 10. The resulting patches contained a therapeutic formulation including approximately 10 mg/10 cm^2 (dry) of selegiline. The resulting patches were able to remain on skin for at least 24 hours, exhibited no peeling or oozing, left no adhesive residue on the skin when removed and were removable without injury to the skin.

EXAMPLE 12

109 parts of GELVA 1753 were mixed for one hour with 10 parts of propylene glycol, 5 parts of selegiline base and 20 parts of ethanol. The resulting therapeutic adhesive formulation was then coated onto a polyester release liner using a bench-top knife-over-roll coater and dried in an oven at 130°F for four minutes. The dried film was laminated onto a PET backing. The dried film had a composition of approximately 8% selegiline and 10% PG, i.e., approximately 8 mg/10 cm^2 (dry). Like all of the other formulations including GELVA 1753, this formulation was acceptable in terms of adhesive transfer and oozing. However, unlike the 10% and 15% formulations (each of which were formulated with a volatile solvent), the adhesive properties of the patches resulting from this batch were found to be unacceptable. The PG remained as part of the formulation after drying and acted with the selegiline in such a way that it retarded adhesion.

EXAMPLE 13

10 parts of PG, 5 parts of selegiline free base, 20 parts of ethanol, and 77.8 parts of DUROTAK 87-2194 were mixed and processed as described above in Example 10. As shown in Table 3, the formulation exhibited cohesive fail-

ure and adhesive transfer.

EXAMPLE 14

83.33 parts of DUROTAK 87-2516 adhesive, 10 parts of PG and 5 parts of selegiline base, as well as 20 parts of ethanol were mixed as previously discussed and coated, using a bench-top knife-over-roll device, on a polyester release liner and dried in an over at 130°F for four minutes. The dried film was then laminated to make PET backing. The resulting formulation contained approximately 8 mg/ 10 cm^2 (dry) of selegiline. As demonstrated in Table 3, patches made from this formulation exhibited adhesive transfer when applied to the skin.

EXAMPLE 15

85.37 parts of GELVA 788 adhesive, 10 parts of PG, 5 parts of selegiline base and 20 parts of ethanol were mixed an processed as described in Example 14. Again, the therapeutic adhesive formulation included approximately 8 mg/10 cm^2 (dry) of selegiline and again adhesive transfer was found to result when these patches were applied to skin.

EXAMPLE 16

1.07 kg of selegiline was added to 8.78 kg of GELVA 655 liquid adhesive with constant mixing. The resulting therapeutic adhesive formulation was then coated onto a silicone coated polyester release liner using a knife-over-roll technique at 93 mg^{+4}/10 cm^2 target coat weight and dried. The dried film was laminated to a PET/EVA backing. The resulting patches included 18 mg/10 cm^2 (dry) of selegiline. As demonstrated in Table 3, this formulation exhibited total adhesive failure.

EXAMPLE 17

0.7 kg of selegiline was mixed with 11.1 kg of DUROTAK 87-2852 liquid adhesive and processed as above in Example 16. A polyester release liner was used. The resulting therapeutic adhesive formulation included 12 mg/10 cm^2 (dry) of selegiline. As shown in Table 3, no adhesive transfer or oozing was realized. This material was made without any solvent other than that provided as part of the adhesive and it exhibited acceptable adhesion results as described in Example 9

EXAMPLE 18

1.07 kg of selegiline was added to 10.29 kg of adhesive and processed as above in Example 16. The resulting therapeutic adhesive formulation included 18 mg/10 cm^2 (dry) of selegiline. The release liner used was a silicone coated release liner. As shown in Table 3, this formulation, by virtue of the higher concentration of highly plasticizing drug, showed some softness.

Claims

1. A therapeutic adhesive formulation for use as a transdermal delivery system comprising:

   an adhesive material;
   a pharmaceutically active agent in protonated form;
   a nonaqueous solvent capable of dissolving said pharmaceutically active agent in either protonated or nonprotonated form;
   and a biocompatible deprotonating agent which is strong enough to substantially deprotonate said pharmaceutically active agent without causing irritation upon prolonged exposure to skin;
   said adhesive material, said pharmaceutically active agent, said nonaqueous solvent and said deprotonating agent being admixed into a substantially homogeneous mixture capable of being used to formulate a transdermal delivery patch for administration of said pharmaceutically active agent.

2. The therapeutic adhesive formulation of claim 1, wherein said adhesive material is selected from the group consisting of acrylics, silicones, polyisoalkylenes, rubbers, vinyl acetates, polyisobutylene rubber, polybutadiene, styrene-butadiene (or isoprene)-styrene block copolymer rubber, acrylic rubber, natural rubber, vinyl-based high molecular weight materials, polyvinyl acetate, polyvinyl alcohol, polyvinyl pyrrolidone; cellulose derivatives, polysaccharides, polyurethane elastomers and polyester elastomers.

3. The therapeutic adhesive formulation of claim 2, wherein said adhesive material is an acrylic adhesive.

4. The therapeutic adhesive formulation of claim 1, wherein said protonated form of said pharmaceutically active agent is selected from the group consisting of selegiline-HCl, propranolol-HCl, ketorolac-HCl, buprenorphine-HCl, scopolamine-HCl, terbutaline-HCl, clonidine-HCl, morphine-HCl, terazosin-HCl, prazosine-HCl, diliazem-HCl, verapamil-HCl, and ciproflaxocin-HCl.

5. The therapeutic adhesive formulation of claim 1, wherein said nonaqueous solvent is an alcohol.

6. The therapeutic adhesive formulation of claim 5, wherein said alcohol is a monoalcohol.

7. The therapeutic adhesive formulation of claim 6, wherein said monoalcohol is selected from the group consisting of ethanol, propanol, isopropanol, butanol, and tertbutyl alcohol.

8. The therapeutic adhesive formulation of claim 5, wherein said alcohol is a normal short chain polyol of between about 2 and about 4 carbons in length.

9. The therapeutic adhesive formulation of claim 8, wherein said alcohol is selected from the group consisting of 1,2 propanediol, 1,4 butanediol, glycerol, ethylene glycol, and propylene glycol.

10. The therapeutic adhesive formulation of claim 5, wherein said alcohol is a generally low molecular weight polyalkylene glycol having an average molecular weight of less than about 400.

11. The therapeutic adhesive formulation of claim 1, wherein said nonaqueous solvent is an acetate.

12. The therapeutic adhesive formulation of claim 1, wherein said deprotonating agent has a pK_b which is at least about 0.75 lower than the pK_b of the nonprotonated form of said pharmaceutically active agent.

13. The therapeutic adhesive formulation of claim 12, wherein said deprotonating agent has a pK_b which is between about 4 and about 10.

14. The therapeutic adhesive formulation of claim 13, wherein said deprotonating agent is selected from the group consisting of polymeric imines, aromatic imines, alkanol imines, polymeric amines, aromatic amines, alkanolamines, and alkyl-aryl amines.

15. The therapeutic adhesive formulation of claim 14, wherein said deprotonating agent is an alkanolamine selected from the group consisting of triethanolamine, diethanolamine, ethanolamine, and propanolamine.

16. The therapeutic adhesive formulation of claim 13, wherein said deprotonating agent is a polymeric imine selected from the group consisting of polyethylene imine polydimethylaminoethyl methacrylate and polyacryloamin.

17. The therapeutic adhesive formulation of claim 12 wherein said deprotonating agent has pharmaceutical activity.

18. The therapeutic adhesive formulation of claim 1, wherein the amount of said adhesive material ranges from between about 30 to about 85 percent by weight based on the weight of the total formulation.

19. The therapeutic adhesive formulation of claim 18, wherein the amount of said adhesive material ranges from between about 45 to about 75 percent by weight based on the weight of the total formulation.

20. The therapeutic adhesive formulation of claim 1, wherein the amount of said pharmaceutically active agent ranges from between about 0.1 to about 45 percent by weight based on the weight of the total formulation.

21. The therapeutic adhesive formulation of claim 20, wherein the amount of said pharmaceutically active agent ranges from between about 2 to about 20 percent by weight based on the weight of the total formulation.

22. The therapeutic adhesive formulation of claim 1, wherein the amount of said nonaqueous solvent ranges from between about 5 to about 30 percent by weight based on the total weight of the formulation.

23. The therapeutic adhesive formulation of claim 22, wherein the amount of said nonaqueous solvent rages from between about 10 to about 20 percent by weight based on the total weight of the formulation.

24. The therapeutic adhesive formulation of claim 1, wherein the amount of said biocompatible deprotonating agent is sufficient to substantially completely deprotonate said pharmaceutically active agent.

25. The therapeutic adhesive formulation of claim 24, wherein the amount of said biocompatible deprotonating agent is at least a stoichiometric amount when compared to the amount of said pharmaceutically active agent.

26. The therapeutic adhesive formulation of claim 1, wherein at least a portion of said biocompatible deprotonating agent is removed prior mixing with said adhesive material.

27. The therapeutic adhesive formulation of claim 1, wherein at least a portion of said biocompatible deprotonating agent is removed after mixing with said adhesive material.

28. The therapeutic adhesive formulation of claim 13 wherein said pharmaceutically active agent has a pK_b of between about 4.75 and about 11.

29. A therapeutic drug delivery patch for the transdermal delivery of a drug comprising:

a backing layer, a peelable cover layer sealably and removably associated with said backing layer and the therapeutic adhesive formulation of claim 1 disposed therebetween so as to be exposed for intimate contact with the skin of a patient when said peelable core layer is removed, said patch being substantially without a means to prevent any reaction between said pharmaceutically active agent and said biocompatible deprotonating agent.

30. A therapeutic drug delivery patch for the transdermal delivery of a drug comprising:

a backing layer, a peelable cover layer sealably and removably associated with said backing layer and the therapeutic adhesive formulation of claim 12 disposed therebetween so as to be exposed for intimate contact with the skin of a patient when said peelable core layer is removed, said patch being substantially without a means to prevent any reaction between said pharmaceutically active agent and said biocompatible deprotonating agent.

31. A therapeutic drug delivery patch of claims 29 or 30, further comprising a means for controlling the rate of a deprotonation reaction between said protonated pharmaceutically active agent and said deprotonating agent.

32. The therapeutic drug delivery patch of claim 31, wherein said means for controlling said deprotonating reaction includes providing a plurality of adhesive layers, at least one of said layers including said protonated pharmaceutically active agent and at least one other of said layers including said biocompatible deprotonating agent.

33. The therapeutic drug delivery patch of claim 31, wherein said means for controlling said deprotonation reaction is a viscosity modifier.

34. A method of producing an adhesive formulation for a therapeutic drug delivery patch adapted for the transdermal delivery of a drug comprising the steps of:

providing a pharmaceutically active agent in protonated form, whose corresponding nonprotonated form has a given pK_b which ranges from between about 4.75 and about 11;
dissolving said protonated pharmaceutically active agent in a nonaqueous solvent, said nonaqueous solvent being capable of dissolving said pharmaceutically active agent in both a protonated and nonprotonated forms;
reacting said dissolved pharmaceutically active agent with a biocompatible deprotonating agent which can substantially deprotonate said pharmaceutically active agent without causing irritation upon prolonged exposure to the skin, said biocompatible deprotonating agent having a pK_b which is at least about 0.75 lower than said pK_b of said pharmaceutically active agent in nonprotonated form, said deprotonated agent thereby becoming protonated; and
incorporating at least said deprotonated pharmaceutically active agent into an adhesive material so as to form a therapeutic adhesive formulation.

35. The method of claim 34 further comprising the step of separating at least a portion of said protonated deprotonating agent from said mixture of deprotonated pharmaceutically active agent, solvent and protonated deprotonating agent prior to incorporating said pharmaceutically active agent into said adhesive agent.

36. The method of claim 34 further comprising the step of separating at least a portion of said protonated deprotonating agent from said mixture of deprotonated pharmaceutically active agent, solvent and protonated deprotonating agent after incorporating said pharmaceutically active agent into said adhesive agent.

37. The method of claim 35 or 36 wherein said protonated deprotonating agent is in the form of a crystal or precipitate.

38. The method of claims 35 or 36 wherein said protonated deprotonating agent is separated by filtration.

39. The method of claims 35 or 36 wherein said protonated deprotonating agent is separated by centrifugation.

40. A therapeutic drug delivery patch for the percutaneous delivery of a drug comprising:

a backing layer;
a peelable cover layer sealably and removably associated with said backing layers;
and a therapeutic adhesive formulation comprising an adhesive material, a first pharmaceutically active agent in nonprotonated, a second pharmaceutically active agent in the form of a protonated salt having a pK_b which is higher than the pK_b of said first pharmaceutically active agent and a nonaqueous solvent capable of dissolving said first and said second pharmaceutically active agents in at least one form;
said therapeutic adhesive formulation being disposed between said backing layer and said peelable cover layer so as to be exposed for intimate contact with the skin of a patient once said peelable layer is removed.

41. A method of producing a therapeutic drug delivery patch for the percutaneous delivery of a drug comprising the steps of:

forming a first layer including at least one pharmaceutically active agent in protonated form;
forming a second layer including at least one deprotonating agent capable of completely deprotonating said pharmaceutically active agent in said first layer;
drying said first and said second layers;
placing said first and said second layers into intimate contact with one another;
and placing said first and said second layers into a therapeutic drug delivery patch.

42. The method of claim 41 wherein said deprotonating agent has a pK_b which is at least 0.75 lower than the pK_b of said pharmaceutically active agent.

43. The method of claim 42 wherein said deprotonating agent has a pK_b which is at least 1.0 lower than the pK_b of said pharmaceutically active agent.

44. The method of claim 41 wherein the pK_b of said pharmaceutically active agent ranges from between about 4.75 and about 11.

45. The method of claim 41 wherein the pK_b of said deprotonating agent ranges from between about 4 and about 10.

46. The method of claim 41 wherein at least one of said layers is an adhesive formulation.

47. The method of claim 41 wherein both of said layers are adhesive formulations.

48. The method of claim 41 further comprising the step of adjusting the diffusion characteristics of said first and said second layers so as to influence the rate of the deprotonating reaction between said pharmaceutically active agent disposing said first layer and said deprotonating agent disposed in said second layer.

49. A method of producing a transdermal therapeutic adhesive formulation including at least one highly plasticizing drug comprising the steps of:

providing between about 65% and about 97%, by weight, of an acrylic polymeric adhesive which includes between about 40% and about 90% of a C_4-C_{12} alkyl acrylate, between about 10% and about 40% by weight of a C_1-C_4 alkyl acrylate hardening monomer; between about 1% and about 20% by weight of a functionalizing monomer which facilitates crosslinking; and a crosslinking agent;

mixing said acrylic polymeric adhesive with a highly plasticizing drug in an amount which is sufficient to provide between about 3% and about 35% of said drug by weight based on the weight of the mixture when said transdermal therapeutic adhesive formulation is dry;

and crosslinking said acrylic polymeric adhesive to form a matrix capable of controlling the release of said highly plasticizing drug.

50. The method of claim 49 wherein between about 3% and about 70% of said drug is mixed with said acrylic polymeric adhesive.

51. The method of claim 49 wherein crosslinking is accomplished *in situ* by drying the mixture.

52. The method of claim 49 wherein said C_4-C_{12} alkyl acrylate is selected from the group consisting of 2-ethylhexyl acrylate, butyl acrylate, n-decyl, n-nonyl, 2 ethyoctyl, isooctyl and dodecyl-acrylate.

53. The method of claim 49 wherein said C_4-C_{12} alkyl acrylate is provided in an amount of between about 60% and about 80% by weight based on the total weight of the acrylic polymeric adhesive.

54. The method of claim 49 wherein said C_1-C_4 alkyl acrylate hardening monomer is selected from the group consisting of methyl acrylate, methyl methacrylate, ethylacrylate, ethyl methacrylate, hydroxyethyl acrylate and hydroxy propyl methacrylate.

55. The method of claim 49 wherein said C_1-C_4 alkyl acrylate hardening monomer is provided in an amount of between about 15% and about 30% by weight based on the total weight of the acrylic polymeric adhesive.

56. The method of claim 49 wherein said functionalizing monomer which facilitates crosslinking is selected from the group consisting of acrylic acid, hydroxy thylacrylate, hydroxy ethylacrylate, methacrylic acid, and acrylamide.

57. The method of claim 49 wherein said functionalizing monomer which facilitates crosslinking is provided in an amount of between about 1% and about 10% by weight based on the total weight of the acrylic polymeric adhesive.

58. The method of claim 49 wherein said C_4-C_{12} alkyl acrylate is selected from the group consisting of 2-ethylhexyl acrylate, butyl acrylate, n-decyl, n-nonyl, 2 ethyoctyl, isooctyl and dodecyl-acrylate and is provided in an amount of between about 60% and about 80% by weight based on the total weight of the acrylic polymeric adhesive and wherein said C_1-C_4 alkyl acrylate hardening monomer is selected from the group consisting of methyl acrylate, methyl methacrylate, ethylacrylate, ethyl methacrylate, hydroxyethyl acrylate and hydroxy propyl methacrylate and is provided in an amount of between about 15% and about 30% by weight based on the total weight of the acrylic polymeric adhesive.

59. The method of claim 58 wherein said highly plasticizing drug is selected from the group consisting of selegiline, fluoxetine, Des-methyl selegiline, tetracaine and chlorpheniramine.

60. The method of claim 59 wherein said highly plasticizing drug is provided in an amount of between about 3% and about 25% by weight of the therapeutic adhesive formulation.

61. The method of claim 60 wherein said highly plasticizing drug is provided in an amount of between about 3% and about 18% by weight of the therapeutic adhesive formulation.

62. The method of claim 49 wherein said crosslinking agent is selected from the group consisting of butyl titinate, polybutyl titinate, aluminum isopropoxide, aluminum zinc acetate, multivalent metals, methylol ureas and melamines.

63. The method of claim 49 wherein said crosslinking agent is provided in an amount of between about 0.005% and about 2% based on the total weight of the acrylic polymeric adhesive.

64. A therapeutic adhesive formulation comprising:

between about 65% and about 97%, by weight, of an acrylic polymeric adhesive which includes between about 40% and about 90% of a C_4-C_{12} alkyl acrylate, between about 10% and about 40% by weight of a C_1-C_4 alkyl acrylate hardening monomer; between about 1% and about 20% by weight of a functionalizing monomer which facilitates crosslinking; and a crosslinking agent; and

between about 3% and about 35% by weight, based on the weight of said mixture, of a highly plasticizing drug.

65. The therapeutic adhesive formulation of claim 64 wherein said C_4-C_{12} alkyl acrylate is selected from the group consisting of 2-ethylhexyl acrylate, butyl acrylate, n-decyl, n-nonyl, 2 ethyoctyl, isooctyl and dodecyl-acrylate.

66. The therapeutic adhesive formulation of claim 64 wherein said C_4-C_{12} alkyl acrylate is provided in an amount of between about 60% and about 80% by weight based on the weight of the adhesive.

67. The therapeutic adhesive formulation of claim 65 wherein said C_1-C_4 alkyl acrylate hardening monomer is selected from the group consisting of methyl acrylate, methyl methacrylate, ethylacrylate, ethyl methacrylate, hydroxyethyl acrylate and hydroxy propyl methacrylate.

68. The therapeutic adhesive formulation of claim 64 wherein said C_1-C_4 alkyl acrylate hardening monomer is provided in an amount of between about 15% and about 30% by weight based on the weight of the adhesive.

69. The therapeutic adhesive formulation of claim 64 wherein said functionalizing monomer which facilitates crosslinking is selected from the group consisting of acrylic acid, hydroxy thylacrylate, hydroxy ethylacrylate, methacrylic acid and acrylamide.

70. The therapeutic adhesive formulation of claim 64 wherein said functionalizing monomer which facilitates crosslinking is provided in an amount of between about 3% and about 8% by weight based on the weight of the adhesive.

71. The therapeutic adhesive formulation of claim 64 wherein said highly plasticizing drug is selected from the group consisting of selegiline, fluoxetine, Des-methyl selegiline, tetracaine and chlorpheniramine.

72. The therapeutic adhesive formulation of claim 71 wherein said highly plasticizing drug is selegiline.

73. The therapeutic adhesive formulation of claim 64 wherein said highly plasticizing drug is provided in an amount of between about 3% and about 25% by weight of the finished adhesive and drug mixture.

74. The therapeutic adhesive formulation of claim 73 wherein said highly plasticizing drug is provided in an amount of between about 3% and about 18% by weight of the finished adhesive and drug mixture.

75. The therapeutic adhesive formulation of claim 74 wherein said crosslinking agent is selected from the group consisting of butyl titinate, polybutyl titinate, aluminum isopropoxide, butyl titinate, aluminum zinc acetate, multivalent metals, methylol ureas and melamines

76. The therapeutic adhesive formulation of claim 75 wherein said crosslinking agent is provided in an amount of between about 0.005% and about 2.0% based on the weight of the adhesive.

77. The therapeutic adhesive formulation of claim 64 wherein said formulation is anhydrous and substantially free of volatile solvents after drying.

78. A drug containing and releasing adhesive mixture comprising:

between about 65 % and about 97 %, by weight of an acrylic polymeric adhesive which includes between about 60% and about 80% of a C_4-C_{12} alkyl acrylate selected from the group consisting of 2-ethylhexyl acrylate, butyl acrylate, n-decyl, n-nonyl, 2 ethyoctyl, isooctyl and dodecyl-acrylate; between about 15% and about 30% by weight of a C_1-C_4 alkyl acrylate hardening monomer selected from the group consisting of methyl acrylate, methyl methacrylate, ethylacrylate, ethyl methacrylate, hydroxyethyl acrylate and hydroxy propyl methacrylate; between about 1% and about 20% by weight of a functionalizing monomer which facilitates crosslinking selected from the group consisting of acrylic acid, hydroxy thylacrylate, hydroxy ethylacrylate, methacrylic acid and acrylamide; and a crosslinking agent provided in an amount of between about 0.005% and about 2.0%; and

between about 3% and about 35% by weight, based on the weight of said mixture, of a highly plasticizing drug selected from the group consisting of selegiline, fluoxetine, Des-methyl selegiline, tetracaine and chlorpheniramine.

79. The therapeutic adhesive formulation of claim 78 wherein said highly plasticizing drug is selegiline.

80. The therapeutic adhesive formulation of claim 78 which does not include a solvent after drying.

81. A method of producing a therapeutic adhesive formulation for use in a transdermal patch comprising the steps of: selecting an acrylic polymeric adhesive which is suitable for use with highly plasticizing drugs based upon it's content of between about 40% and about 90% of a C_4-C_{12} alkyl acrylate and between about 10% and about 40% by weight of a C_1-C_4 alkyl acrylate hardening monomer; and mixing said acrylic polymeric adhesive with a highly plasticizing drug in an amount of between about 3% and about 65% by weight based on the weight of said mixture.

82. The method of producing a therapeutic adhesive formulation for use in a transdermal patch of claim 81 further comprising the step of: selecting an acrylic polymeric adhesive which is suitable for use with highly plasticizing drugs based upon it's content of between about 40% and about 90% of a C_4-C_{12} alkyl acrylate and between about 10% and about 40% by weight of a C_1-C_4 alkyl acrylate hardening monomer; between about 1% and about 20% by weight of a functionalizing monomer which facilitates crosslinking; and a crosslinking agent.

83. The method of producing a therapeutic adhesive formulation for use in a transdermal patch of claim 82 further comprising the step of: drying said mixture of said acrylic polymeric adhesive and said highly plasticizing drug to form a matrix capable of controlling the release of said highly plasticizing drug when placed in a transdermal patch and applied to the skin of a patient and which will not ooze, suffer from adhesive failure, fall off of a patient prematurely or be difficult to remove when necessary.

84. A transdermal drug delivery system comprising a blend of:

(a) one or more polymers; and
(b) a therapeutically effective amount of one or more drugs, at least one of which is of low molecular weight and liquid at or about room temperatures,
wherein said system is substantially free of water and liquids having a normal boiling point (i) below processing temperatures and (ii) equal to or greater than the normal boiling points of the low molecular weight drugs.

FIG. 1

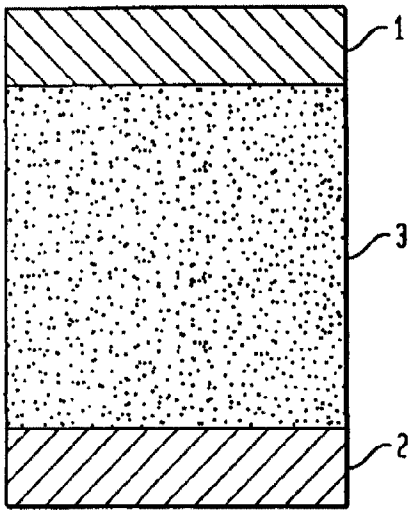
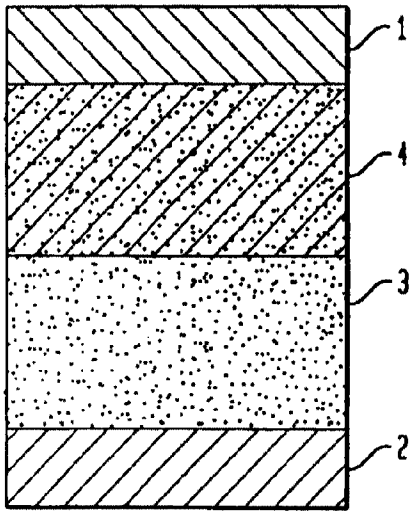


FIG. 2



Electronic Acknowledgement Receipt

EFS ID:	25600072
Application Number:	14870574
International Application Number:	
Confirmation Number:	5148
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Customer Number:	22428
Filer:	Courtenay C. Brinckerhoff/Christine Arthur
Filer Authorized By:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-1160
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Filing Date:	30-SEP-2015
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Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		ids.pdf	1668208 8b8fa8cf12822b576473aa0cccb085284c667cb0	yes	23

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	3
	Information Disclosure Statement (IDS) Form (SB08)	4	9
	Request for Corrected Filing Receipt	10	11
	Application Data Sheet	12	17
	Assignee showing of ownership per 37 CFR 3.73	18	19
	Power of Attorney	20	20
	Oath or Declaration filed	21	23

Warnings:					
Information:					
2	Foreign Reference	EP0887075A2.pdf	2535715 604d6a6e8e1cbcac4d9f10f1c5716397ab006faf	no	24
Warnings:					
Information:					
3	Non Patent Literature	Rietschel.pdf	236307 d6db30f0b4690112d98f1b72895c05e1c63060e4	no	6
Warnings:					
Information:					
4	Non Patent Literature	Feldstein.pdf	1099396 49b79b29d9139d965eded5fd7d40da50198b20ef	no	17
Warnings:					
Information:					
5	Non Patent Literature	Pfister.pdf	6397961 3d3a8d29d5afd1887ef52166f716b9673a352042	no	82
Warnings:					
Information:					
6	Non Patent Literature	DowCorning.pdf	245943 a3de3e544210415d6aeb79cf834d9655dcf5afe6	no	4
Warnings:					
Information:					

7	Non Patent Literature	Janischemail.pdf	110542 c520b7caa686d1992b5b77a34c2bde2baf9d3c64	no	1
Warnings:					
Information:					
8	Non Patent Literature	Manngold.pdf	146046 7f2c585685d631be322b3622336dae6a661a61c5	no	1
Warnings:					
Information:					
9	Non Patent Literature	Novenresponse.pdf	70608 8731a9f9e47d3ee33b9f01abfdd51f31691e4237	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	12510726		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	14/870,574
Filing Date:	9/30/2015
Examiner:	Unassigned
Art Unit:	Unassigned
Confirmation Number:	5148

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

Applicant requests that, in accordance with 37 CFR §1.98(d), the Examiner review all applications relied on for an earlier effective filing date under 35 U.S.C. 120, including Application No. 12/216,811, filed 7/10/2008; Application No. 13/553,972, filed 7/20/2012; Application No. 14/024,985, filed 9/12/2013; and Application No. 14/738,255, filed 6/12/2015,

for copies of references of record therein that are not being provided here, although Applicant would be pleased to provide copies of any such documents at the Examiner's request.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicant does not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), within three (3) months of the filing date of the application.

RELEVANCE OF LISTED DOCUMENTS

Documents A1-A4 are the granted parent patent and published parent applications. Documents A5-A63 and A65-A100 are references and Office Actions of record in Documents A1-A4.

Documents A23, A27, A64, and A101-A107 were cited in an opposition filed in the corresponding European patent.

Documents A5-A27 are also granted patents and published applications with common or overlapping inventorship and/or ownership.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date April 26, 2016 By Courtenay C. Brinckerhoff

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/870,574	09/30/2015	Juan Mantelle	041457-1160

CONFIRMATION NO. 5148

POA ACCEPTANCE LETTER

22428
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

OC000000082612825

Date Mailed: 05/03/2016

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/26/2016.

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

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

/mmasfaw/

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/870,574	09/30/2015	1611	2020	041457-1160	20	4

CONFIRMATION NO. 5148

CORRECTED FILING RECEIPT

22428
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

OC000000082812828

Date Mailed: 05/03/2016

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Juan Mantelle, Miami, FL;

Applicant(s)

NOVEN PHARMACEUTICALS, INC., Miami, FL

Assignment For Published Patent Application

NOVEN PHARMACEUTICALS, INC., Miami, FL

Power of Attorney: The patent practitioners associated with Customer Number 22428

Domestic Priority data as claimed by applicant

This application is a CON of 14/738,255 06/12/2015
which is a CON of 14/024,985 09/12/2013
which is a CON of 13/553,972 07/20/2012
which is a CON of 12/216,811 07/10/2008 PAT 8231906

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: No

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

If Required, Foreign Filing License Granted: 10/14/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/870,574**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

Preliminary Class

424

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

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

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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

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

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

NOT GRANTED

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/870,574	09/30/2015	Juan Mantelle	041457-1160	5148

22428 7590 09/07/2016

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER
JAVIER, MELISSA L

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
09/07/2016	ELECTRONIC

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

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

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

ipdocketing@foley.com

Office Action Summary	Application No. 14/870,574	Applicant(s) MANTELLE, JUAN	
	Examiner Melissa Javier	Art Unit 1611	AIA (First Inventor to File) Status No

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *4/26/2016*.

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

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

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

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

Disposition of Claims*

5)☒ Claim(s) *1-20* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

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

9)☒ Claim(s) *1-20* are subject to restriction and/or election requirement.

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-13, drawn to a transdermal drug delivery system, classified in A61K9/7084.

II. Claims 14 and 15, drawn to a method for administering estradiol, classified in A61M35/00.

III. Claims 16-20, drawn to a method of making a transdermal drug delivery system for administering estradiol, classified in A61K9/1635.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the product can be used in a materially different method, such as measuring the in vitro release of the drug from the polymer matrix.

Inventions I and III are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2)

that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the product can be made by a materially different method, such as the applying the adhesive separately from the polymer matrix containing the estradiol.

Inventions II and III are directed to related methods. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed are direct to a method for administering estradiol, which includes the application of a monolithic transdermal drug delivery system to the skin or mucosa of a subject in there thereof not present in the method of making a monolithic transdermal drug delivery system. The method of making a monolithic transdermal drug delivery system includes the step of forming a polymer matrix that is not present in the method of administering estradiol. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Restriction for examination purposes as indicated is proper because all the inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter; and

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is

the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all

claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Javier whose telephone number is (571)270-7430. The examiner can normally be reached on Monday-Thursday, 8am-6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bethany Barham can be reached on 571-272-6175. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Melissa Javier/
Examiner, Art Unit 1611

Atty. Dkt. No. 041457-1160

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	14/870,574
Filing Date:	9/30/2015
Examiner:	Javier
Art Unit:	1611
Confirmation Number:	5148

RESPONSE TO RESTRICTION REQUIREMENT AND PRELIMINARY AMENDMENT

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

Commissioner:

This paper responds to the Restriction Requirement mailed September 7, 2016, and includes further preliminary amendments to the claims. Applicant hereby petitions for an extension of time to make this response timely. If any additional fees are required for this application, the Commissioner is hereby authorized to charge them to Deposit Account 19-0741.

Amendments to the Claims are reflected in the listing of claims which begins on page 2.

Remarks/Arguments begin on page 5.

Please amend the application as follows:

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1. – 20. (Canceled)

21. (New) A monolithic transdermal drug delivery system for estradiol, consisting of (i) a backing layer, (ii) a single adhesive polymer matrix layer defining an active surface area and, optionally, (iii) a release liner,

wherein the single adhesive polymer matrix layer comprises 2-25% by weight acrylic adhesive, 45-70% by weight silicone adhesive, 2-25% by weight soluble PVP, 5-15% by weight penetration enhancer, and 0. 1-10% by weight estradiol as the only drug, and

wherein the coat weight of the adhesive polymer matrix layer is adjusted such that the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux of from about 0.0125 to about 0.05 $mg/cm^2/day$, based on the active surface area.

22. (New) The transdermal drug delivery system of claim 21, wherein the penetration enhancer comprises oleyl alchol.

23. (New) The transdermal drug delivery system of claim 21, wherein the penetration enhancer comprises dipropylene glycol.

24. (New) The transdermal drug delivery system of claim 21, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

25. (New) The transdermal drug delivery system of claim 21, wherein the acrylic adhesive and silicone adhesive are present in a ratio of from about 1:2 to about 1:6, based on the total weight of the acrylic and silicone adhesives.

26. (New) The transdermal drug delivery system of claim 21, wherein the system is effective to deliver a therapeutically effective amount of estradiol over a period of time selected from the

group consisting of at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days and at least 7 days.

27. (New) The transdermal drug delivery system of claim 21, wherein the system is effective to deliver an amount of estradiol selected from the group consisting of about 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day.

28. (New) The transdermal drug delivery system of claim 21, wherein the system achieves an estradiol flux of from about 0.0125 to about 0.0167 $mg/cm^2/day$, based on the active surface area.

29. (New) The transdermal drug delivery system of claim 21, wherein the system achieves an estradiol flux of about 0.0125 $mg/cm^2/day$, based on the active surface area.

30. (New) The transdermal drug delivery system of claim 21, wherein the system achieves an estradiol flux of about 0.0133 $mg/cm^2/day$, based on the active surface area.

31. (New) The transdermal drug delivery system of claim 21, wherein the system achieves an estradiol flux of about 0.015 $mg/cm^2/day$, based on the active surface area.

32. (New) The transdermal drug delivery system of claim 21, wherein the system achieves an estradiol flux of about 0.0167 $mg/cm^2/day$, based on the active surface area.

33. (New) The transdermal drug delivery system of claim 21, wherein the system achieves an estradiol flux of about 0.0175 $mg/cm^2/day$, based on the active surface area.

34. (New) A method of administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a transdermal drug delivery system according to claim 21.

35. (New) A method of making a transdermal drug delivery system according to claim 21, comprising forming an adhesive polymer matrix comprising 2-25% by weight acrylic adhesive, 45-70% by weight silicone adhesive, 2-25% by weight soluble PVP, 5-15% by weight penetration enhancer, and 0. 1-10% by weight estradiol as the only drug, and applying the adhesive polymer matrix to support layer to form a single adhesive polymer matrix layer,

wherein the coat weight of the adhesive polymer matrix is adjusted such that the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux of from about 0.0125 to about 0.05 mg/cm^2/day, based on the active surface area.

REMARKS

Claims 1-20 are canceled without prejudice or disclaimer. Applicant reserves the right to pursue any canceled subject matter in this application or in one or more continuing applications with the same rights of priority as the instant application.

New claims 21-35 are added to recite specific embodiments described throughout the specification as filed. No new matter is introduced by these amendments.

In response to the Restriction Requirement, Applicant elects the subject matter of Group I. At least new claims 21-33 are directed to this subject matter. Although claims 34 and 35 are directed to subject matter classified in Group II and Group III, respectively, since they depend from claim 21 they are presented for examination, or at least as eligible for rejoining.

Applicants respectfully await examination on the merits.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution.

Respectfully submitted,

Date March 6, 2017

By Courtenay C Brinckerhoff

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288

Atty. Dkt. No. 041457-1160

DW
9

414IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Application No.: 14/870,574

Filing Date: 9/30/2015

Examiner: Melissa L. Javier

Art Unit: 1615

Confirmation No.: 5148

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicant does not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), before the mailing date of the first Office Action on the merits.

RELEVANCE OF LISTED DOCUMENTS

Documents B1-B17 are references and Office Actions of record in the parent and co-pending applications previously made of record.

Document B18 is a Decision issued in an Opposition of a corresponding European patent. Although the patent was revoked because certain claim language not present in the pending claims was found to constitute an impermissible generalization of the original disclosure, the EPO Opposition Division rejected the Opponent's prior art and enablement-type arguments.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account Number 19-0741.

Respectfully submitted,

Date March 6, 2007

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: March 6, 2017

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	14/870,574
Filing Date	9/30/2015
First Named Inventor	Juan Mantelle
Art Unit	1615
Examiner Name	Melissa L. Javier
Attorney Docket Number	041457-1160

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number / Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document / Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document / Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	B1.	TOOLE ET AL., "Evaluation of irritation and sensitisation of two 50 µg/day oestrogen patches," Maturitas, Vol. 43, pp. 257-263, December 2002.	
	B2.	MARTY, "New trends in transdermal technologies: Development of the skin patch, Menorest®," International Journal of Gynecology & Obstetrics, Vol. 52, Suppl. 1, pp. S17-S20, March 1996.	
	B3.	MANTELLE, "DOT Matrix® Technology," Modified-Release Drug Technology, Rathbone et al., eds., Chapter 30, pp. 405-415, May 28, 2008.	
	B4.	NOVARTIS, "Estraderm®," Prescribing information, June 2004.	
	B5.	NOVARTIS, "Vivelle®," Prescribing information, June 2004.	
	B6.	NOVARTIS, "Vivelle-Dot®," Prescribing information, June 2004.	
	B7.	BAYER HEALTHCARE, "Climara®," Prescribing information, 2007	
	B8.	3M PHARMACEUTICALS, "Menostar™," Prescribing information, June 2004.	

Examiner Signature		Date Considered	

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/870,574
Date Submitted: March 6, 2017				**Filing Date**	9/30/2015
				First Named Inventor	Juan Mantelle
				Art Unit	1615
(use as many sheets as necessary)				Examiner Name	Melissa L. Javier
Sheet	2	of	2	Attorney Docket Number	041457-1160

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	B9.	WATSON PHARMA, INC., "Alora®," Prescribing information, May 2005.	
	B10.	SERONO LABORATORIES, INC., "Esclim®," Prescribing information, August 1998.	
	B11.	Office Action issued on 05/05/2016 in application number 14/024,985 (US 2014-0200530)	
	B12.	Notice of Allowance issued on 09/15/2016 in application number 14/024,985 (US 2014-0200530)	
	B13.	Notice of Allowance issued on 01/10/2017 in application number 14/024,985 (US 2014-0200530)	
	B14.	Office Action issued on 05/05/2016 in application number 13/553,972 (US 2013-0156815)	
	B15.	Notice of Allowance issued on 08/26/2016 in application number 13/553,972 (US 2013-0156815)	
	B16.	Notice of Allowance issued on 12/09/2016 in application number 13/553,972 (US 2013-0156815)	
	B17.	Office Action issued on 04/29/2016 in application number 14/738,255 (US 2015-0272905)	
	B18.	Decision in European Opposition issued on 02/14/2017 in application number EP 09 790 211.8.	

Examiner Signature		Date Considered	

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/870,574	Filing Date 09/30/2015	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

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

APPLICATION AS AMENDED – PART II

AMENDMENT **03/06/2017**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 15	Minus	** 20	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

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

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

SLIE
SHARON M. WEST

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

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/870,574	Filing Date 09/30/2015	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

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

APPLICATION AS AMENDED – PART II

AMENDMENT **03/13/2017**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 15	Minus	** 20	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

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

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

SLIE
SHARON M. WEST

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/870,574	09/30/2015	Juan Mantelle	041457-1160	5148

22428 7590 06/15/2017

Foley & Lardner LLP
3000 K STREET N.W.
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WASHINGTON, DC 20007-5109

EXAMINER	
FISHER, MELISSA L	

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
06/15/2017	ELECTRONIC

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

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

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

ipdocketing@foley.com

Office Action Summary	Application No. 14/870,574	Applicant(s) MANTELLE, JUAN	
	Examiner Melissa Fisher	Art Unit 1611	AIA (First Inventor to File) Status No

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *3/6/2017*.

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

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

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

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

Disposition of Claims*

5)☒ Claim(s) *21-35* is/are pending in the application.

5a) Of the above claim(s) *34 and 35* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *21-33* is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Election/Restrictions

Applicant's election of the subject matter of Group I, which reads on new claims 21-33, in the reply filed on 3/6/2017 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.01(a)).

Claims 21-33 will be examined on the merits herein.

Claims 34 and 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 3/6/2017.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed 4/26/2016 and 3/6/2017 have been considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-33 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 21 recites “wherein the coat weight of the adhesive polymer matrix layer is adjusted such that the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux of from about 0.0125 to about 0.05mg/cm^2/day, based on the active surface area." The instant specification does not teach that the coat weight of the adhesive polymer matrix layer is adjusted. The instant specification teaches “the polymer matrix has a coat weight of greater than about 10 mg/cm^2” and “the polymer matrix has a coat weight selected from the group consisting of about 12.5 and about 15 mg/cm^2” (see [0008]). The only components that are taught to be "adjusted” are “the ratio of resin to polymer can be adjusted in order to modify the physical properties of polysiloxane adhesives” (see [0049]) and “[t]he amount of acrylic-based polymer and silicone-based polymer can be adjusted so as to modify the saturation concentration of the drug in the polymer matrix in order to affect the rate of delivery of the drug from the system and through the skin” (see [0057]). This is a new matter rejection.

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—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.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-33 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 21 recites “wherein the coat weight of the adhesive polymer matrix layer is adjusted such that the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux of from about 0.0125 to about 0.05mg/cm^2/day, based on the active surface area."

The limitation "the coat weight of the adhesive polymer matrix layer" in the seventh line. There is insufficient antecedent basis for this limitation in the claim.

Further, the phrase “wherein the coat weight of the adhesive polymer matrix layer is adjusted such that…” is not defined the instant specification as to what constitutes “adjusted such that”, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claims. Specifically, it is unclear what structure is required to achieve the claimed functional characteristics of estradiol concentration and flux that are claimed.

Claims 22-33 are rejected for depending on an indefinite base claim.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

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

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived 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 pre-AIA 35 U.S.C. 103(a) 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.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 21-33 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Kanios (US 6638528) in view of Nuwayser (US 4624665).

Kanios teaches compositions and methods for the transdermal delivery of active agents (see abstract). Kanios teaches matrix-type transdermal delivery systems that comprises an adhesive matrix composition layer, a release liner and a backing layer (see Fig. 1 and col 35, lines 1-6) wherein the matrix preferably comprises estradiol (see column 9) in a preferred amount from about 0.1% to about 10%. It is noted that Applicants' specification defines "monolithic" to include a backing layer and/or release liner (see page 10). Kanios teaches an example with 48.6% polysiloxane adhesive (i.e. a silicone adhesive), 20% polyacrylate adhesive, 10% polyvinylpyrrolidone, 8% dipropylene glycol (a penetration enhancer), 6% oleyl alcohol (a penetration enhancer), and 2.4% estradiol (see Column 36, Table II, example 6). Kanios teaches examples where estradiol is the only drug (see Examples 3-9).

Kanios does not teach greater than 0.156mg/cm^2 of estradiol in the matrix or explicitly teach an estradiol flux that is 0.0125mg/cm^2/day to about 0.050mg/cm^2/day (although it is noted that Kanios teaches the flux of estradiol in μg/cm^2/hr, see Figures 2-6).

Nuwayser teaches a transdermal drug delivery system (see abstract). Nuwayser teaches an estradiol patch (i.e. estradiol as the only drug) (see column 11, lines 60-62). Nuwayser teaches that the flux rates of estradiol are fairly high (see Table 1 and column 6, lines 8-10). Nuwayser teaches that flux rates depend on the concentration of the applied substance in the vehicle (see column 6, lines 10-15). Nuwayser teaches that the size of an estradiol-containing patch system is 2.4cm^2 (see column 13, lines 25-27), which is about 60% of 3.75cm^2.

Regarding claim 21, one of ordinary skill in the art at the time that the invention was made would be motivated to manipulate the amount of estradiol in the matrix in order to control the rate of the flux, as Nuwayser teaches that flux rates depend on the concentration of the applied substance in the vehicle (see column 6, lines 10-15). Additionally, it is noted that Kanios teaches the same polymer matrix components in the same amounts as instantly claimed and the same weight percentage of estradiol as instantly claimed (see instant claims 21-26). A person of ordinary skill in the art would reasonably expect the use of the same polymer matrix components in the same amounts as well as the same weight percentage of estradiol to produce a product with the instantly claimed flux.

Regarding claim 22, Kanios teaches 6% oleyl alcohol (a penetration enhancer), (see Column 36, Table II, example 6).

Regarding claim 23, Kanios teaches 8% dipropylene glycol (a penetration enhancer) (see Column 36, Table II, example 6).

Regarding claim 24, Kanios teaches 8% dipropylene glycol (a penetration enhancer) and 6% oleyl alcohol (a penetration enhancer) (see Column 36, Table II, example 6).

Regarding claim 25, Kanios teaches an example with 48.6% polysiloxane adhesive (i.e. a silicone adhesive) and 20% polyacrylate adhesive (see Column 36, Table II, example 6), which is a ratio of acrylic adhesive to silicon adhesive of 1:2.43.

Regarding claim 26, Kanios teaches the delivery of estradiol for at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days and at least 7 days (see Figure 2).

Regarding claim 27, one of ordinary skill in the art at the time that the invention was made would be motivated to manipulate the amount of estradiol in the matrix in order to control the amount of estradiol delivered in order to control the therapeutic dose. Additionally, it is noted that Kanios teaches the same polymer matrix components in the same amounts as instantly claimed and the same weight percentage of estradiol as instantly claimed (see instant claims 21-26). A person of ordinary skill in the art would reasonably expect the use of the same polymer matrix components in the same amounts as well as the same weight percentage of estradiol to produce a product with the instantly amounted delivered per day.

Regarding claims 28-33, one of ordinary skill in the art at the time that the invention was made would be motivated to manipulate the amount of estradiol in the matrix in order to control the rate of the flux, as Nuwayser teaches that flux rates depend on the concentration of the applied substance in the vehicle (see column 6,

lines 10-15). Additionally, it is noted that Kanios teaches the same polymer matrix components in the same amounts as instantly claimed and the same weight percentage of estradiol as instantly claimed (see instant claims 21-26). A person of ordinary skill in the art would reasonably expect the use of the same polymer matrix components in the same amounts as well as the same weight percentage of estradiol to produce a product with the instantly claimed flux.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory

double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 21-33 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 45-54 and 59-66 of copending Application No. 14/738255.

Although the claims at issue are not identical, they are not patentably distinct from each other because copending Application No. 14/738255 is drawn to a monolithic transdemiai drug delivery system for estradiol, consisting of: (i) a backing layer; (ii) an

adhesive polymer matrix layer comprising an adhesive polymer matrix comprising estradiol as the only drug and defining an active surface area, and optionally, (iii) a release liner, wherein the adhesive polymer matrix layer includes from about 0.195 to about 0.260 mg/cm2 estradiol and achieves an estradiol flux of from about 0.0125 to about 0.0167 mg/em2/day based on the active surface area. Further, the adhesive polymer matrix layer comprises a polymer matrix comprising about 2-25% by weight acrylic adhesive, about 45-70% by weight silicone adhesive, about 2-25% by weight soluble P VP, about 5-15% penetration enhancer, and about 0.1-10% by weight estradiol, all based on the total dry weight of the polymer matrix.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 21-33 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-9 and 21-26 of copending Application No. 14/024985.

Although the claims at issue are not identical, they are not patentably distinct from each other because copending Application No. 14/024985 is drawn to a amonolithic transdermal drug delivery system for estradiol, consisting of (i) a backing layer, (ii) a single adhesive polymer matrix layer defining an active surface area and, optionally, (iii) a release liner, wherein the single adhesive polymer matrix layer comprises an adhesive polymer matrix comprising estradiol as the only drug, wherein the adhesive polymer matrix layer has a coat weight of greater than about 10 mg/cm2

and includes greater than 0.156 mg/cm2 estradiol, and the system achieves an estradiol flux of from about 0.0125 to about 0.05 mg/cm2/day, based on the active surface area. Further, the adhesive polymer matrix comprises about 2-25% by weight acrylic adhesive, about 45-70% by weight silicone adhesive, about 2-25% by weight soluble PVP, about 5-15% penetration enhancer, and about 0.1-10% by weight estradiol, all based on the total dry weight of the adhesive polymer matrix.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claim 21-33 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 8231906.

Although the claims at issue are not identical, they are not patentably distinct from each other because U.S. Patent No. 8231906 is drawn to a monolithic transdermal drug delivery system for estradiol, comprising a single polymer matrix layer defining an active surface area and comprising a polymer matrix comprising estradiol as the only drug, wherein the polymer matrix layer has a coat weight selected from the group consisting of 12.5 mg/cm2 and 15 mg/cm2, includes greater than 0.156 mg/cm2 estradiol, and achieves an estradiol flux that is greater than 0.01 mg/cm2/day, based on the active surface area. Further, the polymer matrix comprises about 2-25% by weight acrylic adhesive, about 45-70% by weight silicone adhesive, about 2-25% by weight soluble PVP, and about 5-15% penetration enhancer, all based on the total dry weight of the polymer matrix.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Fisher whose telephone number is (571)270-7430. The examiner can normally be reached on Monday-Friday, 8am-5pm.

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

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bethany Barham can be reached on 571-272-6175. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Melissa Fisher/
Primary Examiner, Art Unit 1611

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/870,574	MANTELLE, JUAN	
	Examiner	Art Unit	
	Melissa Fisher	1611	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Melissa Fisher*.

(2) *Courtenay Brinckerhoff*.

(3) *Richard Guy*.

(4) _____.

Date of Interview: *6/8/2017*.

Type: ☐ Telephonic ☐ Video Conference
☒ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *None*.

Identification of prior art discussed: *None*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussed the attached agenda.

Specifically, Applicant's representative and Dr. Guy explained how the included data supported the unexpected results that increasing the coat weight of the drug-containing adhesive layer resulted in an increased flux per unit area, and permitted the development of smaller transdermal drug delivery systems that achieve comparable daily dosages.

The Examiner noted that the information would be considered, but would need to be filed as a Declaration on the record for the instant application .

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

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

☒ Attachment

/Melissa Fisher/ Primary Examiner, Art Unit 1611	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Notice of References Cited	Application/Control No. 14/870,574	Applicant(s)/Patent Under Reexamination MANTELLE, JUAN	
	Examiner Melissa Fisher	Art Unit 1611	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-6,638,528 B1	10-2003	Kanios; David	A61K9/7069	424/443
*	B	US-4,624,665 A	11-1986	Nuwayser; Elie S.	A61K9/7084	424/448
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Atty. Dkt. No. 041457-1160

414IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Application No.: 14/870,574

Filing Date: 9/30/2015

Examiner: Melissa L. Javier

Art Unit: 1615

Confirmation No.: 5148

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicant does not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.L.F./ 0141

Atty. Dkt. No. 041457-1160

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), before the mailing date of the first Office Action on the merits.

RELEVANCE OF LISTED DOCUMENTS

Documents B1-B17 are references and Office Actions of record in the parent and co-pending applications previously made of record.

Document B18 is a Decision issued in an Opposition of a corresponding European patent. Although the patent was revoked because certain claim language not present in the pending claims was found to constitute an impermissible generalization of the original disclosure, the EPO Opposition Division rejected the Opponent's prior art and enablement-type arguments.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account Number 19-0741.

Respectfully submitted,

Date March 6, 2007

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.L.F./

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/870,574
Date Submitted: March 6, 2017				**Filing Date**	9/30/2015
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	1615
				Examiner Name	Melissa L. Javier
Sheet	1	of	2	Attorney Docket Number	041457-1160

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	B1.	TOOLE ET AL., "Evaluation of irritation and sensitisation of two 50 µg/day oestrogen patches," Maturitas, Vol. 43, pp. 257-263, December 2002.	
	B2.	MARTY, "New trends in transdermal technologies: Development of the skin patch, Menorest®," International Journal of Gynecology & Obstetrics, Vol. 52, Suppl. 1, pp. S17-S20, March 1996.	
	B3.	MANTELLE, "DOT Matrix® Technology," Modified-Release Drug Technology, Rathbone et al., eds., Chapter 30, pp. 405-415, May 28, 2008.	
	B4.	NOVARTIS, "Estraderm®," Prescribing information, June 2004.	
	B5.	NOVARTIS, "Vivelle®," Prescribing information, June 2004.	
	B6.	NOVARTIS, "Vivelle-Dot®," Prescribing information, June 2004.	
	B7.	BAYER HEALTHCARE, "Climara®," Prescribing information, 2007	
	B8.	3M PHARMACEUTICALS, "Menostar™," Prescribing information, June 2004.	

Examiner Signature		Date Considered	

4811-9674-6564.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.L.F./

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/870,574
Date Submitted: March 6, 2017				**Filing Date**	9/30/2015
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	1615
				Examiner Name	Melissa L. Javier
Sheet	2	of	2	Attorney Docket Number	041457-1160

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	B9.	WATSON PHARMA, INC., "Alora®," Prescribing information, May 2005.	
	B10.	SERONO LABORATORIES, INC., "Esclim®," Prescribing information, August 1998.	
	B11.	Office Action issued on 05/05/2016 in application number 14/024,985 (US 2014-0200530)	
	B12.	Notice of Allowance issued on 09/15/2016 in application number 14/024,985 (US 2014-0200530)	
	B13.	Notice of Allowance issued on 01/10/2017 in application number 14/024,985 (US 2014-0200530)	
	B14.	Office Action issued on 05/05/2016 in application number 13/553,972 (US 2013-0156815)	
	B15.	Notice of Allowance issued on 08/26/2016 in application number 13/553,972 (US 2013-0156815)	
	B16.	Notice of Allowance issued on 12/09/2016 in application number 13/553,972 (US 2013-0156815)	
	B17.	Office Action issued on 04/29/2016 in application number 14/738,255 (US 2015-0272905)	
	B18.	Decision in European Opposition issued on 02/14/2017 in application number EP 09 790 211.8.	

Examiner Signature	/Melissa L Fisher/	Date Considered	06/11/2017

4811-9674-6564.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.L.F./

PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: April 22, 2016

(use as many sheets as necessary)

Sheet 1 of 6

Complete if Known	
Application Number	14/870,574
Filing Date	09/30/2015
First Named Inventor	Juan Mantelle
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	041457-1160

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2015/0272905	10/01/2015	MANTELLE	
	A2	2014/0200530	07/17/2014	MANTELLE	
	A3	2013/0156815	06/20/2013	MANTELLE	
	A4	8,231,906	07/31/2012	MANTELLE	
	A5	8,343,538	04/13/2006	KANIOS ET AL.	
	A6	5,446,070	08/29/1995	MANTELLE	
	A7	4,915,950	04/1990	MIRANDA ET AL.	
	A8	6,562,363	05/13/2003	MANTELLE ET AL.	
	A9	6,221,383	04/24/2001	MIRANDA ET AL.	
	A10	6,235,306	05/22/2001	MIRANDA ET AL.	
	A11	2005/0169977 A1	08/04/2005	KANIOS	
	A12	2005/0129749 A1	06/16/2005	STRAUSS	
	A13	2006/0240087 A1	10/26/2006	HOUZE ET AL.	
	A14	2006/0233870 A1	10/19/2006	HOUZE ET AL.	
	A15	2006/0078602 A1	04/13/2006	KANIOS	
	A16	4,994,278	02/19/1991	SABOLTSKY ET AL.	
	A17	4,494,278	2/19/1991	SABLOTSKY ET AL.	
	A18	5,300,291	4/5/1994	SABLOTSKY ET AL.	
	A19	5,958,446	9/28/1999	MIRANDA ET AL.	
	A20	5,474,783	12/12/1995	MIRANDA ET AL.	
	A21	4,814,168	3/21/1989	SABLOTSKY ET AL.	
	A22	4,994,267	2/19/1991	SABLOTSKY	
	A23	5,656,286	8/12/1997	MIRANDA ET AL.	
	A24	6,024,976	2/15/2000	MIRANDA ET AL.	
	A25	6,337,086	1/8/2002	KANIOS ET AL.	
	A26	6,638,528	10/2003	KANIOS	
	A27	7,456,159 B2	11/25/2008	HOUZE ET AL.	
	A28	RE 35,474	3/11/1997	WOODARD ET AL.	Reissue of USP 4,655,767
	A29	4,655,767	4/7/1987	WOODARD ET AL.	
	A30	2005/2022073	09/15/2005	JACKSON ET AL.	
	A31	2003/099695	05/29/2003	MUELLER	
	A32	4,591,622	5/27/1986	BLIZZARD ET AL.	
	A33	5,584,355	4/22/1986	BLIZZARD ET AL.	
	A34	4,585,836	4/29/1986	HOMAN ET AL.	
	A35	4,390,520	6/28/1983	NAGAI ET AL.	
	A36	5,665,377	09/1997	GONELLA	
	A37	2003/0228354	12/2003	MURAOKA ET AL.	
	A38	5,730,999	03/24/1998	LEHMANN ET AL.	
	A39	5,505,956	04/09/1996	KIM ET AL.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.L.F./

PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: April 22, 2016

(use as many sheets as necessary)

Sheet 2 of 6

Complete if Known	
Application Number	14/870,574
Filing Date	09/30/2015
First Named Inventor	Juan Mantelle
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	041457-1160

U.S. PATENT DOCUMENTS

Examiner	Cite No.[1]	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant
	A40	5,350,581	09/27/1994	KOCHINKE	
	A41	4,983,395	01/08/1991	CHANG ET AL.	
	A42	4,559,222	12/17/1985	ENSCORE ET AL.	
	A43	5,762,952	06/09/1998	BARNHART ET AL.	
	A44	4,591,622	05/27/1986	BLIZZARD ET AL.	
	A45	4,585,836	04/29/1986	HOMAN ET AL.	
	A46	5,474,787	12/12/1995	GRAY ET AL.	
	A47	2002/0100185 A1	08/01/2002	SITZ ET AL.	
	A48	6,808,739 B2	10/26/2004	SITZ ET AL.	
	A49	5,151,271	09/29/1992	OTSUKA ET AL.	
	A50	5,906,830	05/25/1999	FARINAS ET AL.	
	A51	5,902,603	05/11/1999	CHEN ET AL.	
	A52	5,837,280	11/17/1998	KENEALY ET AL.	
	A53	5,567,488	10/22/1996	ALLEN ET AL.	
	A54	5,271,940	12/21/1993	CLEARY ET AL.	
	A55	4,911,707	03/27/1990	HEIBER ET AL.	
	A56	4,746,515	05/24/1988	CHENG ET AL.	
	A57	5,904,931	05/1999	LIPP ET AL.	
	A58	4,938,759	07/1990	ENSCORE ET AL.	
	A59	5,928,666	07/1999	FARINAS ET AL.	
	A60	4,769,028	09/1998	HOFFMANN ET AL.	
	A61	4,624,665	11/1986	NUWAYESER	
	A62	6,156,335	12/2000	ROVATI ET AL.	
	A63	2009/0041831	02/2009	MILLER ET AL.	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	A64	EP 0 887 075 A2	12/30/1998	BERTEK, INC.		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.L.F./

PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: April 22, 2016

(use as many sheets as necessary)

Sheet 3 of 6

Complete if Known	
Application Number	14/870,574
Filing Date	09/30/2015
First Named Inventor	Juan Mantelle
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	041457-1160

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A65	VAUGHAN, "Using Solubility Parameters in Cosmetics Formulation," *J. Soc. Cosmet. Chem.*, Vol. 36, pp. 319-333 (1985).	
	A66	SOBIESKI ET AL., "Silicone Pressure Sensitive Adhesives," *Handbook of Pressure-Sensitive Adhesive Technology*. 2nd ed., pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).	
	A67	"Acrylic Adhesives," *Handbook of Pressure-Sensitive Adhesive Technology*, 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, N.Y. (1989)	
	A68	NAGAI ET AL., "New Drug Delivery Systems," Kurashiki Printing Co. Ltd., Academic Document 2009-00984-005, published January 31, 2000.	
	A69	SEKINE ET AL., "New Cosmetic Handbook," Nikko Chemical Co. Ltd., et al., Academic Documents 2008-02180-001, published October 30, 2006.	
	A70	NOVARTIS PHARMACEUTICALS CORPORATION, "Vivelle-Dot® (estradiol transdermal system)," prescription labeling, August 2004.	
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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

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PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/870,574
Date Submitted: April 22, 2016				**Filing Date**	09/30/2015
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	4	of	6	Attorney Docket Number	041457-1160

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A78	Office Action issued on 09/09/2010 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A79	Office Action issued on 01/20/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A80	Office Action issued on 06/30/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A81	Office Action issued on 09/13/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A82	Office Action issued on 11/08/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A83	Office Action issued on 05/29/2012 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A84	Notice of Allowance issued on 06/19/2012 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A85	Office Action issued on 12/29/2010 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A86	Office Action issued on 04/14/2010 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A87	Office Action issued on 06/10/2009 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A88	Office Action issued on 10/26/2011 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A89	Office Action issued on 05/13/2011 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A90	Office Action issued on 06/13/2012 by the Examiner in application number 11/245,084 (US 8,343,538)	

Examiner Signature		Date Considered	

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PTO/SB/08 (09-06)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: April 22, 2016

(use as many sheets as necessary)

Sheet 5 of 6

Complete if Known	
Application Number	14/870,574
Filing Date	09/30/2015
First Named Inventor	Juan Mantelle
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	041457-1160

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A91	Notice of Allowance issued on 08/22/2012 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A92	Office Action issued on 04/12/2013 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A93	Office Action issued on 09/04/2013 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A94	Office Action issued on 03/05/2014 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A95	Office Action issued on 05/05/2015 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A96	Notice of Allowance issued on 10/02/2015 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A97	Office Action issued on 05/20/2015 by the Examiner in application number 14/024,985 (US 2014/0200530)	
	A98	Notice of Allowance issued on 10/02/2015 by the Examiner in application number 14/024,985 (US 2014/0200530)	
	A99	Office Action issued on 08/12/2015 by the Examiner in application 14/738,255 (US 2015/0272905)	
	A100	Office Action issued on 10/26/2015 by the Examiner in application 14/738,255 (US 2015/0272905)	
	A101	RIETSCHEL ET AL., "Effects of harvesting techniques on hydration dynamics: gravimetric studies of stratum corneum," J. Soc. Cosmet. Chem., Vol. 29, pp. 777-782, December 1978.	
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	A103	PFISTER, "Transdermal and Dermal Therapeutic Systems: Current Status," Transdermal and Topical Drug Delivery Systems, Ghosh et al., eds., Chapter 2, pp. 33-112, 1997.	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/870,574
Date Submitted: April 22, 2016				**Filing Date**	09/30/2015
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	6	of	6	Attorney Docket Number	041457-1160

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	A104	Dow Corning, :"Dow Corning® BIO-PSA Standard Silicone Adhesives," Product Information, 07/28/2008.	
	A105	JANISCH ET AL., Email correspondence, March 10, 2016.	
	A106	MANNGOLD, 04/28/2004 letter to Angela Nwaneri re: Duro-Tak® 87-4287 and 87-2287.	
	A107	Noven Pharmaceuticals, Inc., Response filed in European application number 09790211.8 on 12/19/2014.	

Examiner Signature	/Melissa L Fisher/	Date Considered	06/11/2017

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	16040	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L2	5541	L1 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L3	934	L2 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L4	35	L3 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L5	266	L3 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L6	51	L3 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L7	90	L1 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L8	261	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L9	42	L8 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L10	154	L8 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
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L93	135	L81 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/06/11 13:52
L94	2	"6638528".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
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L97	16040	estradiol and transdermal	US-PGPUB; USPAT;	OR	OFF	2017/06/11

			USOCR; FPRS; EPO; JPO; DERWENT			13:52
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L99	934	L98 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
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L101	266	L99 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L102	51	L99 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L103	90	L97 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L104	261	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L105	42	L104 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L106	154	L104 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L107	188	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
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L109	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2017/06/11 13:52
L110	725	L97 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/06/11 13:52
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L114	934	L113 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L115	35	L114 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L116	266	L114 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52

L117	51	L114 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L118	90	L112 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L119	261	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
L120	42	L119 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/06/11 13:52
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SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/870,574	09/30/2015	424	1611	041457-1160

APPLICANTS
NOVEN PHARMACEUTICALS, INC., Miami, FL

INVENTORS
Juan Mantelle, Miami, FL;

**** CONTINUING DATA ***************************
This application is a CON of 14/738,255 06/12/2015
which is a CON of 14/024,985 09/12/2013
which is a CON of 13/553,972 07/20/2012
which is a CON of 12/216,811 07/10/2008 PAT 8231906

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
10/14/2015

Foreign Priority claimed	☐ Yes ☑ No	☐ Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
35 USC 119(a-d) conditions met	☐ Yes ☑ No					
Verified and Acknowledged	/MELISSA L FISHER/ Examiner's Signature	Initials	FL	1	20	4

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UNITED STATES

TITLE
TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

FILING FEE RECEIVED	FEES: Authority has been given in Paper	☐ All Fees
2020	No._____ to charge/credit DEPOSIT ACCOUNT	☐ 1.16 Fees (Filing)
	No._____ for following:	☐ 1.17 Fees (Processing Ext. of time)
		☐ 1.18 Fees (Issue)
		☐ Other _____
		☐ Credit

Outline for June 8, 2017 Examiner Interview

Summary Of Claimed Subject Matter

The claimed subject matter includes transdermal drug delivery systems estradiol that have a smaller active surface area than the prior art Vivelle-Dot® patches, but achieve daily dosages that are about equal to or greater than the Vivelle-Dot® patches. That is, the subject matter includes transdermal drug delivery systems that achieve daily dosages that are about equal to a Vivelle-Dot® patch, in a smaller size. *See, e.g.*, Specification, at paragraph [0014].

As stated in the specification, "the Applicant surprisingly discovered that increasing the coat weight of the drug-containing adhesive layer resulted in an increased flux per unit area, and thus permitted the development of smaller transdermal drug delivery systems that achieve comparable daily dosages." Specification, at paragraph [0014].

All claims recite a monolithic transdermal drug delivery system consisting of (i) a backing layer and (ii) a single adhesive polymer matrix layer defining an active surface area and comprising an adhesive polymer matrix comprising estradiol as the only drug.[1]

The claims of the '972, '985, and '255 applications recite that the polymer matrix has a coat weight of greater than about 10 mg/cm^2 and includes greater than 0.156 mg/cm^2 estradiol, and that the transdermal drug delivery system achieves an estradiol flux of from about 0.0125 to about 0.05 $g/cm^2/day$, based on the active surface area.

The claims of the '574 application recite that the coat weight of the polymer matrix is adjusted such that system includes greater than 0.156 mg/cm^2 estradiol, and that the transdermal drug delivery achieves an estradiol flux of from about 0.0125 to about 0.05 $g/cm^2/day$, based on the active surface area.

[1] Some claims recite an optional release liner that is removed prior to use.

Summary Of Issues To Be Discussed

- Understanding in the art regarding passive drug flux from a transdermal drug delivery system (Fick's 1st Law of Diffusion)
- Impact of polymer components on drug flux (predicted by Fick's 1st Law)
- Additional experimental data demonstrating surprising and unexpected result that increasing coat weight increases estradiol flux (not predicted by Fick's 1st Law)

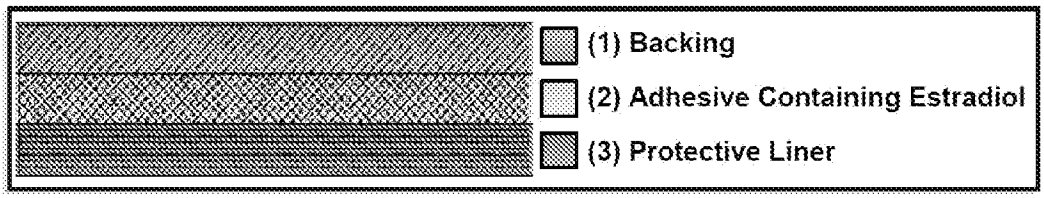
Introduction of Expert

Dr. Richard Guy, Professor of Pharmaceutical Sciences, University of Bath (UK) (in the Department of Pharmacy & Pharmacology)

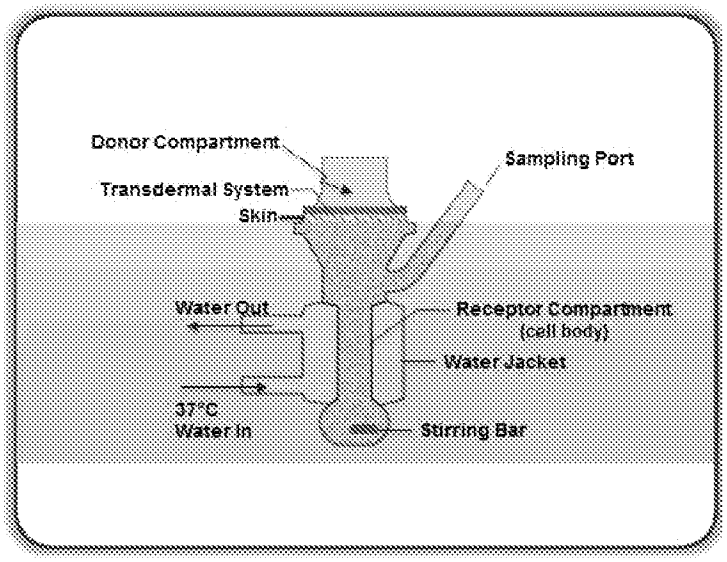
- over 30 years' research experience in the field of topical and transdermal drug delivery, including the study of drug absorption into and through the skin
- Bachelor of Arts in chemistry from Oxford University (UK) (1977)
- Master of Arts in chemistry from Oxford University (1980)
- Ph.D. in pharmaceutical chemistry from the University of London (UK) (1980).
- D.Sc. from Oxford University (2016).
- co-author on over 350 peer-reviewed articles and over 70 book chapters.
- experience as a consultant (and scientific advisory board member) to numerous pharmaceutical companies involved in the development of transdermal drug delivery formulations (including patches and other gels)
- engaged by the Applicant (Noven Pharmaceuticals, Inc.) to serve as an expert witness in ANDA litigation involving U.S. Patent No.8,231,906 (the '906 Patent), in the U.S. District Court for the District of Delaware (C.A. No. 15-249) (the "ANDA litigation).
- engaged by the Applicant to prepare a Declaration for U.S. patent applications 13/553,972, 14/024,985, 14/738,255, and 14/870,574 and attend the Patent Office Interview
- His compensation does not depend in any way on the outcome of the examination of the pending applications or on the outcome of the ANDA litigation.

TECHNICAL BACKGROUND

The inventions claimed in the pending applications generally relate to transdermal drug delivery systems (*e.g.*, transdermal "patches") for the delivery of estradiol, methods of administering estradiol to a patient using the claimed transdermal drug delivery systems, and delivering estradiol using them, and methods of making them. The claimed transdermal drug delivery systems are "monolithic" drug-in-adhesive systems that consist of (i) a backing layer; (ii) a drug-in-adhesive polymer matrix layer, and, optionally, (iii) a release liner that is removed prior to use, as illustrated below.



The claims recite that the adhesive polymer matrix layers include a certain amount estradiol per unit area and achieve a certain estradiol flux. The flux of a drug is the rate at which it diffuses through the skin. An *in vitro* flux study may be conducted to assess the flux of a drug from a transdermal drug delivery system. The image below shows a typical Franz diffusion cell set up used to conduct an *in vitro* flux study.



In general, the receptor compartment is filled with a receiver solution that is stirred and held at a constant (typically, physiological) temperature. A transdermal system is placed on a skin sample in the donor compartment, and the contents of the receptor compartment are sampled (withdrawn) periodically and analyzed for drug (for example, estradiol) content. From this information, the cumulative amount of drug delivered over time and the flux of drug across the skin as a function of time is calculated.

An illustration of the type of experimental data collected with this approach is shown below for one particular formulation; the results are presented as the average cumulative amounts of drug delivered, and the average drug flux, as a function of time, with the corresponding standard deviations for 4 replicate Franz diffusion cells.

(hours)	(mcg/cm2)	(mcg/cm2)	(mcg/cm2 hr)	(mcg/cm2 hr)
Average Time	Average Cum.	Cum. Stdev	Average Flux	Flux Stdev
0.00	0.00	0.00	0.00	0.00
9.92	2.55	0.49	0.26	0.05
23.95	12.64	1.99	0.72	0.11
33.65	20.85	2.91	0.85	0.10
48.03	33.45	4.10	0.88	0.08
57.58	41.70	4.81	0.86	0.08
72.20	54.23	5.71	0.86	0.06
81.02	61.43	6.07	0.82	0.04

These results may be plotted graphically as illustrated in the specification and the additional experimental data that will be discussed.

FICK'S FIRST LAW OF DIFFUSION

As of June 10, 2008, a person of ordinary skill in the art understood that the passive flux of a drug can be quantitatively described and modelled by Fick's 1st law. Fick's 1st law is often used to describe drug delivery (in units of amount per time, *e.g.*, mg/day or μg/hour) from a transdermal patch across the skin:

$J = A \times k_p \times \Delta C$

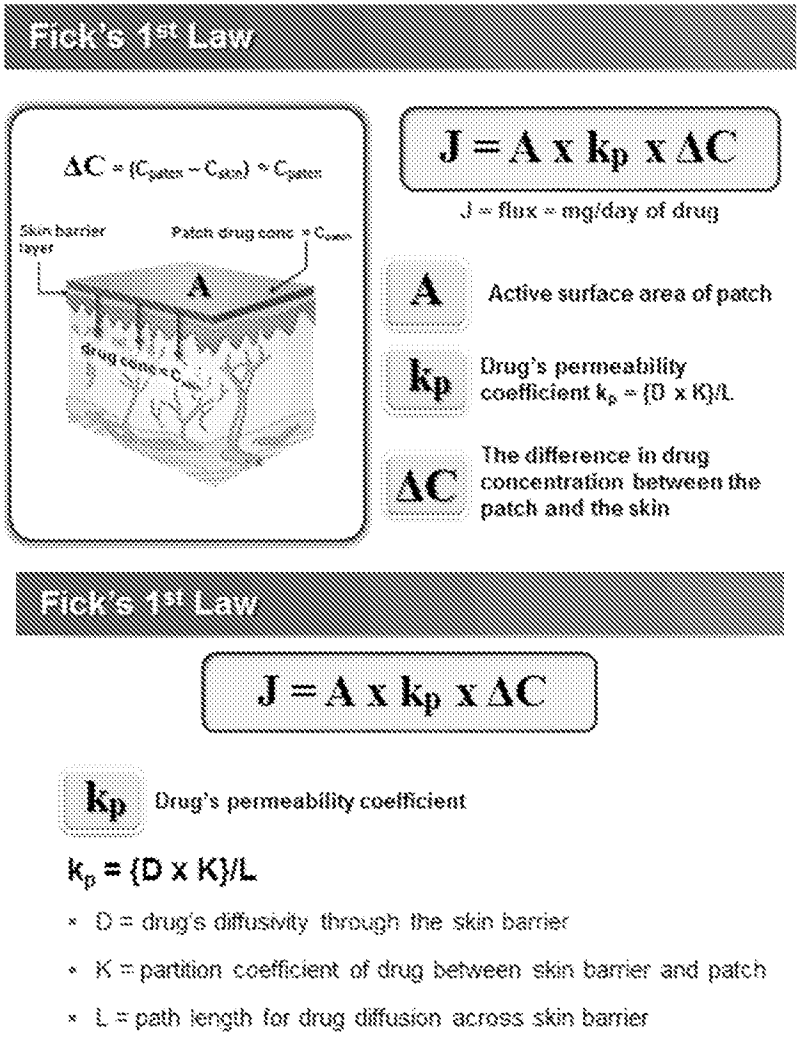
In this formula:

A is the active surface area of the patch.

k_p is the drug's permeability coefficient across the skin, and can be defined as $k_p = \{D \times K\}/L$, where D is the drug's diffusivity through the skin barrier, K is its partition coefficient between the skin barrier and the patch, and L is the path length for diffusion across the skin barrier.

ΔC is the difference in concentration of the drug between that in the patch (C_{patch}) and that on the "downstream" side of the skin barrier ($C_{downstream}$). In many examples of transdermal delivery, when depletion of drug from the patch is limited, ΔC can be approximated to C_{patch}.

The following images illustrate these factors:



Fick's 1st law indicates that there are four general ways to increase flux:

- Increase the active surface area of the patch to cause a proportional change in flux.
- Increase the drug concentration in the patch until it reaches its limiting solubility.
- Adjust the formulation to increase K, *e.g.*, cause drug concentration to approach more closely its limiting solubility.
- Introduce a penetration enhancer into the formulation to increase D and/or alter the value of K.

Nothing in Fick's 1st law indicates or predicts that increasing the coat weight (thickness) of a polymer matrix would increase flux. This is because no factor in Fick's 1st law embodies or includes coat weight.

THE UNEXPECTED DISCOVERY OF THE INVENTION

As noted above, "the Applicant surprisingly discovered that increasing the coat weight of the drug-containing adhesive layer resulted in an increased flux per unit area, and thus permitted the development of smaller transdermal drug delivery systems that achieve comparable daily dosages." Specification, at paragraph [0014]. As stated in paragraph [0015] in the specification:

> This result was surprising because coat weight is typically selected to control the duration of delivery, but is not generally understood to impact delivery rate. Thus, while it is known in the art to increase coat weight to provide delivery over a longer period of time, it was not known that increasing coat weight could increase delivery rate or flux, and thus permit the development of a smaller system while maintaining daily dosage.

Indeed, as explained above, nothing in Fick's 1st law indicates or predicts that increasing the coat weight (thickness) of a polymer matrix would increase flux.

THE EXAMPLE IN THE SPECIFICATION

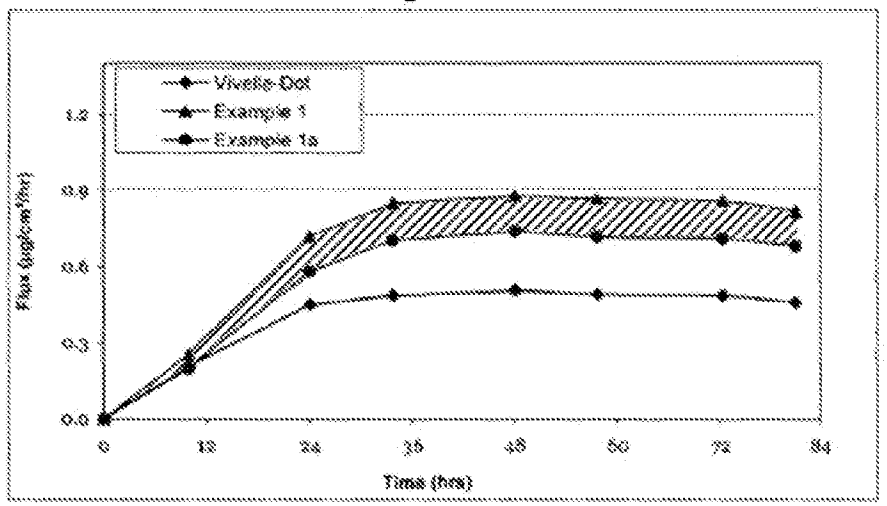
The specification illustrates this surprising and unexpected effect in Example 1, which describes an *in vitro* flux study conducted to assess the flux of estradiol from different systems. Figure 1 reports the flux of drug across the skin for the systems tested in Example 1.

Example 1 sets forth the polymer matrix formulation used to prepare Example 1 and Example 1a. As noted in the prosecution history of the '906 Patent, in the Amendment and Reply filed April 20, 2011, the specification as filed had a clerical error in the formulation listed (see below), but the flux data presented in Figure 1 is correct.

	Example 1	Actual Formulation
Silicone (4502)	56.9	66.9
Acrylic (Gelva 788)	20	10
PVP (Kollidon K-30)	7.5	7.5
DPG	8	8
Oleyl Alcohol	6	6
Estradiol	1.6	1.6

As described in the specification, test systems were prepared by applying the polymer matrix to a release liner at two different coat weights: 12.5 mg/cm^2 (Example 1a, ●) and 15 mg/cm^2 (Example 1, ▲), and estradiol flux was assessed in an *in vitro* flux study. As reported in Figure 1, the system with the higher coat weight exhibited a greater flux.

Figure 1



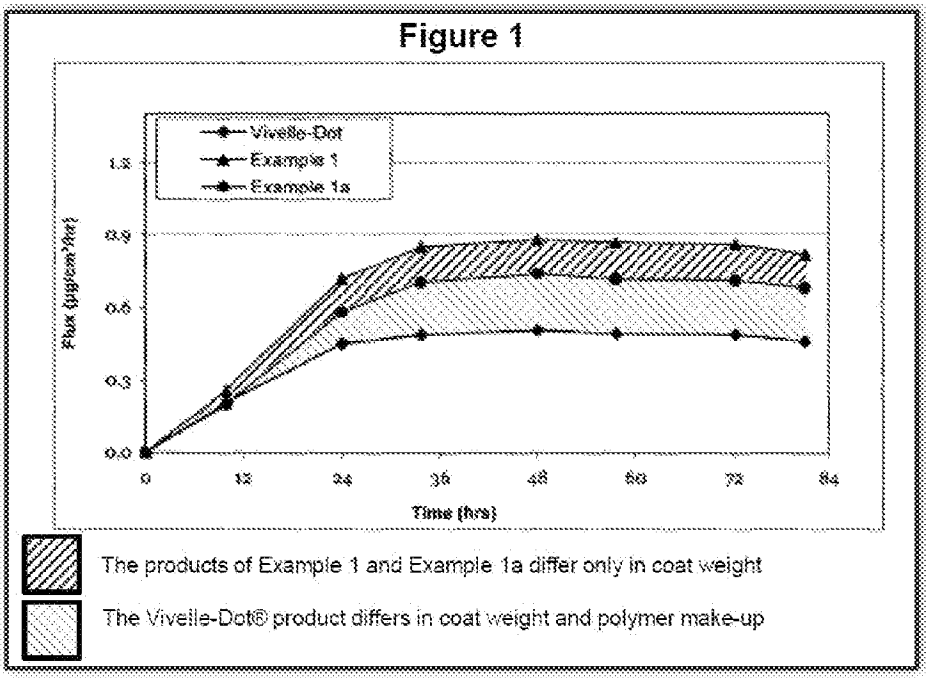
The only difference between Example 1 and Example 1a is the coat weight of the polymer matrix

The only experimental variable different between Example 1a and Example 1 is the coat weight of the polymer matrix. The difference in flux reported in Figure 1 between Example 1a and Example 1 can only be attributed, therefore, to the difference in coat weight, which is a surprising and unexpected result that is not predicted by Fick's 1st Law.

Figure 1 also reports results achieved with a Vivelle-Dot® system. As described in the prescribing information, Vivelle-Dot® is a monolithic transdermal drug delivery system for estradiol with a polymer matrix layer that includes estradiol as the only drug, acrylic adhesive, silicone adhesive, oleyl alcohol, povidone, and dipropylene glycol. The specification states that each Vivelle-Dot® patch includes 0.156 mg/cm^2 estradiol and has a polymer matrix coat weight of 10 mg/cm^2. *See, e.g.*, Specification at paragraph [0013]; [0074]. Although Vivelle-Dot® includes the same polymer matrix components of the Example 1 formulation, I have been informed that the Vivelle-Dot® formulation includes different amounts of some components, including different relative amounts of acrylic adhesive and silicone adhesive, with a greater relative amount of acrylic adhesive. That is, the formulation of Examples 1 and 1a have less acrylic adhesive and more silicone adhesive than the Vivelle-Dot® formulation.

Prior art such as U.S. Patent No. 6,024,976 (the "'976 Patent") and Mantelle, *et al.*, *Effect of Silicone/Acrylic PSA Blends on Skin Permeation*, 26 *Proc. Internat'l Symp. Controlled Release of Bioactive Materials* 5123, 415-16 (Revised July 1999) (the "Mantelle Article"), and post-filing date publications such as Juan A. Mantelle, "Dot Matrix® Technology," in MODIFIED RELEASE DRUG DELIVERY TECHNOLOGY (2nd ed. 2008) 405-14 (the "Mantelle Chapter") teach that the difference in relative amounts of acrylic adhesive and silicone adhesive between the formulation of Examples 1/1a and the Vivelle-Dot® formulation contributes to the difference in flux seen in Figure 1 between Vivelle-Dot® and Example 1 and between Vivelle-Dot® and Example 1a.

Figure 1



It is not possible to quantify from available data the relative contributions of coat weight and polymer composition to the differences in flux observed between the Vivelle-Dot® system and Examples 1/1a systems. However, based on the difference in flux between the Example 1 and 1a systems (which, as explained above, can only be due to the difference in coat weight), and in view of other experimental data discussed below, it is Dr. Guy's expert opinion that the difference in coat weight is contributing to the difference in flux.

EXPERIMENTAL DATA – IMPACT OF POLYMER MAKE-UP ON FLUX

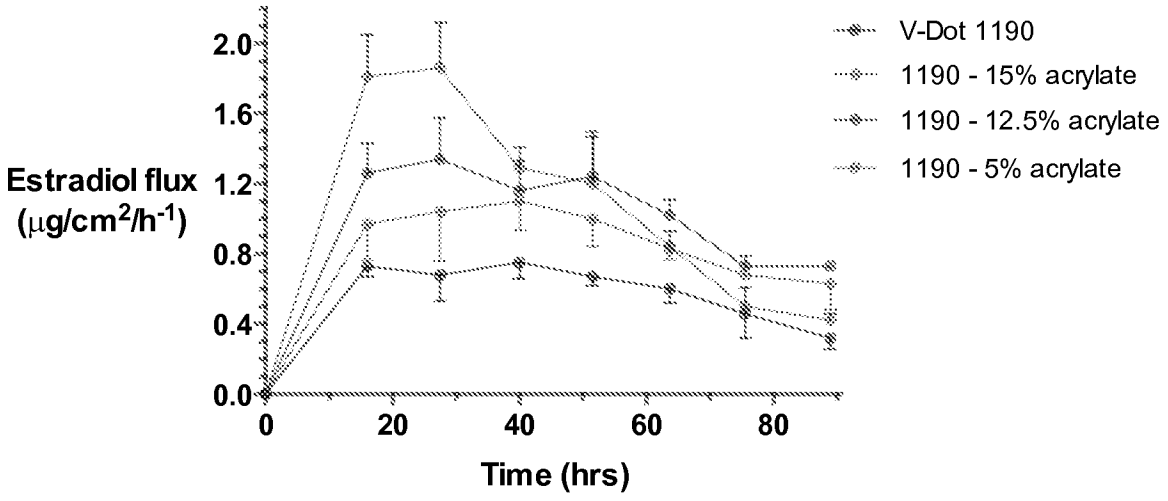
As noted above, it was known in the art that the relative amounts of acrylic adhesive and silicone adhesive used in an estradiol polymer matrix can impact the flux of estradiol. This is described in the '976 Patent, which explains that this is because estradiol's solubility in acrylic adhesives differs from that in silicone adhesives. The potential effect of the relative amounts of acrylic adhesive and silicone adhesive is illustrated in Examples 10-13 and Figure 6 of the '976 patent, and in the Mantelle Article. Thus, it was known in the art that the relative amounts of acrylic adhesive and silicone adhesive in an estradiol polymer matrix can impact estradiol flux, and that

increasing the relative amount of silicone polymer generally increased the flux but may alter the drug delivery profile such that the increased flux is not sustained.

Flux Study 1190 conducted by Noven also illustrates this effect. Flux Study 1190 tested five different formulations at the same target coat weight (15 mg/cm^2) and used a Vivelle-Dot® system (◆) as an internal control. The five formulations differed in the relative amounts of acrylic adhesive and silicone adhesive.

Component (% by weight)	5% Acrylic	10% Acrylic	12.5% Acrylic	15% Acrylic	17.5% Acrylic
Acrylic Adhesive	5	10	12.5	15	17.5
Silicon Adhesive	71.9	66.9	64.5	61.9	59.4
Dipropylene Glycol	8	8	8	8	8
Oleyl Alcohol	6	6	6	6	6
PVP	7.5	7.5	7.5	7.5	7.5
Estradiol	1.6	1.6	1.6	1.6	1.6

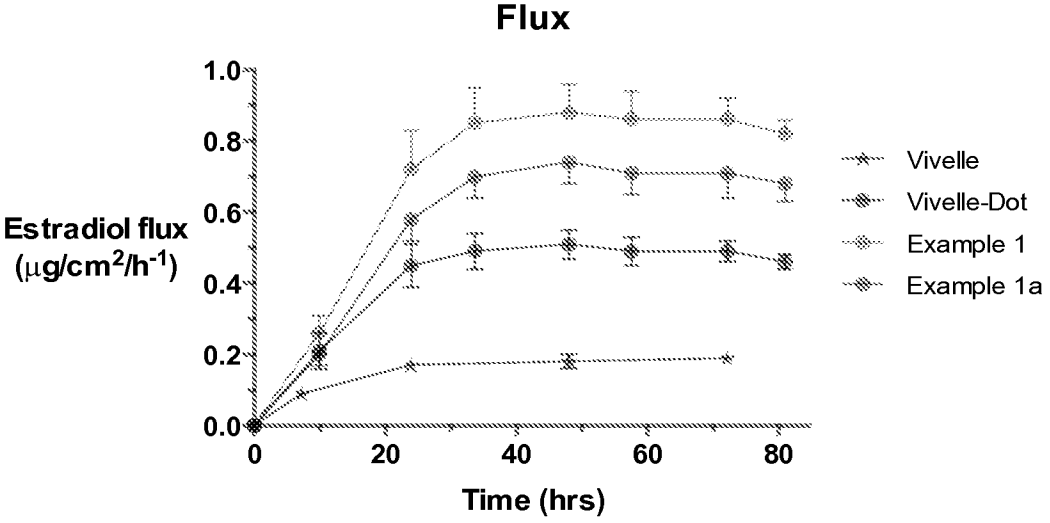
A representative sample of the data from this Flux Study are shown in the figure below. The results show that initial flux increased as the relative amount of acrylic polymer decreased but the initially higher flux from the 5% acrylic composition was not sustained:

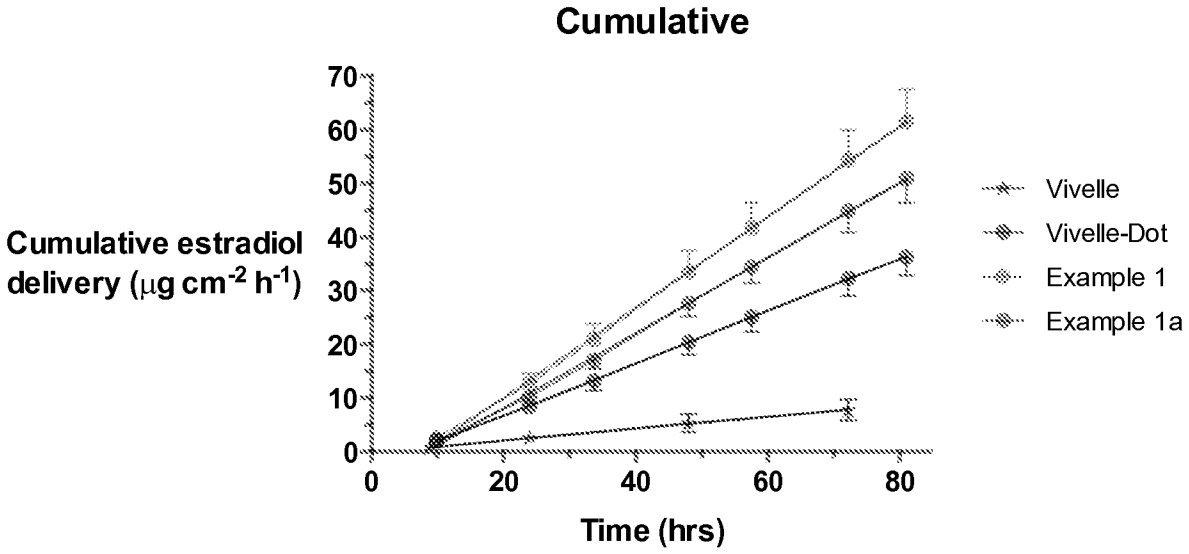


EXPERIMENTAL DATA – IMPACT OF COAT WEIGHT ON FLUX

As noted above, while it was known in the art that the relative amounts of acrylic adhesive and silicone adhesive in an estradiol polymer matrix can impact estradiol flux, it was not known or expected that the coat weight of the polymer matrix would impact flux, but Noven conducted a number of other flux studies that showed this effect with monolithic transdermal drug delivery systems for estradiol as described in the pending applications.

Flux Study 1326 is the flux study reported in Example 1 of the pending applications. As discussed above, the same formulation (1.6 % estradiol, 10% acrylic adhesive, 66.9% silicone adhesive, 6% oleyl alcohol, 7.5% povidone, and 8% dipropylene glycol) was tested at coat weights of 12.5 mg/cm^2 and 15 mg/cm^2. Both Vivelle® and Vivelle-Dot® were used as internal controls. As noted above, the results (see below) show that the increase in the coat weight of the polymer matrix from Example 1a to Example 1 resulted in an increased flux of estradiol.



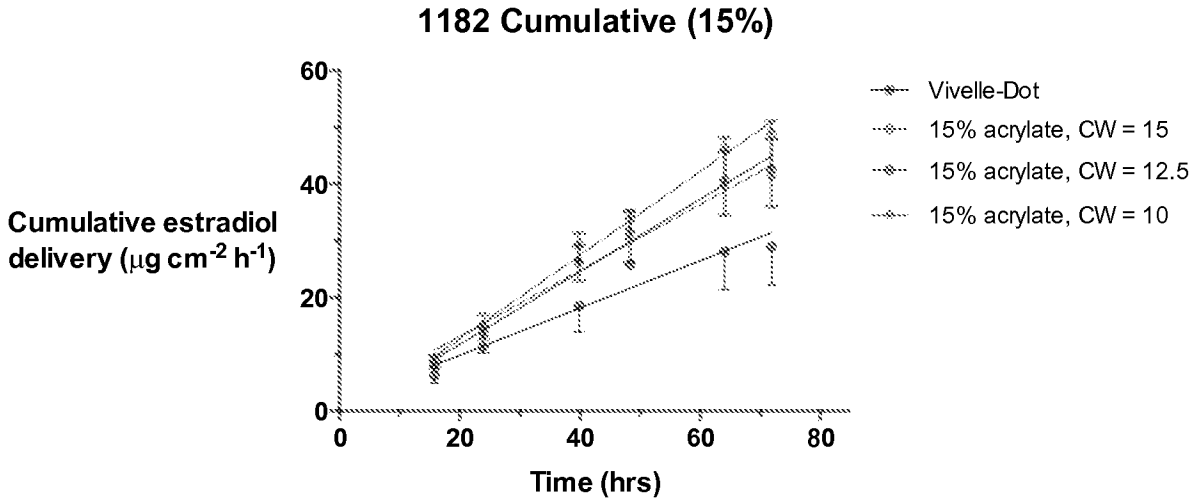


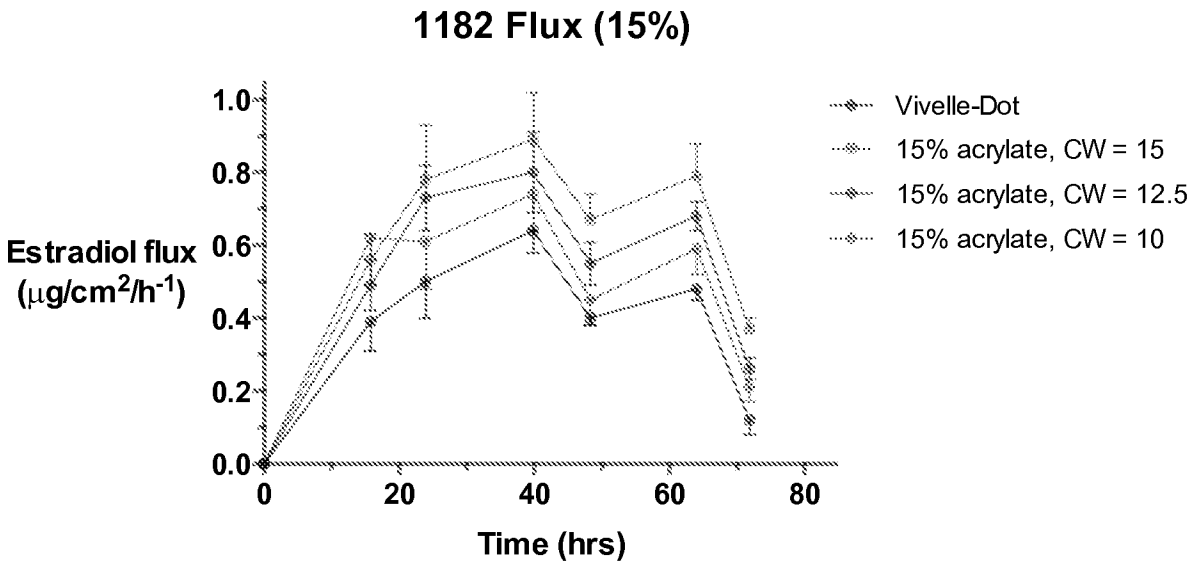
Flux Study 1182 conducted by Noven tested four different formulations at three different target coat weights and used a Vivelle-Dot® system as an internal control. The four formulations differed in the relative amounts of acrylic adhesive and silicone adhesive, as follows:

Component (% by weight)	10% Acrylic	15% Acrylic	17.5% Acrylic	20% Acrylic
Acrylic Adhesive	10	15	17.5	20
Silicon Adhesive	66.9	61.9	59.4*	56.9
Dipropylene Glycol	8	8	8	8
Oleyl Alcohol	6	6	6	6
PVP	7.5	7.5	7.5	7.5
Estradiol	1.6	1.6	1.6	1.6

*Reported as 59.9%, but likely used 59.4% Silicone Adhesive.

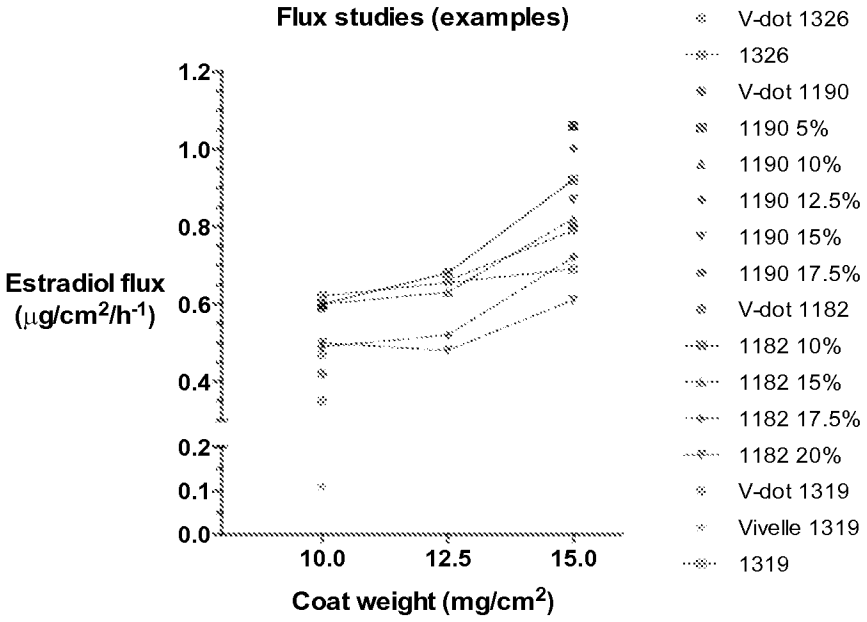
The different target coat weights assessed were 10 mg/cm^2, 12.5 mg/cm^2 and 15 mg/cm^2. The overall results show that increasing coat weight from 10 mg/cm^2 to 15 mg/cm^2 surprisingly and unexpectedly increased flux. For illustration, results for the composition with 15% acrylic polymer at a coat weight of 10 mg/cm^2, 12.5 mg/cm^2, and 15 mg/cm^2 (⋙) are set forth below (Vivelle-Dot® was used as an internal control).





Collectively, the results from Flux Studies 1190 and 1182 indicate that while the relative amounts of acrylic adhesive and silicone adhesive impact the flux of estradiol—as was known in the art—the coat weight of the polymer matrix also impacts flux—which was not known in the art, and indeed was a surprising and unexpected result not predicted by Fick's 1st law of diffusion.

The estimated estradiol fluxes from Flux Studies 1190 and 1182 are shown below:

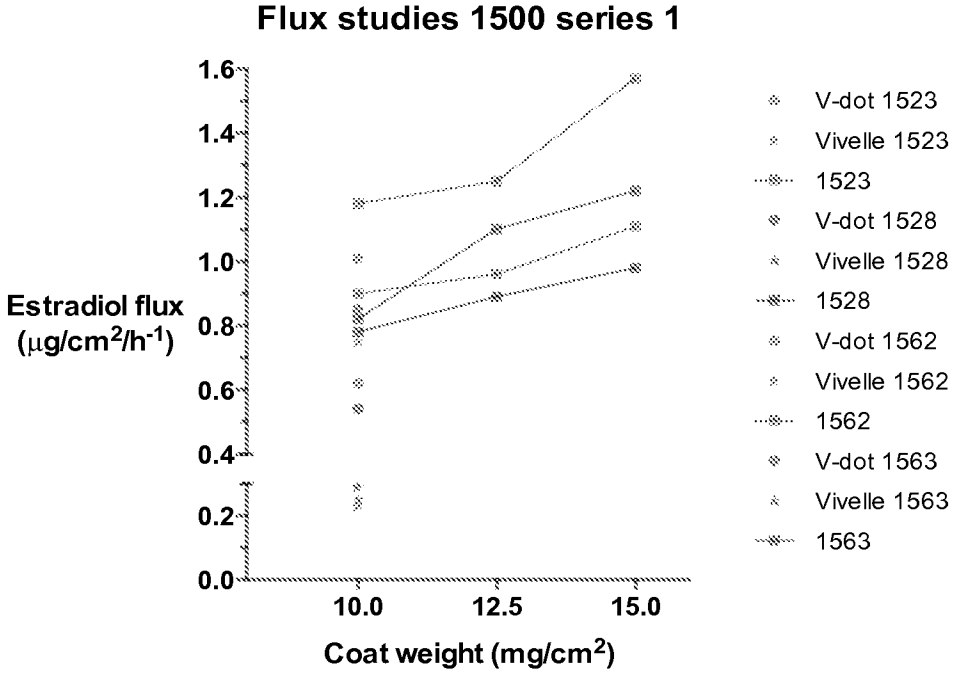


Flux Studies 1523, 1528, 1562 and 1563 assessed other formulations at different target coat weights, as outlined in the following table.

Flux Study	Formulation Components (% by weight)						Coat Wt. (mg/cm^2)	Drug Flux ($\mu g/cm^2 \cdot h$)
	Acrylate	Silicone	DPG	OAlc	PVP	Estradiol		
1523	10	69.4	8	6	5	1.6	15	1.57
	10	69.4	8	6	5	1.6	12.5	1.25
	10	69.4	8	6	5	1.6	10	1.18
	Control (flux): Vivelle-Dot® (1.01 $\mu g/cm^2 \cdot h$)							
1528	10	69.4	8	6	5	1.6	15	0.98
	10	69.4	8	6	5	1.6	12.5	0.89
	10	69.4	8	6	5	1.6	10	0.78
	Control (flux): Vivelle-Dot® (0.54 $\mu g/cm^2 \cdot h$)							
1562 (Form. 1)	10	69.4	8	6	5	1.6	15	1.11
	10	69.4	8	6	5	1.6	12.5	0.96
	10	69.4	8	6	5	1.6	10	0.90

Flux Study	Formulation Components (% by weight)						Coat Wt. (mg/cm^2)	Drug Flux ($\mu g/cm^2 \cdot h$)
	Acrylate	Silicone	DPG	OAlc	PVP	Estradiol		
	Control (flux): Vivelle-Dot® (0.62 $\mu g/cm^2 \cdot h$)							
1563 (Form. 1)	10	69.4	8	6	5	1.6	15	1.22
	10	69.4	8	6	5	1.6	12.5	1.10
	10	69.4	8	6	5	1.6	10	0.82
	Control (flux): Vivelle-Dot® (0.85 $\mu g/cm^2 \cdot h$)							

The estimated estradiol fluxes from Flux Studies 1523, 1528, 1562, and 1563 are illustrated below, and again show the surprising and unexpected impact of polymer matrix coat weight on flux:



Flux Studies 1562 and 1563 were repeated with different formulations at coat weights of 12.5 mg/cm^2 and 15 mg/cm^2 using both Vivelle and Vivelle-Dot® as internal controls.

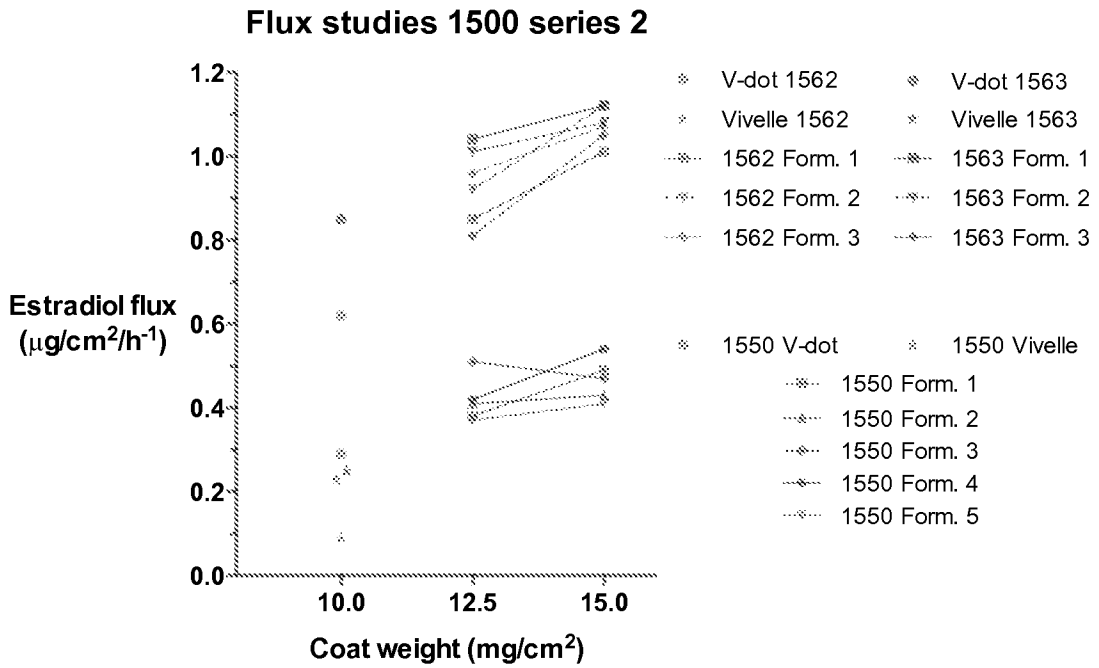
Flux Study	Formulation Components (% by weight)						Coat Wt. (mg/cm^2)	Drug Flux (µg/cm^2•h)
	Acrylate	Silicone	DPG	OAlc	PVP	Estradiol		
1562 (Form. 1)	10	69.4	8	6	5	1.6	15	1.01
	10	69.4	8	6	5	1.6	12.5	0.85
1562 (Form. 2)	7	72.6	8	6	5	1.4	15	1.12
	7	72.6	8	6	5	1.4	12.5	0.92
1562 (Form. 3)	7	74.6	8	6	3	1.4	15	1.07
	7	74.6	8	6	3	1.4	12.5	0.96
1562 Control (flux): Vivelle-Dot® (0.62 µg/cm^2•h)								
1563 (Form. 1)	10	69.4	8	6	5	1.6	15	1.12
	10	69.4	8	6	5	1.6	12.5	1.04
1563 (Form. 2)	7	72.6	8	6	5	1.4	15	1.08
	7	72.6	8	6	5	1.4	12.5	1.01
1563 (Form. 3)	7	74.6	8	6	3	1.4	15	1.05
	7	74.6	8	6	3	1.4	12.5	0.81
1563 Control (flux): Vivelle-Dot® (0.85 µg/cm^2•h)								

Flux Study 1550 assessed other formulations at different target coat weights, as outlined in the following table.

Formulation	Formulation Components (% by weight)						Coat Wt. (mg/cm^2)	Drug Flux (µg/cm^2•h)
	Acrylate	Silicone	DPG	OAlc	PVP	Estradiol		
Form. 1	10	71.6	8	6	3	1.4	15	0.49
	10	71.6	8	6	3	1.4	12.5	0.38

Formulation	Formulation Components (% by weight)						Coat Wt. (mg/cm^2)	Drug Flux ($\mu g/cm^2 \cdot h$)
	Acrylate	Silicone	DPG	OAlc	PVP	Estradiol		
Form. 2	10	69.4	8	6	5	1.6	15	0.43
	10	69.4	8	6	5	1.6	12.5	0.41
Form. 3	7	72.6	8	6	5	1.4	15	0.47
	7	72.6	8	6	5	1.4	12.5	0.51
Form. 4	7	74.6	8	6	3	1.4	15	0.54
	7	74.6	8	6	3	1.4	12.5	0.42
Form. 5	10	73.4	6	6	3	1.6	15	0.41
	10	73.4	6	6	3	1.6	12.5	0.37
Control (flux): Vivelle-Dot® (0.29 $\mu g/cm^2 \cdot h$)								

The estimated estradiol fluxes from 1562 and 1563 (second series) and 1550 are illustrated below, and again show the surprising and unexpected impact of polymer matrix coat weight on flux:



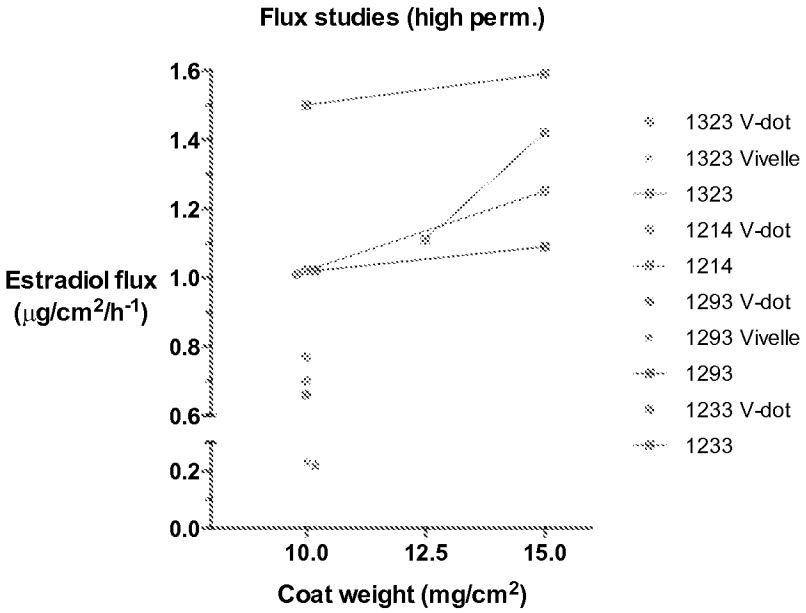
EXPERIMENTAL DATA – IMPACT OF SKIN PERMEABILITY ON FLUX

Since drug flux is a measure of the rate at which drug passes through the skin, the permeability of the skin sample used in a flux study can impact the results. The permeability of human skin varies from person to person and region of skin to region of skin. Noven accounted for this variability by using internal controls, such as Vivelle®-Dot or Vivelle®, since it was very familiar with the flux of these FDA-approved systems which were developed at Noven .

The impact of skin permeability on flux and the usefulness of an internal control in this context is illustrated in Flux Studies 1214, 1233, and 1293, which assessed the flux of formulations having the same components as the Example 1 formulation at target coat weights of 10 mg/cm^2 and 15 mg/cm^2 (and used Vivelle-Dot® and Vivelle as internal controls).

Study #	Formulation Components (% by weight)						Coat Wt. (mg/cm^2)	Drug Flux (µg/cm^2•h)
	Acrylate	Silicone	DPG	OAlc	PVP	Estradiol		
1323	10	66.9	8	6	7.5	1.6	15	1.42
	10	66.9	8	6	7.5	1.6	12.5	1.11
Control (flux): Vivelle-Dot® (0.77 µg/cm^2•h)								
Control (flux): Vivelle® (0.23 µg/cm^2•h)								
1214	10	66.9	8	6	7.5	1.6	15	1.25
	10	66.9	8	6	7.5	1.6	10	1.02
Control (flux): Vivelle-Dot® (0.7 µg/cm^2•h)								
1293	10	66.9	8	6	7.5	1.6	15	1.09
	10	66.9	8	6	7.5	1.6	10	1.02
Control (flux): Vivelle-Dot® (0.66 µg/cm^2•h)								
Control (flux): Vivelle® (0.22 µg/cm^2•h)								
1233	10	66.9	8	6	7.5	1.6	15	1.59
	10	66.9	8	6	7.5	1.6	10	1.50
Control (flux): Vivelle-Dot® (1.01 µg/cm^2•h)								

The cumulative flux results are illustrated below:



In these studies, the estradiol flux from Vivelle-Dot® was higher than usual, indicating that the donor skin had a higher permeability than usual. While the product label and the patient information leaflet indicate that the estradiol transdermal flux from the Vivelle®-Dot system is nominally 0.4 μg cm^{-2} h^{-1}, the values observed in these flux studies were 1.5 to 2.5-fold higher. The high fluxes seen from the test formulations are therefore completely consistent with that from the Vivelle®-Dot control (and reinforce the clear benefit of including this system as an internal check in experiments such as these).

Pending Independent Claims

U.S. Patent Application Nos. 13/553,972 (041457-0992)

14. **(Allowed)** A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system consisting of (i) a backing layer and (ii) a single adhesive polymer matrix layer defining an active surface area and comprising an adhesive polymer matrix comprising estradiol as the only drug, wherein the polymer matrix has a coat weight of greater than about 10 mg/cm^2 and includes greater than 0.156 mg/cm^2 estradiol, and the system achieves an estradiol flux of from about 0.0125 to about 0.05 $g/cm^2/day$, based on the active surface area.

16. **(Allowed)** A method of making a monolithic transdermal drug delivery system for administering estradiol consisting of (i) a backing layer, (ii) a single adhesive polymer matrix layer and, optionally, (iii) a release liner, comprising forming an adhesive polymer matrix comprising estradiol as the only drug and a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble PVP, and applying the adhesive polymer matrix to a support layer to form a single adhesive polymer matrix layer such that the adhesive polymer matrix layer has a coat weight of greater than about 10 mg/cm^2 and includes greater than 0.156 mg/cm^2 estradiol, wherein the system achieves an estradiol flux of from about 0.0125 to about 0.05 $mg/cm^2/day$, based on the active surface area.

U.S. Patent Application Nos. 14/024,985 (041457-1016)

1. **(Allowed)** A monolithic transdermal drug delivery system for estradiol, consisting of (i) a backing layer, (ii) a single adhesive polymer matrix layer defining an active surface area and, optionally, (iii) a release liner, wherein the single adhesive polymer matrix layer comprises an adhesive polymer matrix comprising estradiol as the only drug, wherein the adhesive polymer matrix layer has a coat weight of greater than about 10 mg/cm^2 and includes greater than 0.156 mg/cm^2 estradiol, and the system achieves an estradiol flux of from about 0.0125 to about 0.05 mg/cm^2/day, based on the active surface area.

U.S. Patent Application Nos. 14/738,255 (041457-1133)

45. (New) A monolithic transdermal drug delivery system for estradiol, consisting of:

(i) a backing layer;

(ii) an adhesive polymer matrix layer comprising an adhesive polymer matrix comprising estradiol as the only drug and defining an active surface area, and

optionally, (iii) a release liner,

wherein the adhesive polymer matrix layer includes from about 0.195 to about 0.260 mg/cm^2 estradiol and achieves an estradiol flux of from about 0.0125 to about 0.0167 mg/cm^2/day, based on the active surface area.

59. (New) A transdermal drug delivery system for estradiol, consisting of:

(i) a backing layer,

(ii) an adhesive polymer matrix layer defining an active surface area and,

optionally, (iii) a release liner,

wherein the adhesive polymer matrix layer comprises an adhesive polymer matrix comprising about 2-25% by weight acrylic adhesive, about 45-70% by weight silicone adhesive, about 2-25% by weight soluble PVP, about 5-15% penetration enhancer, and about 0.1-10% by weight estradiol as the only drug, and includes from about 0.195 to about 0.260 mg/cm^2 estradiol, achieves an estradiol flux of from about 0.0125 to about 0.0167 mg/cm^2/day, based on the active

surface area, and comprises an amount of estradiol effective to deliver a therapeutically effective amount of estradiol over a period of time of at least 1 day.

U.S. Patent Application Nos. 14/870,575 (041457-1160)

21. (New) A monolithic transdermal drug delivery system for estradiol, consisting of (i) a backing layer, (ii) a single adhesive polymer matrix layer defining an active surface area and, optionally, (iii) a release liner,

wherein the single adhesive polymer matrix layer comprises 2-25% by weight acrylic adhesive, 45-70% by weight silicone adhesive, 2-25% by weight soluble PVP, 5-15% by weight penetration enhancer, and 0. 1-10% by weight estradiol as the only drug, and

wherein the coat weight of the adhesive polymer matrix layer is adjusted such that the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux of from about 0.0125 to about 0.05 mg/cm^2/day, based on the active surface area.

35. (New) A method of making a transdermal drug delivery system according to claim 21, comprising forming an adhesive polymer matrix comprising 2-25% by weight acrylic adhesive, 45-70% by weight silicone adhesive, 2-25% by weight soluble PVP, 5-15% by weight penetration enhancer, and 0. 1-10% by weight estradiol as the only drug, and applying the adhesive polymer matrix to support layer to form a single adhesive polymer matrix layer,

wherein the coat weight of the adhesive polymer matrix is adjusted such that the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux of from about 0.0125 to about 0.05 mg/cm^2/day, based on the active surface area.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14870574	MANTELLE, JUAN
	Examiner	Art Unit
	MELISSA FISHER	1611

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search (see attached search history)	6/11/2017	MF
Inventor search in EAST	6/11/2017	MF
Google Scholar search (keywords used: monolithic transdermal estradiol)	6/11/2017	MF

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/M.F./ Primary Examiner.Art Unit 1611

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	14/870,574
Filing Date:	9/30/2015
Examiner:	FISHER
Art Unit:	1611
Confirmation Number:	5148

AMENDMENT AND REPLY UNDER 37 CFR § 1.111

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

This paper responds to the non-final Office Action mailed June 15, 2017. If any extensions of time are needed for timely acceptance, Applicant hereby petitions for such an extension of time. If any additional fees are required for this application, including any extension of time fees, the Commissioner is hereby authorized to charge them to Deposit Account 19-0741.

Amendments to the Claims are reflected in the listing of claims which begins on page 2.

Remarks/Arguments begin on page 5.

Please amend the application as follows:

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

Claims 1-35 (Canceled)

36. (New) A monolithic transdermal drug delivery system for estradiol, consisting of (i) a backing layer, (ii) a single adhesive polymer matrix layer defining an active surface area and, optionally, (iii) a release liner, wherein the single adhesive polymer matrix layer comprises an adhesive polymer matrix comprising estradiol as the only drug, wherein the adhesive polymer matrix layer has a coat weight of greater than 10 mg/cm^2 and includes greater than 0.156 mg/cm^2 estradiol, and the system achieves an estradiol flux of from 0.0125 to about 0.05 $mg/cm^2/day$, based on the active surface area.

37. (New) The transdermal drug delivery system of claim 36, wherein the adhesive polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble PVP.

38. (New) The transdermal drug delivery system of claim 36, wherein the adhesive polymer matrix comprises about 2-25% by weight acrylic adhesive, about 45-70% by weight silicone adhesive, about 2-25% by weight soluble PVP, about 5-15% penetration enhancer, and about 0.1-10% by weight estradiol, all based on the total dry weight of the adhesive polymer matrix.

39. (New) The transdermal drug delivery system of claim 38, wherein the penetration enhancer comprises oleyl alcohol.

40. (New) The transdermal drug delivery system of claim 38, wherein the penetration enhancer comprises dipropylene glycol.

41. (New) The transdermal drug delivery system of claim 38, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

42. (New) The transdermal drug delivery system of claim 38, wherein the acrylic adhesive and silicone adhesive are present in a ratio of from about 1:2 to about 1:6, based on the total weight of the acrylic and silicone adhesives.

43. (New) The transdermal drug delivery system of claim 36, wherein the adhesive polymer matrix comprises an amount of estradiol effective to deliver a therapeutically effective amount of estradiol over a period of time selected from the group consisting of at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days and at least 7 days.

44. (New) The transdermal drug delivery system of claim 36, wherein the adhesive polymer matrix comprises an amount of estradiol effective to deliver an amount of estradiol selected from the group consisting of about 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day.

45. (New) The transdermal drug delivery system of claim 36, wherein the system achieves an estradiol flux of 0.0125 mg/cm^2/day, based on the active surface area.

46. (New) The transdermal drug delivery system of claim 36, wherein the system achieves an estradiol flux of 0.0133 mg/cm^2/day, based on the active surface area.

47. (New) The transdermal drug delivery system of claim 36, wherein the system achieves an estradiol flux of about 0.015 mg/cm^2/day, based on the active surface area.

48. (New) The transdermal drug delivery system of claim 36, wherein the system achieves an estradiol flux of about 0.0167 mg/cm^2/day, based on the active surface area.

49. (New) The transdermal drug delivery system of claim 36, wherein the system achieves an

estradiol flux of about 0.0175 mg/cm ^{2}/day, based on the active surface area.

50. (New) The transdermal drug delivery system of claim 36, wherein the adhesive polymer matrix comprises about 1.6% by weight estradiol, based on the total dry weight of the adhesive polymer matrix.

REMARKS

Applicant respectfully requests reconsideration in view of the foregoing amendments, the following remarks, and the Rule 132 Declaration of Dr. Guy submitted herewith (previously submitted in U.S. 13/533,972, granted as U.S. Patent 9,730,900, and U.S. 14/024,985, granted as U.S. Patent 9,724,310).

Status of the Claims

Claims 21-35 are canceled without prejudice or disclaimer. Applicant reserves the right to pursue any canceled subject matter in this application or in one or more continuing applications with the same rights of priority as the instant application.

New claims 36-50 are added to recite specific embodiments described throughout the specification as filed, and generally parallel claims granted in related U.S. Patent 9,724,310, except that the coat weight of the adhesive polymer matrix layer and the lower end of the recited estradiol flux are recited without "about." These claims are directed to elected subject matter and do not introduce any new matter.

Upon entry of these amendments, claims 36-50 will be pending. These claims are presented for reconsideration.

Statement of Substance of Interview

Applicant thanks Examiner Fisher for the courtesies extended during the Patent Office Interview on June 8, 2017. Applicant's Statement of the Substance of the Interview is provided here, in accordance with MPEP § 713.04. Applicant concurs with the Examiner's summary of the substance of the Applicant-Initiated Interview held June 8, 2017, and confirms that the substance of the agenda attached to the Examiner's summary was discussed. Applicant submits herewith the Declaration under 37 C.F.R. § 1.132 of Dr. Richard H. Guy that presents the evidence discussed during the interview. Applicant submits herewith an Information Disclosure

Statement that makes of record the Mantelle Article discussed in Dr. Guy's Declaration. The other references discussed in Dr. Guy's Declaration already are of record. Applicant believes that the application is in condition for allowance for at least the reasons set forth below.

§ 112 Rejections

The examined claims were rejected for alleged indefiniteness, and for allegedly failing to comply with the written description requirement. Applicant respectfully disagrees on the merits, but notes that the cancellation of these claims obviates these rejections.

§ 103 Rejections

The examined claims were rejected for alleged obviousness over the combination of Kanios (U.S. 6,638,528) and Nuwayser (U.S. 4,624,665). Applicant respectfully traverses this rejection in as much as it may be applied to the instant claims.

As reflected in independent claim 36, the claims under examination are directed to monolithic transdermal drug delivery systems for estradiol, consisting of (i) a backing layer, (ii) a single adhesive polymer matrix layer defining an active surface area and, optionally, (iii) a release liner, wherein the single adhesive polymer matrix layer comprises an adhesive polymer matrix comprising estradiol as the only drug, wherein the adhesive polymer matrix layer has a coat weight of greater than 10 mg/cm^2 and includes greater than 0.156 mg/cm^2 estradiol, and the system achieves an estradiol flux of from 0.0125 to about 0.05 mg/cm $^{2/}$day, based on the active surface area. The cited combination of references does not teach or suggest such transdermal drug delivery systems.

At the outset, Applicant emphasizes that neither Kanios nor Nuwayser teaches or suggests preparing a transdermal drug delivery system having an adhesive polymer matrix layer with a coat weight of greater than 10 mg/cm^2 and greater than 0.156 mg/cm^2 estradiol, let alone provides a reasonable expectation that such a system would achieve an estradiol flux of from 0.0125 to about 0.05 mg/cm $^{2/}$day, based on the active surface area.

As recognized in the Office Action, although Kanios discloses matrix-type transdermal drug delivery systems, Kanios does not teach or suggest a system comprising an adhesive polymer matrix layer that includes greater than 0.156 mg/cm^2 estradiol or that achieves an estradiol flux of from about 0.0125 to about 0.05 mg/cm^2/day, based on the active surface area, as recited in independent claim 36. Kanios also does not discuss coat weight, or describe the coat weight of its example compositions, let alone teach or suggest a system as claimed having an adhesive polymer matrix layer as claimed having a coat weight of greater than 10 mg/cm^2.

Although Nuwayser was cited for its statement that "flux rates depend on the concentration of the applied substance in the vehicle," a person of ordinary skill in the art would not have understood this statement to pertain to coat weight, or to a specific amount of estradiol per unit area, or otherwise suggest the subject matter of the instant claims. In this regard, Applicant notes that the concentration of drug in a formulation is a distinct parameter from the amount of drug per unit area of a transdermal system (*e.g.*, "greater than 0.156 mg/cm^2 estradiol"). For example, the amount of drug per unit area of a monolithic transdermal drug delivery system as claimed depends on both the concentration of the drug in the polymer matrix formulation and the coat weight (*e.g.*, thickness) of the polymer matrix. As explained in the Guy Declaration, while the concentration of drug in a polymer matrix formulation was known to impact flux, the coat weight was not. See, e.g., Guy Declaration, ¶¶ 14-18.

Applicant notes further that Nuwayser is directed to a very different type of transdermal drug delivery system than those recited in the instant claims. For example, where the instant claims recite transdermal drug delivery systems consisting of (i) a backing layer, (ii) an adhesive polymer matrix layer defining an active surface area and, optionally, (iii) a release liner, Nuwayser is directed to reservoir-type systems that have a reservoir of a viscous liquid base material in which are suspended solid drug-containing microparticles. The systems of Nuwayser are not transdermal drug delivery systems as claimed, because they include a membrane layer disposed between the drug-containing reservoir and skin. *See* Nuwayser, Figs. 1-2 (**14**); col. 10, last para. Moreover, the systems of Nuwayser do not have an adhesive polymer matrix layer

defining an active surface area as claimed, because they have microparticles comprising biodegradable polymers and drug that are suspended in a liquid viscous base material that passes through a porous membrane for drug delivery. Thus, Nuwayser also fails to teach or suggest a system having an adhesive polymer matrix layer that has a coat weight of greater than 10 mg/cm^2.

Applicant also emphasizes that a person of ordinary skill in the art would not have extrapolated any principles relating to drug delivery from Nuwayser's systems to an adhesive polymer-matrix type composition as claimed, because Nuwayser's systems operate by a very different mechanism than the claimed systems. For example, Nuwayser's systems rely on the viscous liquid base material to form a film on the skin that forces hydration of the stratum corneum to promote drug delivery, and also require release of the drug from the microparticles into the viscous base material and passage of the base material through a membrane in order to achieve drug delivery.

Thus, the cited combination of references would not have suggested the claimed transdermal drug delivery systems, or provided a reasonable expectation of success. Rather, it is only the instant specification that teaches that monolithic transdermal drug delivery systems for estradiol consisting of (i) a backing layer, (ii) a single adhesive polymer matrix layer defining an active surface area and, optionally, (iii) a release liner, wherein the single adhesive polymer matrix layer comprises an adhesive polymer matrix comprising estradiol as the only drug, wherein the adhesive polymer matrix layer has a coat weight of greater than 10 mg/cm^2 and includes greater than 0.156 mg/cm^2 estradiol, can achieve an estradiol flux of from about 0.0125 to about 0.05 mg/cm^2/day, based on the active surface area.

As discussed in the specification, Applicant was surprised by the discovery that increasing the coat weight of the adhesive polymer matrix layer "resulted in an increased flux per unit area, and thus permitted the development of smaller transdermal drug delivery systems that achieve comparable daily dosages." Specification, paragraph [0015]. As explained in the specification, "[t]his result was surprising because coat weight is typically selected to control the

duration of delivery, but is not generally understood to impact delivery rate." *Id.* Indeed, "while it is known in the art to increase coat weight to provide delivery over a longer period of time, it was not known that increasing coat weight could increase delivery rate or flux, and thus permit the development of a smaller system while maintaining daily dosage." *Id. See also* Guy Declaration, ¶ 21.

The invention is important because it permits the development of smaller transdermal drug delivery systems that provide comparable drug delivery to the subject as a larger system. That is, a patient can use a smaller system instead of a larger system, which improves patient satisfaction and patient compliance, reduces the area of skin subject to occlusion and irritation, and reduces manufacturing costs. This result was surprising because coat weight is typically selected to control the duration of drug delivery, but was not understood to impact delivery rate (e.g., daily dose delivered). Rather, as reflected in the Vivelle-Dot® product line, the state of the art used the ***size*** of a system to predictably adjust drug flux, using larger systems to provide higher daily doses:

Vivelle-Dot® Product Line

Size	2.5 cm^2	3.75 cm^2	5.0 cm^2	7.5 cm^2	10 cm^2
Estradiol Content	0.39	0.585	0.78	1.17	1.56
Daily Dose	0.025	0.0375	0.05	0.075	0.1
Target Total Drug Delivery*	0.0875	0.13125	0.175	0.2625	0.35
% Drug Delivered	22.4 %	22.4 %	22.4 %	22.4 %	22.4 %

* =Daily Dose x 3.5, since the systems are to be replaced twice weekly.

As further evidence on these points, Applicant submits the Rule 132 Declaration of Dr. Guy previously submitted in U.S. 13/533,972, granted as U.S. Patent 9,730,900, and U.S. 14/024,985, granted as U.S. Patent 9,724,310. Dr. Guy's declaration provides background information on transdermal drug delivery and drug flux (including a discussion of Fick's 1st Law of Diffusion), discusses the impact of polymer components on drug flux (predicted by Fick's 1st Law), and discusses the surprising and unexpected result embodied in the claims that increasing coat weight increases estradiol flux (not predicted by Fick's 1st Law).

For at least these reasons, the claimed transdermal drug delivery systems would not have been obvious.

Obviousness-Type Double Patenting Rejections

The examined claims were provisionally rejected under the doctrine of obviousness-type double patenting over claims of co-pending application 14/738,255 and co-pending application 14/024,985 (now U.S. Patent 9,724,310), and were rejected under the doctrine of obviousness-type double patenting over claims of U.S. Patent No. 8,231,906. Without acquiescing to the merits of these rejections, and solely to expedite allowance, Applicant submits herewith a Terminal Disclaimer over co-pending application 14/738,255, U.S. Patent 9,724,310, and U.S. Patent No. 8,231,906, rendering these rejections moot.

Conclusion

Applicant believes that the application is in condition for allowance. Should there be any questions regarding this submission, or should any issue remain, the Examiner is urged to contact the undersigned by telephone in order to advance prosecution.

Respectfully submitted,

Date August 29, 2017

By /Courtenay C. Brinckerhoff/

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Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288

Electronic Patent Application Fee Transmittal

Application Number:	14870574
Filing Date:	30-Sep-2015
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff/Katie Newcomb
Attorney Docket Number:	041457-1160

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	30211385
Application Number:	14870574
International Application Number:	
Confirmation Number:	5148
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Customer Number:	22428
Filer:	Courtenay C. Brinckerhoff/Katie Newcomb
Filer Authorized By:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-1160
Receipt Date:	29-AUG-2017
Filing Date:	30-SEP-2015
Time Stamp:	16:16:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$180
RAM confirmation Number	083017INTEFSW16172401
Deposit Account	190741
Authorized User	Katie Newcomb

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

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Affidavit-traversing rejectns or objectns rule 132	132decl.pdf	1432767 a490c7b359349e78ce5cdcc7bab8af5c2bfaebc4	no	29
Warnings:					
Information:					
2	Affidavit-traversing rejectns or objectns rule 132	cv.pdf	554175 51cd3217c2559d0a15d2e03715bf62a99190c7ee	no	78
Warnings:					
Information:					
3		1160_IDS.pdf	68343 e686d3b492e528289a58764bb97934d78b171c21	yes	3

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal Letter	1	2
Information Disclosure Statement (IDS) Form (SB08)	3	3

Warnings:					
Information:					
4	Non Patent Literature	MANTELLEetal_1999.pdf	697485 7947f8e1e909221833aee86107bfe0e83014887b	no	3
Warnings:					
Information:					
5	Other Reference-Patent/App/Search documents	13553972_NOA_03232017.pdf	412552 a44d0e470e372006ec9345feab73a28f993259ef	no	7
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7	Other Reference-Patent/App/Search documents	14024985_NOA_04262017.pdf	412029 5b2834e69c89f454ff278131f14e968442b8ee2d	no	7
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Information:					
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Warnings:					
Information:					
9	Amendment/Req. Reconsideration-After Non-Final Reject	1160_Amdt.pdf	142364 c3f85e106af493f4e3c32557c000f39742abb095	no	11
Warnings:					
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10	Fee Worksheet (SB06)	fee-info.pdf	30822 7ae38acc79019489e9e8f3e07e4ce23fbc7a8030	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4600400		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Examiner:	Javier
Art Unit:	1611

App. No.	13/553,972	Filing Date: 7/20/2012	Conf. No.: 3635	Atty. Dkt No.041457-0992
App. No.	14/024,985	Filing Date: 9/12/2013	Conf. No.: 7031	Atty. Dkt No.041457-1016
App. No.	14/738,255	Filing Date: 6/12/2015	Conf. No.: 5737	Atty. Dkt No.041457-1133
App. No.	14/870,574	Filing Date: 9/30/2015	Conf. No.: 5148	Atty. Dkt No.041457-1160

DECLARATION UNDER 37 CFR § 1.132 OF RICHARD H. GUY, PH.D.

I, Richard H. Guy, Ph.D., hereby declare and say that:

I. QUALIFICATIONS AND EXPERIENCE

1. I have more than 30 years' research experience in the field of topical and transdermal drug delivery, including the study of drug absorption into and through the skin. During that time my research interests have spanned a wide range of subjects including the characterization of skin barrier function, transdermal drug delivery, enhancement of percutaneous absorption, iontophoresis, noninvasive biosensing, and the prediction and assessment of skin penetration and topical bioavailability.

2. I am currently Professor of Pharmaceutical Sciences at the University of Bath (UK) in the Department of Pharmacy & Pharmacology. I have held this position since 2004. From 2006-2008, I also served as Head of the Department of Pharmacy & Pharmacology at the University of Bath. Prior to joining the faculty at the University of Bath in 2004, I was Scientific Director of the Centre interuniversitaire de recherche et d'enseignement (Universities of Geneva (CH) and Lyon (FR)), and Professor of Biopharmaceutics in the Faculty of Sciences at the University of Geneva (CH). I held these positions between 1996 and 2004. Prior to that, I served as an

Assistant (1980-87), Associate (1987-1991) and Full Professor (1991-96) of Biopharmaceutical Sciences and Pharmaceutical Chemistry at the University of California, San Francisco ("UCSF"). During my time at UCSF (1987-1996), I was also Vice-Chair of the Department of Biopharmaceutical Sciences.

3. I obtained my Bachelor of Arts degree in chemistry from Oxford University (UK) in 1977, my Master of Arts degree in chemistry from Oxford University in 1980, and my Ph.D. in pharmaceutical chemistry from the University of London (UK) in 1980. I was awarded a D.Sc. by Oxford University in 2016.

4. I have co-authored more than 350 peer-reviewed articles and over 70 book chapters. Many of my peer-reviewed articles describe my research into understanding the mechanisms of topical and transdermal drug delivery. For example, in early work, I was involved in the development of diffusion and pharmacokinetic models of skin penetration and their application to the feasibility assessment of candidates for transdermal drug delivery. Subsequently, my research centered on a sustained effort to understand the mechanisms of skin penetration enhancement induced by chemical enhancers and other approaches, including (in particular) iontophoresis, and sonophoresis.

5. I have served as the Associate Editor of the Journal of Pharmaceutical Sciences (2002-2007) and currently serve on the editorial advisory boards of the European Journal of Pharmaceutical Sciences, Skin Pharmacology & Physiology, and the European Journal of Pharmaceutics and Biopharmaceutics.

6. Over the course of my career, I have earned numerous professional awards and honors, which are described in my curriculum vitae. For example, I am an elected Fellow of the Royal Society of Chemistry (UK, 1988), the American Association of Pharmaceutical Scientists (US, 1990), the American Association for the Advancement of Science (US, 1992), the Academy of Pharmaceutical Sciences, Great Britain (UK, 2007) and the Controlled Release Society College of Fellows (UK, 2010). More recently, I became a Fellow of the UCL School of Pharmacy,

University College, London, in recognition of my "distinguished contribution to the pharmaceutical sciences."

7. I am also a co-inventor of 12 issued U.S. patents in the field of transdermal drug delivery and glucose biosensing.

8. In the course of my career, I have served as a consultant (and scientific advisory board member) to numerous pharmaceutical companies, which have been involved in the development of transdermal drug delivery formulations (including both patches and other vehicles, such as gels). My role has involved assisting with the identification and evaluation of potential drug candidates for transdermal delivery and, quite often, with offering advice on formulation and/or enhancement strategies by which the skin absorption of target compounds might be increased to ensure therapeutic activity. I have authored or co-authored more than 30 articles and book chapters on aspects of transdermal delivery (including, most recently, "Transdermal Drug Delivery: 30+ Years of War and Still Fighting! S. Wiedersberg and R.H. Guy. J. Control. Release 190: 150-156 (2014)") and I have co-edited two books on the subject: [1] *Transdermal Delivery Systems: Developmental Issues and Research Initiatives.* Edited by J. Hadgraft and R.H. Guy. New York: Marcel Dekker, 1989; reprinted 1993. A 2nd Edition, revised and expanded, was published in 2003. [2] *Mechanisms of Transdermal Drug Delivery.* Edited by R.O. Potts and R.H. Guy. New York: Marcel Dekker, 1997. Several publications and book chapters address the manner in which drug pharmacokinetics can be modified and controlled by transdermal delivery, and describe the different patch designs, which have been used, their performance and benefits. The feasibility of transdermal delivery for certain drugs has been explored as well in this body of work, a subject which has been the focus of multiple interactions with the pharmaceutical industry as a consultant and scientific advisor.

9. A copy of my curriculum vitae, which includes my education background, work and research history, and a list of selected publications and presentations, is attached to this declaration as Exhibit 1.

10. Any opinions expressed herein are based on my education, research, knowledge and experience over the past 30 years in the field of transdermal drug delivery.

11. I was engaged by Noven Pharmaceuticals, Inc. ("Noven"), to serve as an expert witness in ANDA litigation involving U.S. Patent No.8,231,906 (the '906 Patent), in the U.S. District Court for the District of Delaware (C.A. No. 15-249) (the "ANDA litigation). I understand that U.S. patent applications 13/553,972, 14/024,985, 14/738,255, and 14/870,574 (the "pending applications") claim priority to the '906 Patent, and are assigned to Noven. I was engaged by Noven to prepare this declaration for the pending applications.

12. Noven is compensating me for my time associated with the pending applications at my customary consulting rate of $400 per hour. My compensation does not depend in any way on the outcome of the examination of the pending applications or on the outcome of the ANDA litigation.

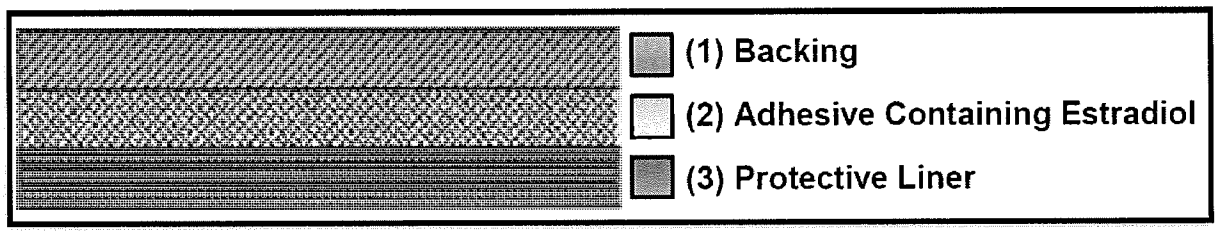
II. THE PENDING CLAIMS

13. I understand that the claims of the pending applications are directed to monolithic transdermal drug delivery systems for estradiol consisting of (i) a backing layer, (ii) a single adhesive polymer matrix layer defining an active surface area and comprising an adhesive polymer matrix comprising estradiol as the only drug, and, optionally, (iii) a release liner, methods for administering estradiol using such systems, and methods for making such systems. With regard to the adhesive polymer matrix, I understand that the claims of the '972, '985, and ' 255 applications recite that the adhesive polymer matrix has a coat weight of greater than about 10 mg/cm^2, includes greater than 0.156 mg/cm^2 estradiol, and achieves an estradiol flux of from about 0.0125 to about 0.05 $mg/cm^2/day$, based on the active surface area, with some claims reciting additional features. I understand that the claims of the '574 application recite that the coat weight of the adhesive polymer matrix layer is adjusted such that the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux of from about 0.0125 to about 0.05 $mg/cm^2/day$, based on the active surface area.

III. TECHNICAL BACKGROUND

14. I understand that the '906 Patent and the pending applications have a priority date of July 10, 2008. Thus, I discuss below what would have been known to a person of ordinary skill in the field of transdermal drug delivery as of July 10, 2008.

15. The inventions claimed in the pending applications generally relate to transdermal drug delivery systems (*e.g.*, transdermal "patches") for the delivery of estradiol, methods of administering estradiol to a patient using the claimed transdermal drug delivery systems, and delivering estradiol using them, and methods of making them. The claimed transdermal drug delivery systems are "monolithic" drug-in-adhesive systems that consist of (i) a backing layer; (ii) a drug-in-adhesive polymer matrix layer, and, optionally, (iii) a release liner that is removed prior to use, as illustrated below.



16. The claims recite that the adhesive polymer matrix layers include a certain amount estradiol per unit area and achieve a certain estradiol flux.

17. The flux of a drug is the rate at which it diffuses through the skin. As of June 10, 2008, a person of ordinary skill in the art understood that the passive flux of a drug can be quantitatively described and modelled by Fick's 1st law. Fick's 1st law is often used to describe drug delivery (in units of amount per time, *e.g.*, mg/day or µg/hour) from a transdermal patch across the skin:

$J = A \times k_p \times \Delta C$

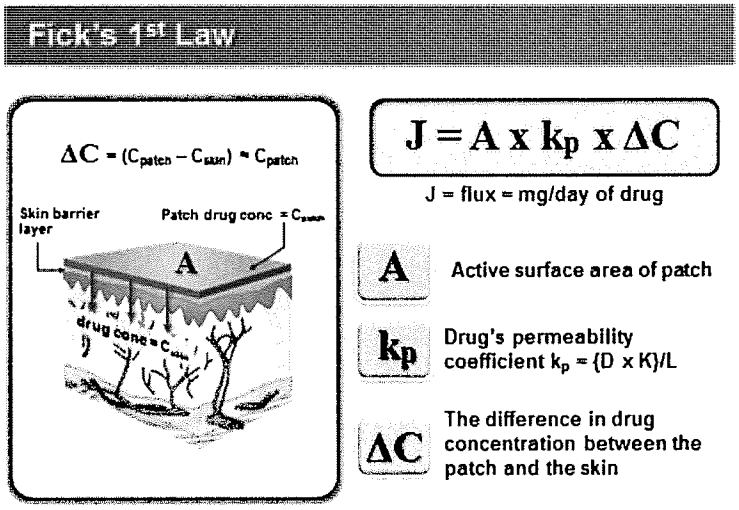
In this formula:

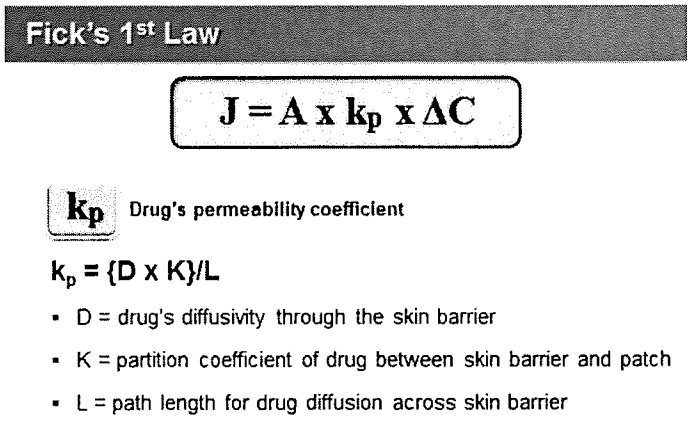
A is the active surface area of the patch.

k_p is the drug's permeability coefficient across the skin, and can be defined as $k_p = \{D \times K\}/L$, where D is the drug's diffusivity through the skin barrier, K is its partition coefficient between the skin barrier and the patch, and L is the path length for diffusion across the skin barrier.

ΔC is the difference in concentration of the drug between that in the patch (C_{patch}) and that on the "downstream" side of the skin barrier ($C_{downstream}$). In many examples of transdermal delivery, when depletion of drug from the patch is limited, ΔC can be approximated to C_{patch}.

The following images illustrate these factors:





18. Fick's 1st law indicates that there are four general ways to increase flux:

- Increase the active surface area of the patch to cause a proportional change in flux.
- Increase the drug concentration in the patch until it reaches its limiting solubility.
- Adjust the formulation to increase K, *e.g.*, cause drug concentration to approach more closely its limiting solubility.
- Introduce a penetration enhancer into the formulation to increase D and/or alter the value of K.

Nothing in Fick's 1st law indicates or predicts that increasing the coat weight (thickness) of a polymer matrix would increase flux. This is because no factor in Fick's 1st law embodies or includes coat weight.

IV. THE INVENTION

19. As set forth in the specification of the pending applications, the subject matter includes transdermal drug delivery systems for the transdermal delivery of estrogen that have a smaller active surface area than the prior art Vivelle-Dot® patches, but achieve daily dosages that are about equal to or greater than the Vivelle-Dot® patches. That is, the subject matter includes transdermal drug delivery systems that achieve daily dosages that are about equal to a Vivelle-Dot® patch, in a smaller size. *See, e.g.*, Specification, at paragraph [0014].

20. As stated in the specification, "the Applicant surprisingly discovered that increasing the coat weight of the drug-containing adhesive layer resulted in an increased flux per unit area, and thus permitted the development of smaller transdermal drug delivery systems that achieve comparable daily dosages." Specification, at paragraph [0014].

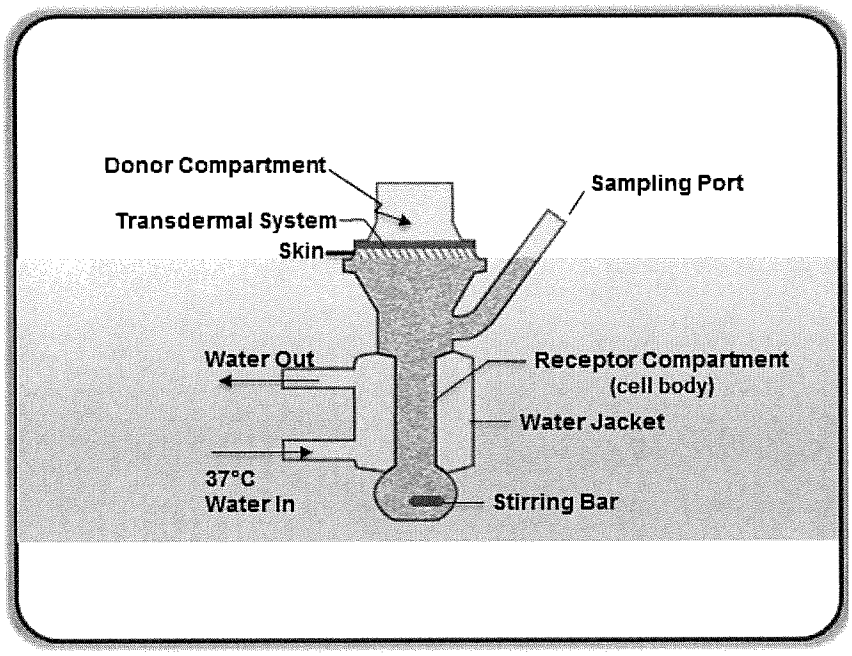
21. As stated in paragraph [0015] in the specification:

> This result was surprising because coat weight is typically selected to control the duration of delivery, but is not generally understood to impact delivery rate. Thus, while it is known in the art to increase coat weight to provide delivery over a

> longer period of time, it was not known that increasing coat weight could increase delivery rate or flux, and thus permit the development of a smaller system while maintaining daily dosage.

I agree with this statement because, as explained above, nothing in Fick's 1st law indicates or predicts that increasing the coat weight (thickness) of a polymer matrix would increase flux. That is, in accordance with Fick's 1st law, simply increasing the thickness of the patch formulation, *i.e.*, increasing the coat weight, would not increase flux, because coat weight *per se* would not affect any of the parameters/variables that determine flux according to Fick's 1st law. Thus, a person of ordinary skill in the art would not have thought of coat weight as a parameter to be adjusted to affect the flux of a drug from a transdermal patch. Indeed, the person of ordinary skill in the art would not have viewed coat weight as having any effect on flux and would not have been motivated to consider adjusting coat weight as a flux enhancement method. Rather, coat weight was understood by persons of ordinary skill in the art to affect only the duration over which a certain flux could be maintained. That is, persons of ordinary skill in the art understood that an increase in coat weight would potentially extend the time period over which the patch would achieve a given flux, and so might be adjusted to modify the wear period of a patch. However, neither Fick's 1st law, nor any other principle of transdermal drug delivery known in the art, indicated that increasing the coat weight of the drug-containing polymer matrix would increase flux.

22. The specification illustrates this surprising and unexpected effect in Example 1, which describes an *in vitro* flux study conducted to assess the flux of estradiol from different systems. The image below shows a typical Franz diffusion cell set up used to conduct an *in vitro* flux study.



In general, the receptor compartment is filled with a receiver solution that is stirred and held at a constant (typically, physiological) temperature. A transdermal system is placed on a skin sample in the donor compartment, and the contents of the receptor compartment are sampled (withdrawn) periodically and analyzed for drug (for example, estradiol) content. From this information, the cumulative amount of drug delivered over time and the flux of drug across the skin as a function of time is calculated. An illustration of the type of experimental data collected with this approach is shown below for one particular formulation; the results are presented as the average cumulative amounts of drug delivered, and the average drug flux, as a function of time, with the corresponding standard deviations for 4 replicate Franz diffusion cells.

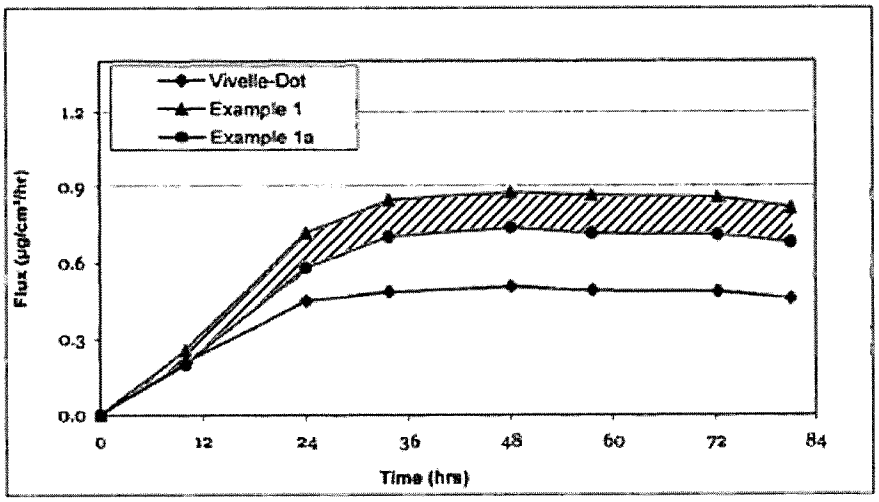
(hours) Average Time	(mcg/cm2) Average Cum.	(mcg/cm2) Cum. Stdev	(mcg/cm2 hr) Average Flux	(mcg/cm2 hr) Flux Stdev
0.00	0.00	0.00	0.00	0.00
9.92	2.55	0.49	0.26	0.05
23.95	12.64	1.99	0.72	0.11
33.65	20.85	2.91	0.85	0.10
48.03	33.45	4.10	0.88	0.08
57.58	41.70	4.81	0.86	0.08
72.20	54.23	5.71	0.86	0.06
81.02	61.43	6.07	0.82	0.04

23. Figure 1 reports the flux of drug across the skin for the systems tested in Example 1. Example 1 sets forth the polymer matrix formulation used to prepare Example 1 and Example 1a. As noted in the prosecution history of the '906 Patent, in the Amendment and Reply filed April 20, 2011, the specification as filed had a clerical error in the formulation listed (see below), but the flux data presented in Figure 1 is correct.

	Example 1	Actual Formulation
Silicone (4502)	56.9	66.9
Acrylic (Gelva 788)	20	10
PVP (Kollidon K-30)	7.5	7.5
DPG	8	8
Oleyl Alcohol	6	6
Estradiol	1.6	1.6

As described in the specification, test systems were prepared by applying the polymer matrix to a release liner at two different coat weights: 12.5 mg/cm^2 (Example 1a, •) and 15 mg/cm^2 (Example 1, ▲), and estradiol flux was assessed in an *in vitro* flux study. As reported in Figure 1, the system with the higher coat weight exhibited a greater flux.

Figure 1



The only difference between Example 1 and Example 1a is the coat weight of the polymer matrix

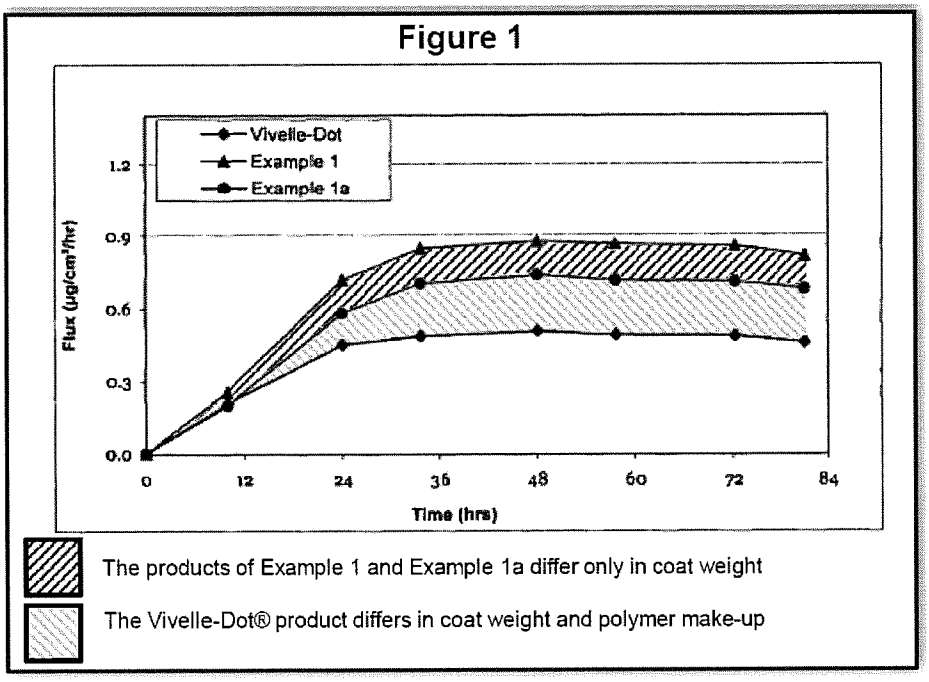
The only experimental variable different between Example 1a and Example 1 is the coat weight of the polymer matrix. The difference in flux reported in Figure 1 between Example 1a and Example 1 can only be attributed, therefore, to the difference in coat weight, which is a surprising and unexpected result that is not predicted by Fick's 1st Law.

24. Figure 1 also reports results achieved with a Vivelle-Dot® system. As described in the prescribing information, Vivelle-Dot® is a monolithic transdermal drug delivery system for estradiol with a polymer matrix layer that includes estradiol as the only drug, acrylic adhesive, silicone adhesive, oleyl alcohol, povidone, and dipropylene glycol. The specification states that each Vivelle-Dot® patch includes 0.156 mg/cm^2 estradiol and has a polymer matrix coat weight of 10 mg/cm^2. *See, e.g.*, Specification at paragraph [0013]; [0074]. Although Vivelle-Dot® includes the same polymer matrix components of the Example 1 formulation, I have been informed that the Vivelle-Dot® formulation includes different amounts of some components, including different relative amounts of acrylic adhesive and silicone adhesive, with a greater relative amount of acrylic adhesive. That is, the formulation of Examples 1 and 1a have less acrylic adhesive and more silicone adhesive than the Vivelle-Dot® formulation. I have been

informed that the precise formulation of Vivelle-Dot® is confidential, proprietary information of a third party that Noven is contractually obligated to maintain confidential.

25. I understand from prior art such as U.S. Patent No. 6,024,976 (the "'976 Patent") and Mantelle, *et al.*, *Effect of Silicone/Acrylic PSA Blends on Skin Permeation*, 26 *Proc. Internat'l Symp. Controlled Release of Bioactive Materials* 5123, 415-16 (Revised July 1999) ("Mantelle Article"), and from Juan A. Mantelle, "Dot Matrix® Technology," in MODIFIED RELEASE DRUG DELIVERY TECHNOLOGY (2nd ed. 2008) 405-14 ("Mantelle Chapter"), and the experimental data presented below, that the difference in relative amounts of acrylic adhesive and silicone adhesive between the formulation of Examples 1 and 1a and the Vivelle-Dot® formulation contributes to the difference in flux seen in Figure 1 between Vivelle-Dot® and Example 1 and Example 1a.

Figure 1



I cannot quantify the relative contributions of coat weight and polymer composition to the differences in flux observed between the Vivelle-Dot® system and Examples 1 and 1a systems. However, based on the difference in flux between the Example 1 and 1a systems (which, as explained above, can only be due to the difference in coat weight), and in view of other experimental data discussed below, it is my opinion that the difference in coat weight is

contributing to the difference in flux between the Vivelle-Dot® system and the Example 1 and 1a systems.

V. EXPERIMENTAL DATA – IMPACT OF POLYMER MAKE-UP ON FLUX

26. As noted above, I understand from prior art such as the '976 Patent and the Mantelle Article that the relative amounts of acrylic adhesive and silicone adhesive used in an estradiol polymer matrix can impact the flux of estradiol. As described in the '976 Patent, this is because estradiol's solubility in acrylic adhesives differs from that in silicone adhesives. The potential effect of the relative amounts of acrylic adhesive and silicone adhesive is illustrated in Examples 10-13 and Figure 6 of the '976 patent, which reports:

> FIG. 6 shows estradiol flux progressively increased with increased silicone polymer content during the first 22 hours of delivery, but was affected to a much lesser degree during the remainder of the study (22 to 99 hours). Thus, significant adjustment of the estradiol delivery rate during the initial phase of delivery was accomplished, with minor effects on the later delivery phase, by modulating the polysiloxane to polyacrylate polymer ratio. FIG. 6 also illustrates that the delivery characteristics over time can be adjusted by the appropriate choice of polymers and respective weight ratios. For example, the formulation of Example 10 delivers drug at approximately the same rate over time whereas the formulation of Example 13 delivers more quickly in the early phase than the latter.

A similar effect is reported in the Mantelle Article, which states:

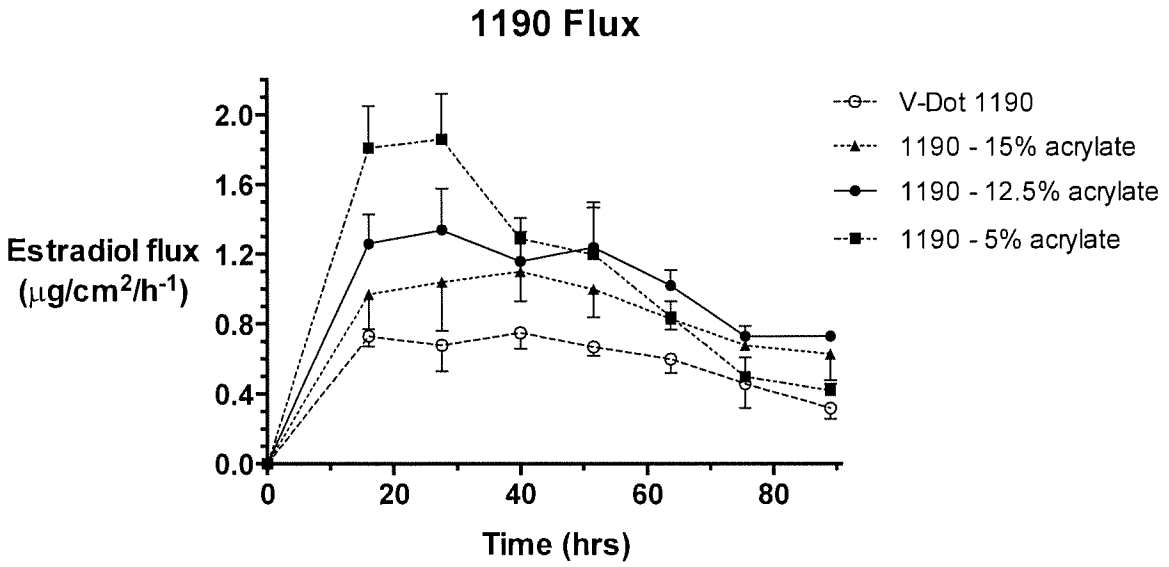
> As shown, varying the silicone to acrylic psa ratio from 56.9:20 to 61.9:15 to 66.9:10 resulted in an average flux rate increase … with the additional effect of having altered the initial burst effect and subsequent sustenance of the pseudo-zero-order delivery profile. As can be seen in Figure 2, higher silicone to acrylic psa ratios resulted in a shift of the permeation profile from a pseudo-zero-order to a first order delivery system incapable of sustaining the targeted 84 hour delivery.

Thus, it was known in the art that the relative amounts of acrylic adhesive and silicone adhesive in an estradiol polymer matrix can impact estradiol flux, and that increasing the relative amount of silicone polymer generally increased the flux but may alter the drug delivery profile such that the increased flux is not sustained.

27. This effect is shown by the results for Flux Study 1190 conducted by Noven. Flux Study 1190 tested five different formulations at the same target coat weight (15 mg/cm^2) and used a Vivelle-Dot® system (♦) as an internal control. The five formulations differed in the relative amounts of acrylic adhesive and silicone adhesive, as follows:

Component (% by weight)	5% Acrylic	10% Acrylic	12.5% Acrylic	15% Acrylic	17.5% Acrylic
Acrylic Adhesive	5	10	12.5	15	17.5
Silicon Adhesive	71.9	66.9	64.5	61.9	59.4
Dipropylene Glycol	8	8	8	8	8
Oleyl Alcohol	6	6	6	6	6
PVP	7.5	7.5	7.5	7.5	7.5
Estradiol	1.6	1.6	1.6	1.6	1.6

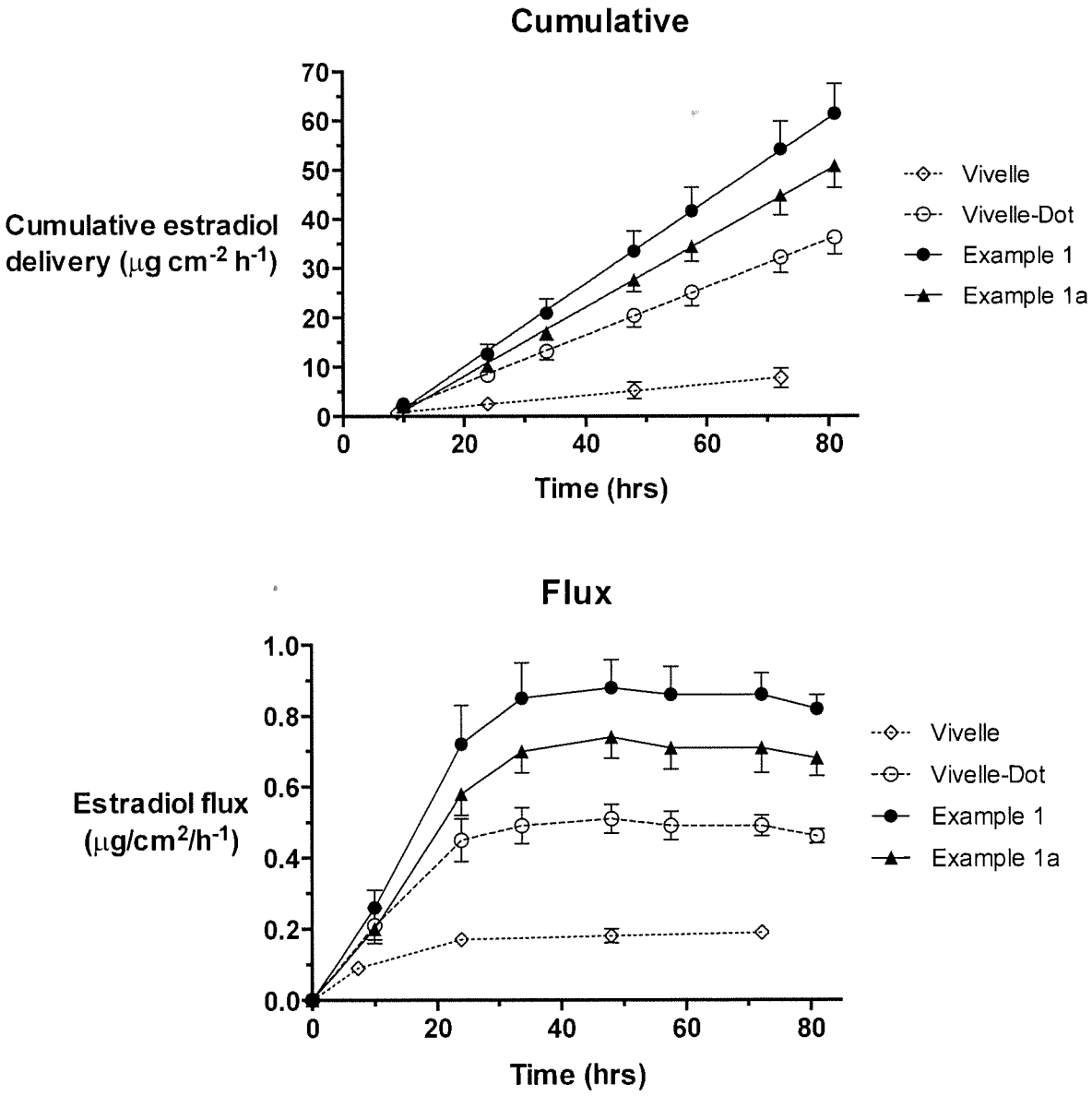
A representative sample of the data from this Flux Study are shown in the figure below. The results (reported as the average of 5 replicates) show that initial flux increased as the relative amount of acrylic polymer decreased but the initially higher flux from the 5% acrylic composition was not sustained:



VI. EXPERIMENTAL DATA – IMPACT OF COAT WEIGHT ON FLUX

28. As noted above, while it was known in the art that the relative amounts of acrylic adhesive and silicone adhesive in an estradiol polymer matrix can impact estradiol flux, it was not known or expected that the coat weight of the polymer matrix would impact flux, but Noven conducted a number of other flux studies that showed this effect with monolithic transdermal drug delivery systems for estradiol as described in the pending applications.

29. Flux Study 1326 is the flux study reported in Example 1 of the pending applications. As discussed above, the same formulation (1.6 % estradiol, 10% acrylic adhesive, 66.9% silicone adhesive, 6% oleyl alcohol, 7.5% povidone, and 8% dipropylene glycol) was tested at coat weights of 12.5 mg/cm^2 and 15 mg/cm^2. Both Vivelle® and Vivelle-Dot® were used as internal controls. As noted above, the results (see below) (reported as the average of 4 replicates) show that the increase in the coat weight of the polymer matrix from Example 1a to Example 1 resulted in an increased flux of estradiol.

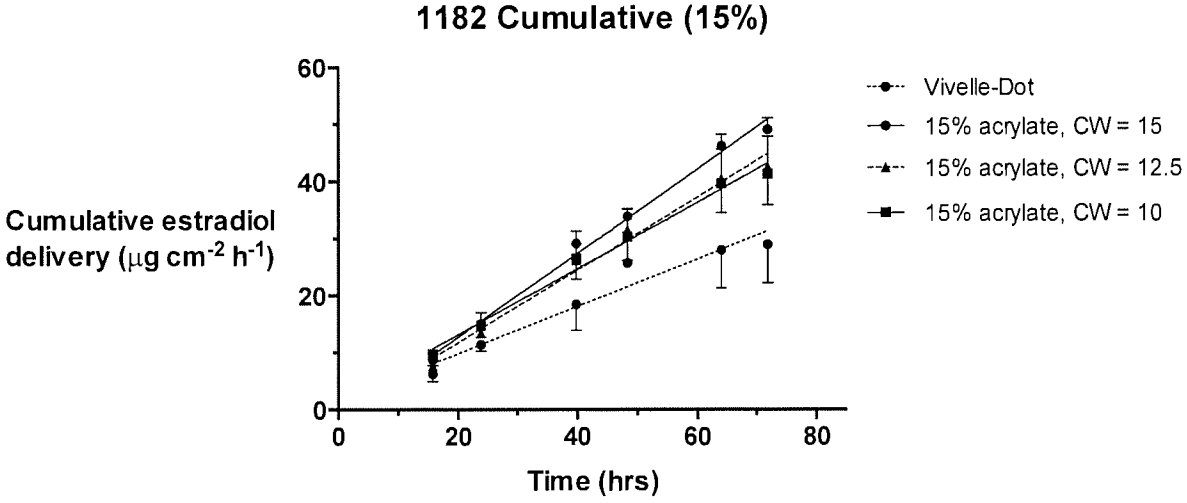


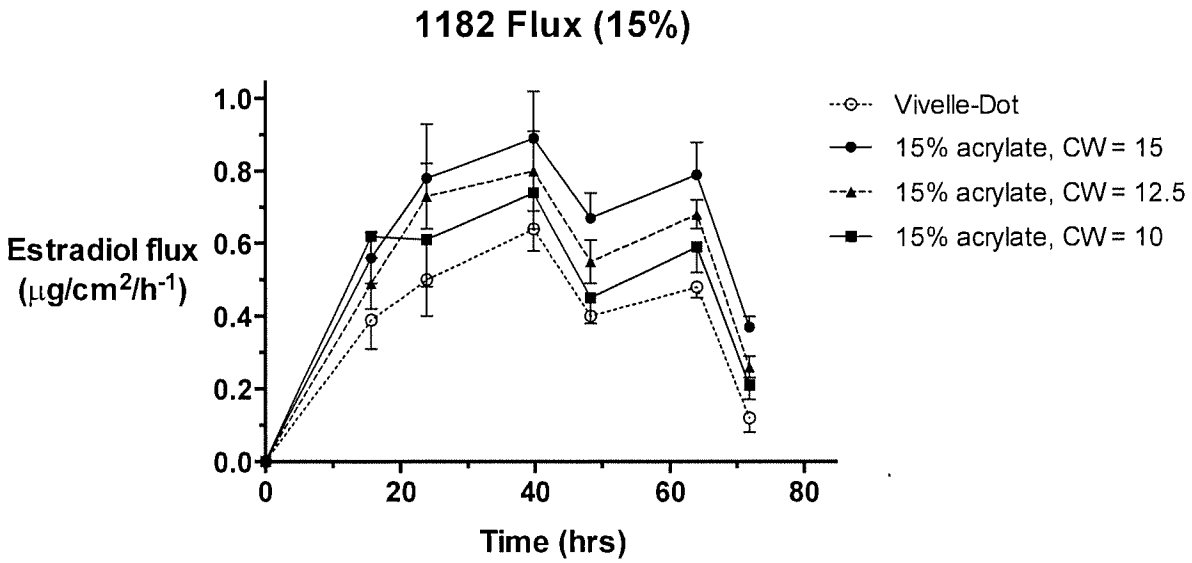
30. Flux Study 1182 conducted by Noven tested four different formulations at three different target coat weights and used a Vivelle-Dot® system as an internal control. The four formulations differed in the relative amounts of acrylic adhesive and silicone adhesive, as follows:

Component (% by weight)	10% Acrylic	15% Acrylic	17.5% Acrylic	20% Acrylic
Acrylic Adhesive	10	15	17.5	20
Silicon Adhesive	66.9	61.9	59.4*	56.9
Dipropylene Glycol	8	8	8	8
Oleyl Alcohol	6	6	6	6
PVP	7.5	7.5	7.5	7.5
Estradiol	1.6	1.6	1.6	1.6

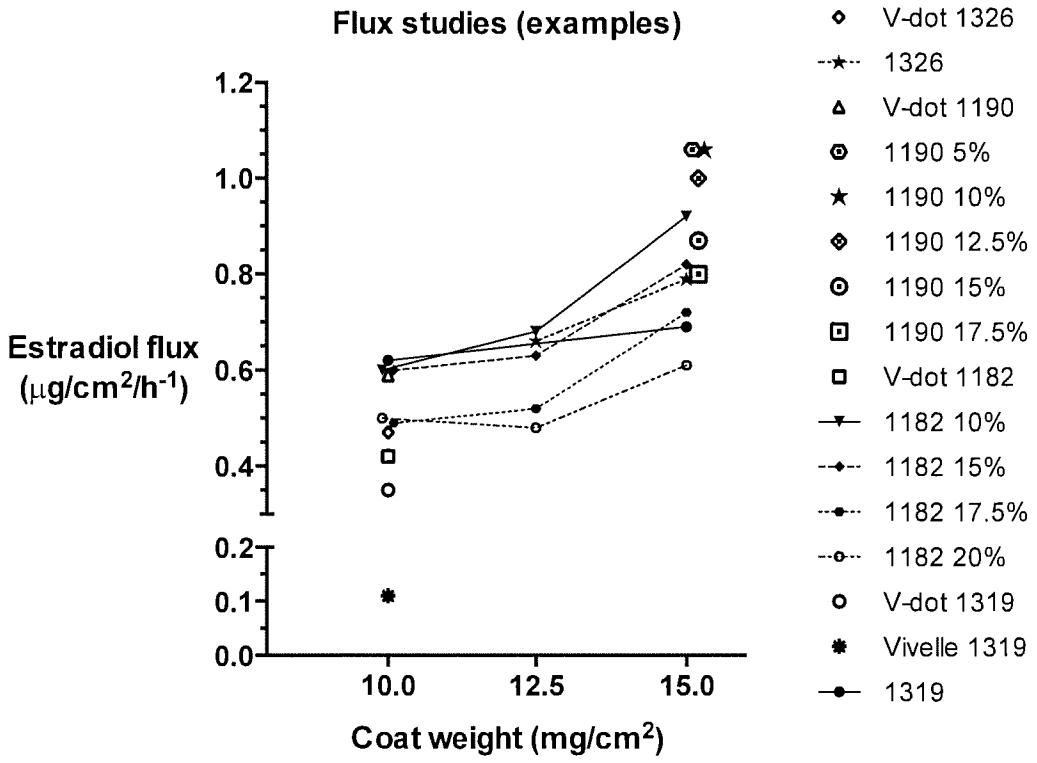
*Reported as 59.9%, but likely used 59.4% Silicone Adhesive.

The different target coat weights assessed were 10 mg/cm^2, 12.5 mg/cm^2 and 15 mg/cm^2. The overall results show that increasing coat weight from 10 mg/cm^2 to 15 mg/cm^2 surprisingly and unexpectedly increased flux. For illustration, results (reported as the average of 4 replicates) for the composition with 15% acrylic polymer at a coat weight of 10 mg/cm^2, 12.5 mg/cm^2, and 15 mg/cm^2 are set forth below (Vivelle-Dot® was used as an internal control).





31. The estimated estradiol fluxes from Flux Studies 1190 and 1182 (reported as the average of 5 and 4 replicates, respectively) are shown below (some values are slightly displaced along the x-axis to facilitate visualization of each data point; for example, the estimated flux for 1182 10% at a coat weight of 10 mg/cm^2 is plotted at 9.9 on the x-axis and the estimated flux for 1182 15% at a coat weight of 10 mg/cm^2 is plotted at 10.1 on the x-axis, because they both had an estimated flux of 0.6 μg/cm^2/hr):



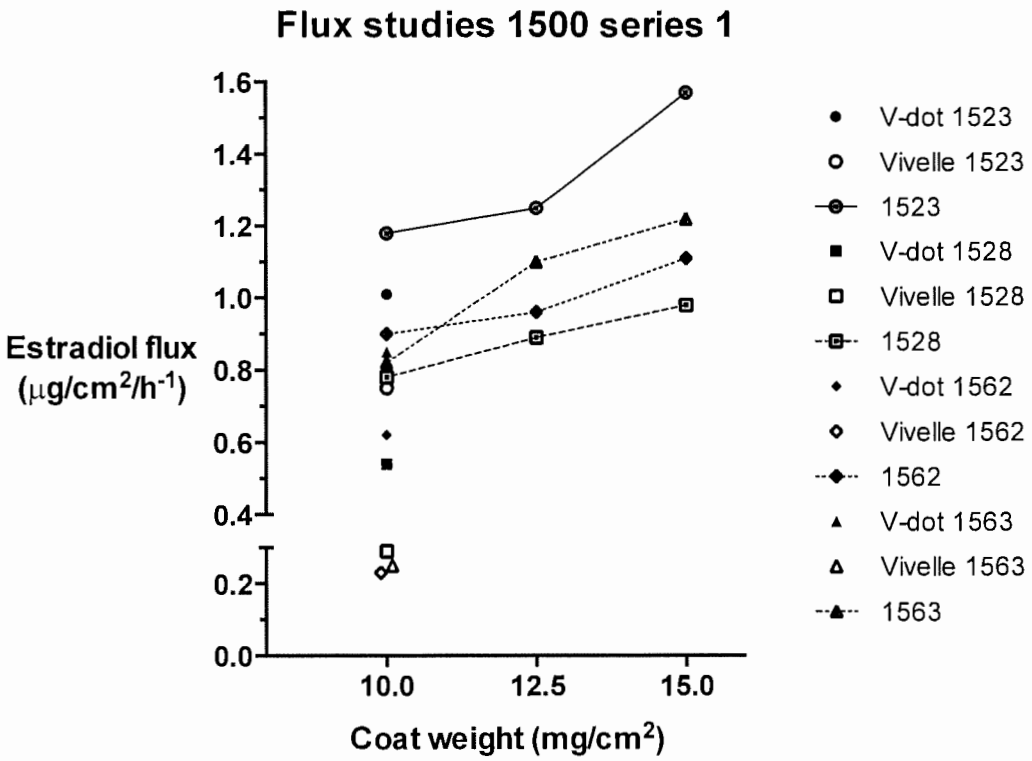
32. Collectively, the results from Flux Study 1190 and Flux Study 1182 indicate that while the relative amounts of acrylic adhesive and silicone adhesive impact the flux of estradiol—as was known in the art—the coat weight of the polymer matrix also impacts flux—which was not known in the art, and indeed was a surprising and unexpected result not predicted by Fick's 1st law of diffusion.

33. Flux Studies 1523, 1528, 1562 and 1563 assessed other formulations at different target coat weights, as outlined in the following table.

Flux Study	Formulation Components (% by weight)						Coat Wt. (mg/cm^2)	Drug Flux ($\mu g/cm^2 \cdot h$)
	Acrylate	Silicone	DPG	OAlc	PVP	Estradiol		
1523	10	69.4	8	6	5	1.6	15	1.57
	10	69.4	8	6	5	1.6	12.5	1.25
	10	69.4	8	6	5	1.6	10	1.18
	Control (flux): Vivelle-Dot® (1.01 $\mu g/cm^2 \cdot h$)							

Flux Study	Formulation Components (% by weight)						Coat Wt. (mg/cm^2)	Drug Flux ($\mu g/cm^2 \cdot h$)
	Acrylate	Silicone	DPG	OAlc	PVP	Estradiol		
1528	10	69.4	8	6	5	1.6	15	0.98
	10	69.4	8	6	5	1.6	12.5	0.89
	10	69.4	8	6	5	1.6	10	0.78
	Control (flux): Vivelle-Dot® (0.54 $\mu g/cm^2 \cdot h$)							
1562 (Form. 1)	10	69.4	8	6	5	1.6	15	1.11
	10	69.4	8	6	5	1.6	12.5	0.96
	10	69.4	8	6	5	1.6	10	0.90
	Control (flux): Vivelle-Dot® (0.62 $\mu g/cm^2 \cdot h$)							
1563 (Form. 1)	10	69.4	8	6	5	1.6	15	1.22
	10	69.4	8	6	5	1.6	12.5	1.10
	10	69.4	8	6	5	1.6	10	0.82
	Control (flux): Vivelle-Dot® (0.85 $\mu g/cm^2 \cdot h$)							

34. The estimated estradiol fluxes from Flux Studies 1523, 1528, 1562, and 1563 are illustrated below (reported as the average of 3 or 4 replicates; some values are again slightly displaced along the x-axis to facilitate visualization of the data points), and again show the surprising and unexpected impact of polymer matrix coat weight on flux:



35. Flux Studies 1562 and 1563 were repeated with different formulations at coat weights of 12.5 mg/cm^2 and 15 mg/cm^2 using both Vivelle and Vivelle-Dot® as internal controls.

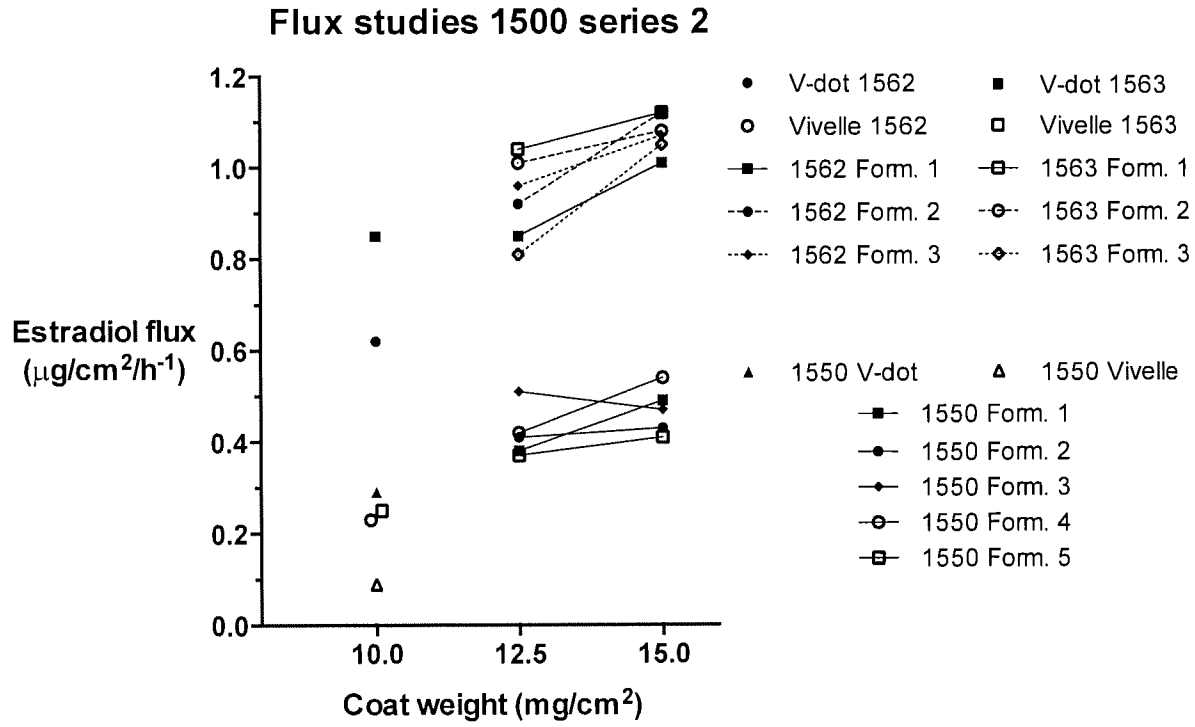
Flux Study	Formulation Components (% by weight)						Coat Wt. (mg/cm^2)	Drug Flux (μg/cm^2•h)
	Acrylate	Silicone	DPG	OAlc	PVP	Estradiol		
1562 (Form. 1)	10	69.4	8	6	5	1.6	15	1.01
	10	69.4	8	6	5	1.6	12.5	0.85
1562 (Form. 2)	7	72.6	8	6	5	1.4	15	1.12
	7	72.6	8	6	5	1.4	12.5	0.92
1562 (Form. 3)	7	74.6	8	6	3	1.4	15	1.07
	7	74.6	8	6	3	1.4	12.5	0.96
1562 Control (flux): Vivelle-Dot® (0.62 μg/cm^2•h)								
1563	10	69.4	8	6	5	1.6	15	1.12

Flux Study	Formulation Components (% by weight)						Coat Wt. (mg/cm^2)	Drug Flux ($\mu g/cm^2 \cdot h$)
	Acrylate	Silicone	DPG	OAlc	PVP	Estradiol		
(Form. 1)	10	69.4	8	6	5	1.6	12.5	1.04
1563 (Form. 2)	7	72.6	8	6	5	1.4	15	1.08
	7	72.6	8	6	5	1.4	12.5	1.01
1563 (Form. 3)	7	74.6	8	6	3	1.4	15	1.05
	7	74.6	8	6	3	1.4	12.5	0.81
1563 Control (flux): Vivelle-Dot® (0.85 $\mu g/cm^2 \cdot h$)								

36. Flux Study 1550 assessed other formulations at different target coat weights, as outlined in the following table.

Formulation	Formulation Components (% by weight)						Coat Wt. (mg/cm^2)	Drug Flux ($\mu g/cm^2 \cdot h$)
	Acrylate	Silicone	DPG	OAlc	PVP	Estradiol		
Form. 1	10	71.6	8	6	3	1.4	15	0.49
	10	71.6	8	6	3	1.4	12.5	0.38
Form. 2	10	69.4	8	6	5	1.6	15	0.43
	10	69.4	8	6	5	1.6	12.5	0.41
Form. 3	7	72.6	8	6	5	1.4	15	0.47
	7	72.6	8	6	5	1.4	12.5	0.51
Form. 4	7	74.6	8	6	3	1.4	15	0.54
	7	74.6	8	6	3	1.4	12.5	0.42
Form. 5	10	73.4	6	6	3	1.6	15	0.41
	10	73.4	6	6	3	1.6	12.5	0.37
Control (flux): Vivelle-Dot® (0.29 $\mu g/cm^2 \cdot h$)								

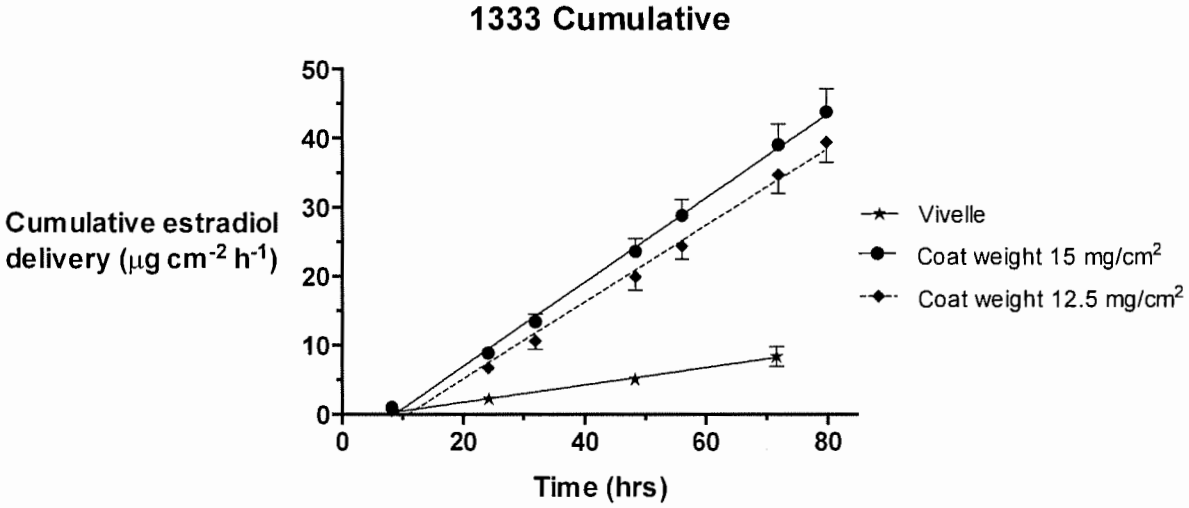
37. The estimated estradiol fluxes from 1562 and 1563 (second series) (reported as the average of 3 replicates; some values are slightly displaced along the x-axis to facilitate visualization of the data points) and 1550 are illustrated below (reported as the average of 4 replicates), and again show the surprising and unexpected impact of polymer matrix coat weight on flux:

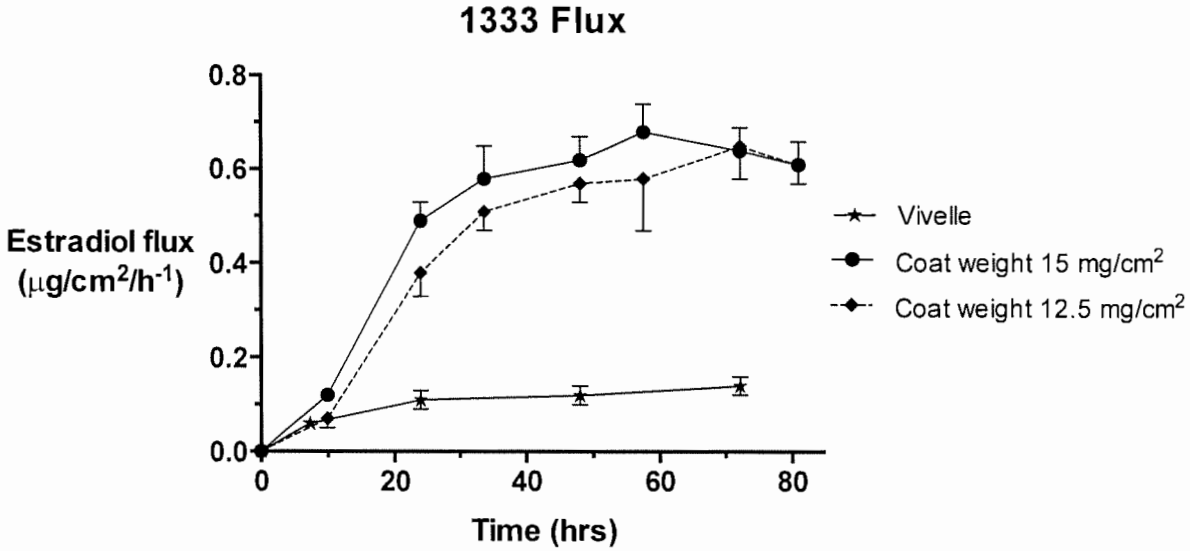


38. Although the results for Flux Study 1550 - Formulation 3 show a higher flux for the lower coat weight, that does not change my opinion that the totality of the data show the surprising and unexpected result that increasing coat weight increases flux. Indeed, Formulation 3 of Flux Study 1550 is the same formulation as Formulation 2 of Flux Study 1562 and Formulation 2 of Flux Study 1563 and, in both of those flux studies, this formulation exhibited a higher flux at the higher coat weight.

39. I also reviewed Flux Study 1333, which assessed the flux of a formulation having the same components as the Example 1 formulation at a target coat weight of 12.5 mg/cm^2 and 15 mg/cm^2 and used a Vivelle® system as an internal control. Although the researcher, who

oversaw this study, prepared the graphs shown below (reporting the average of 4 replicates), which indicate that increasing coat weight increased flux, the experimental data reported by the technician correlate the 12.5 mg/cm^2 sample with the higher flux results. I understand that the researcher, who oversaw this study, believes that the technician switched or mislabeled the samples. However, regardless of whether this set of flux results are reported correctly, they do not change my opinion that the totality of the data, when viewed in its entirety, consistently show the surprising and unexpected result that increasing coat weight increases flux. Indeed, as shown above, several other studies using the same formulations show that the higher coat weight was correlated with greater flux.





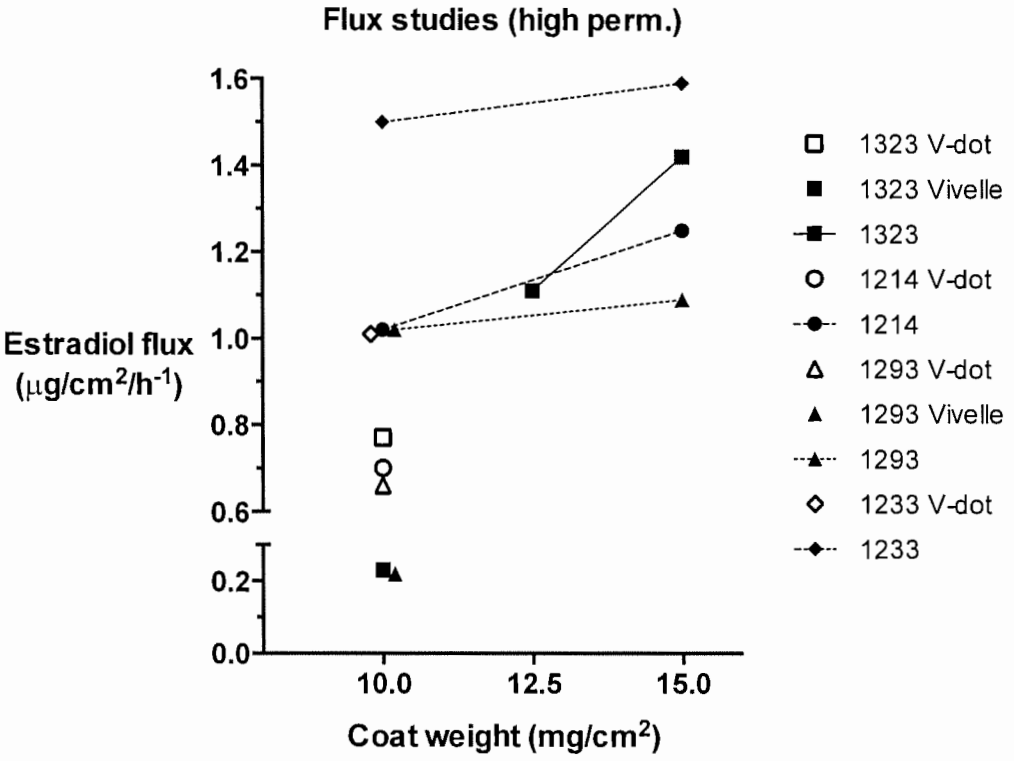
VII. EXPERIMENTAL DATA – IMPACT OF SKIN PERMEABILITY ON FLUX

40. Since drug flux is a measure of the rate at which drug passes through the skin, the permeability of the skin sample used in a flux study can impact the results. The permeability of human skin varies from person to person and region of skin to region of skin. I understand that Noven accounted for this variability by using internal controls, such as Vivelle®-Dot or Vivelle®, since it was very familiar with the flux of these FDA-approved systems which were developed at Noven .

41. The impact of skin permeability on flux and the usefulness of an internal control in this context is illustrated in Flux Studies 1214, 1233, and 1293, which assessed the flux of formulations having the same components as the Example 1 formulation at target coat weights of 10 mg/cm^2 and 15 mg/cm^2 (and used Vivelle-Dot® and Vivelle as internal controls).

Study #	Formulation Components (% by weight)						Coat Wt. (mg/cm^2)	Drug Flux ($\mu g/cm^2 \cdot h$)
	Acrylate	Silicone	DPG	OAlc	PVP	Estradiol		
1323	10	66.9	8	6	7.5	1.6	15	1.42
	10	66.9	8	6	7.5	1.6	12.5	1.11
Control (flux): Vivelle-Dot® (0.77 $\mu g/cm^2 \cdot h$)								
Control (flux): Vivelle® (0.23 $\mu g/cm^2 \cdot h$)								
1214	10	66.9	8	6	7.5	1.6	15	1.25
	10	66.9	8	6	7.5	1.6	10	1.02
Control (flux): Vivelle-Dot® (0.7 $\mu g/cm^2 \cdot h$)								
1293	10	66.9	8	6	7.5	1.6	15	1.09
	10	66.9	8	6	7.5	1.6	10	1.02
Control (flux): Vivelle-Dot® (0.66 $\mu g/cm^2 \cdot h$)								
Control (flux): Vivelle® (0.22 $\mu g/cm^2 \cdot h$)								
1233	10	66.9	8	6	7.5	1.6	15	1.59
	10	66.9	8	6	7.5	1.6	10	1.50
Control (flux): Vivelle-Dot® (1.01 $\mu g/cm^2 \cdot h$)								

The cumulative flux results (reported as the average of 4 or 5 replicates; some values are once more slightly displaced along the x-axis to facilitate visualization of each data point) are illustrated below:



42. In these studies, the estradiol flux from Vivelle-Dot® was higher than usual, indicating that the donor skin had a higher permeability than usual. While the product label and the patient information leaflet indicate that the estradiol transdermal flux from the Vivelle®-Dot system is nominally 0.4 μg cm^{-2} h^{-1}, the values observed in these flux studies were 1.5 to 2.5-fold higher. The high fluxes seen from the test formulations are therefore completely consistent with that from the Vivelle®-Dot control (and reinforce the clear benefit of including this system as an internal check in experiments such as these).

VIII. NO PRIOR ART SUGGESTS THAT COAT WEIGHT WOULD IMPACT FLUX

43. As I noted above, a person of ordinary skill in the art would not have thought of coat weight as a parameter to be adjusted to affect the flux of a drug from a transdermal patch. In this

regard, I confirm that none of the prior art references cited by the Patent Office Examiner during examination of the pending applications suggests that increasing coat weight would increase flux. Rather, to the extent any of the prior art cited by the Patent Office Examiner discusses coat weight, the references simply provide ranges of typical coat weights. Indeed, prior to the teachings of the specification, the coat weight (thickness) of the polymer matrix was understood to be relevant to the patch's ability to sustain desired flux over time. Thus, while the person of ordinary skill in the art would have expected an increase in coat weight to extend the period that the patch could sustain a given flux (*i.e.*, the number of days for which a patch would deliver the target daily dose), he or she would not have expected an increase in coat weight to increase flux (*i.e.*, the daily dose). Rather, the prior art shows that the most predictable way to obtain a greater flux of drug across the skin from a transdermal patch is to increase its size, since there is a direct relationship between flux and active surface area in Fick's 1st law of diffusion. This is seen, for example, in the different strengths of Vivelle-Dot®, which differ only in active surface area.

44. .

45. Thus, the prior art does not teach or suggest that coat weight is a parameter to be adjusted to affect the rate of drug flux.

However, the pending applications describe this surprising and unexpected result and demonstrate it in Example 1. Moreover, the additional experimental data discussed above provide further support for the surprising and unexpected effect.

* * *

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

June 13, 2017

Date

Richard H. Guy

Richard H. GUY – *Curriculum Vitae*

Richard Guy received an M.A. in Chemistry from Oxford University, and his Ph.D. in Pharmaceutical Chemistry from the University of London in 1980. He then joined the faculty of the University of California, San Francisco (UCSF), where he was Assistant (1980-87), Associate (1987-1991) and finally Full Professor (1991-1996) of Biopharmaceutical Sciences & Pharmaceutical Chemistry. From 1987 until 1996, Dr. Guy was Vice-Chair of the Department of Biopharmaceutical Sciences at UCSF. During the next 8 years, Dr. Guy was Scientific Director of the *Centre interuniversitaire de recherche et d'enseignement* (Universities of Geneva and Lyon), and Professor of Biopharmacy in the Faculty of Sciences at the University of Geneva. In 2004, he assumed his present position as Professor of Pharmaceutical Sciences at the University of Bath and was Head of the Department of Pharmacy & Pharmacology at Bath from 2006 to 2008. He has also fulfilled the broader role of University Research Advisor. He remains an Adjunct Professor of Bioengineering and Therapeutic Sciences at UCSF.

Dr. Guy's principal achievements have been made in the areas of skin barrier function characterization, transdermal drug delivery, enhancement of percutaneous absorption, iontophoresis, noninvasive biosensing of blood glucose and other analytes, and the prediction and assessment of skin penetration and topical bioavailability. In total, Dr. Guy has published over 350 peer-reviewed articles and over 70 book chapters. He has co-authored one book and co-edited 7 others. He is also co-inventor of 12 patents. His research is presently supported by the U.S. Food & Drug Administration and the pharmaceutical and personal care industries. Current h-index (Scopus) is 67, with over 15,000 citations to Dr. Guy's publications.

Specific ongoing projects include: the development and validation of *in vitro-in vivo* correlations for the assessment of topical drug product bioequivalence; investigation of polymeric film-forming systems as sustained release platforms for topical drugs; determination of the disposition of drug and formulation excipients (including nanoparticles) post-application to the skin and nail using coherent Raman scattering and confocal microscopy; and derivation and evaluation of predictive models of percutaneous penetration for pharmaceutical and cosmetic 'actives', and for potentially toxic chemicals, which contact the skin.

Dr. Guy was an Associate Editor of the Journal of Pharmaceutical Sciences (2002-07) and currently serves on the editorial advisory boards of Diabetes Technology and Therapeutics, the European Journal of Pharmaceutical Sciences, Skin Pharmacology & Physiology, and the European Journal of Pharmaceutics and Biopharmaceutics. He was President of the Controlled Release Society (CRS) in 2000-01, and has served as a member of the Academy of Pharmaceutical Sciences (GB) board. Dr. Guy serves as a consultant and scientific advisor to several companies in the pharmaceutical, cosmetic and biotechnology industries.

Dr. Guy is an elected Fellow of the Royal Society of Chemistry (1988), the American Association of Pharmaceutical Scientists (1990), the American Association for the Advancement of Science (1992), the Academy of Pharmaceutical Sciences, Great Britain (2007) and the Controlled Release Society (CRS) College of Fellows (2010). He was the first recipient of the CRS Young Investigator Award in 1988, when he also won the British Pharmaceutical Conference Science Award. Dr. Guy was awarded, for his work in "reverse iontophoresis" and noninvasive glucose monitoring, the Prix Applications Médicales de l'Electricité, 1997 by the Institut Electricité Santé, Paris, France. In April 2000, Dr. Guy received the APV Research Award for Outstanding Achievements in the Pharmaceutical Sciences and, in 2007, he won the "Prix Pharmapeptides" from the Universities of Geneva and Lyon. In 2010, Dr. Guy became a Fellow of The School of Pharmacy (now the UCL School of Pharmacy), University of London, in recognition of "his distinguished contribution to the pharmaceutical sciences", and he received the CRS Founders Award in 2013. The Maurice-Marie Janot Award from the Association Pharmacie Galénique Industrielle (APGI) followed in 2016 for his "original and innovative papers in the domain of pharmaceutics, biopharmaceutics and pharmaceutical technology", the same year that he was awarded the degree of Doctor of Science from Oxford University.

Curriculum Vitae - Richard H. Guy

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1977	B.A., Chemistry (First Class) Oxford University, Oxford, England
1980	M.A., Chemistry Oxford University, Oxford, England
1977-80	Ph.D., Pharmaceutical Chemistry University of London, London, England
2016	D.Sc., Medical Sciences Division Oxford University, Oxford, England

Specialty; Subspecialty

Chemistry; Physical Pharmaceutical Chemistry

Academic and Professional Positions Held

1978-80	Teaching Fellow School of Pharmacy, University of London, London, England
1980-87	Assistant Professor Departments of Biopharmaceutical Sciences and Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California
1982-96	Research Associate Department of Dermatology, School of Medicine University of California, San Francisco, California
1986-2000	Honorary Professor The Welsh School of Pharmacy, Cardiff University, Cardiff, Wales
1987-91	Associate Professor

	Departments of Biopharmaceutical Sciences and Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California
1987-96	Member Bioengineering Graduate Group, School of Medicine University of California, San Francisco; and College of Engineering, University of California - Berkeley, California
	Vice-Chairman Department of Biopharmaceutical Sciences, School of Pharmacy University of California, San Francisco, California
1989	Academic Visitor (sabbatical) Department of Chemistry Imperial College of Science, Technology & Medicine, University of London London, England
	Chercheur (sabbatical) Centre International de Recherches Dermatologiques Sophia Antipolis, Valbonne, France
1991-96	Professor Departments of Biopharmaceutical Sciences and Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California
1994-95	Visiting Professor (sabbatical) Faculté de Pharmacie de Châtenay-Malabry, Université de Paris-Sud, France
1995	Visiting Professor (sabbatical) Facultad de Farmacia, Departamento de Farmacología, Farmacia y Tecnología Farmacéutica, Universidade de Santiago de Compostela, Spain
1996-2001	Adjunct Professor [Professeur Associé] Faculté des Sciences, Université de Genève, Genève, Switzerland
1996 -2001	Directeur Scientifique Centre interuniversitaire de recherche et d'enseignement, "Pharmapeptides" Universités de Genève et Lyon, Campus Universitaire, Archamps, France
1996-	Adjunct Professor Department of Bioengineering and Therapeutic Sciences, School of Pharmacy, University of California, San Francisco, California
1997-98	Professeur Invité Faculté de Pharmacie, Université Claude Bernard, Lyon, France
2001-03	Directeur Ecole romande de pharmacie, Universités de Genève et Lausanne Genève, Lausanne, Switzerland

2001-04	Professeur Faculté des Sciences, Université de Genève, Genève, Switzerland
	Directeur Centre interuniversitaire de recherche et d'enseignement, "Pharmapeptides" Universités de Genève et Lyon, Campus Universitaire, Archamps, France
	Visiting Professor University of Greenwich, England
2004-	Professor of Pharmaceutical Sciences University of Bath, Department of Pharmacy & Pharmacology Bath, England
2006-08	Head, Department of Pharmacy & Pharmacology University of Bath, Bath, England
2008-10	University Research Adviser University of Bath, Bath, England
2015	Academic Visitor (sabbatical) Physical & Theoretical Chemistry Laboratory, Department of Chemistry Oxford University

Honors and Awards

1984	Pennwalt Award for the "Best Pharmaceutical Paper," Controlled Release Society. San Francisco, California
1984-87	Special Emphasis Research Career Award, National Institute of Occupational Safety and Health, "Cutaneous Toxicity: Predictive Pathways"
1987	Walter F. Enz Lecturer, Department of Pharmaceutical Chemistry, University of Kansas. Lawrence, Kansas
	4th Annual Minnetonka Lectureship in Pharmaceutics, College of Pharmacy, University of Minnesota. Minneapolis, Minnesota
1988	Young Investigator Award (1st recipient), Controlled Release Society
	British Pharmaceutical Conference Science Award
	Elected Fellow of the Royal Society of Chemistry
1990	Elected Fellow of the American Association of Pharmaceutical Scientists
	Lecturer in the University of Medicine & Dentistry of New Jersey Distinguished Lecture Series in Biomaterials and Biomedical Devices, Rutgers University. Piscataway, New Jersey

1992 Elected Fellow of the American Association for the Advancement of Science

1993 Visiting Eminent Scholar Series in Drug Delivery, University of Florida, Gainesville, Florida

1997 Recipient, *Prix Applications Médicales de l'Electricité, 1997*, Electricité de France, Institut Electricité Santé, Paris, France

1999 Lauréat du Concours "Création d'enterprise de technologies innovantes", Ministère de l'Education Nationale, de la Recherche et de la Technologie, France

2000 Recipient, APV (International Association for Pharmaceutical Technology) Research Award for Outstanding Achievements in the Pharmaceutical Sciences

2005 APGI (Association de Pharmacie Galénique Industrielle) Sanofi-Aventis Young Investigator Award to Anke Sieg, Ph.D., former doctoral student, for her thesis performed under the co-direction of Dr. M.B. Delgado-Charro & Prof. R.H. Guy

2006 Research cited in *The Better World Report. "Technology Transfer Stories: 25 Innovations that Changed the World". 2006 edition.* http://www.autm.net/documents/AUTM_BWR.pdf. 'Tiny monitor gives diabetics frequent, automatic readings', ch. 6, pp. 55-58. The first non-invasive continuous monitoring device, pioneered at the University of California, San Francisco, helps patients better manage diabetes.

2007 Elected Fellow of the Academy of Pharmaceutical Sciences, Great Britain (APSGB).

Prix Pharmapeptides, Universities of Geneva and Lyon.

2010 Elected to the College of Fellows of the Controlled Release Society

Elected Fellow of The School of Pharmacy, University of London (now the UCL School of Pharmacy), in recognition of *"his distinguished contribution to the pharmaceutical sciences"*

2013 Founders Award, Controlled Release Society

2014 Award from the Royal Pharmaceutical Society of Great Britain to the RPSGB Pharmaceutical Science Expert Advisory Panel (RHG is a member) in recognition of its contribution to promoting the pharmaceutical sciences

2016 D.Sc., Medical Sciences Division, Oxford University, Oxford, England

Maurice-Marie Janot Award from the Association de Pharmacie Galénique Industrielle (APGI) for original and innovative research in pharmaceutics, biopharmaceutics and pharmaceutical technology.

Description of Current Research Program

Research focuses on skin barrier function characterization, transdermal drug delivery, enhancement of percutaneous absorption, iontophoresis, noninvasive biosensing, and the prediction and assessment of skin penetration and topical bioavailability. Specific ongoing projects include: measurement of the skin's biomechanical properties at the nanoscale using atomic force microscopy; the potential of polymeric film-forming systems as sustained release platforms for topical drugs; determination of the disposition of drug and formulation excipients (including nanoparticles) post-application to the skin and to

the nail using coherent Raman scattering and confocal microscopy; the impact of laser, microneedle and other poration technologies on drug delivery into and through skin and nail; examination of a graphene-based biosensor for noninvasive, transdermal glucose monitoring; development of *in vitro – in vivo* correlations with which to assess the bio(in)equivalence of topical drug products; and derivation and evaluation of predictive models of percutaneous penetration for pharmaceutical and cosmetic 'actives', and for potentially toxic chemicals, which come into contact with skin.

PUBLICATIONS

Journal Articles

(1) The Estimation of Diffusion Coefficients Using the Rotating Diffusion Cell. R.H. Guy and R. Fleming. *Int. J. Pharmaceut.* **3**, 143-149 (1979).

(2) A Novel Method to Study the Permeability of a Phospholipid Barrier. R.H. Guy and R. Fleming. *J. Chem. Soc., Chem. Commun.*, 729-730 (1979).

(3) Long-Time Solution of the Equations Describing the Flow of $^{22}Na^{+}$ in a Finite Composite System Containing a Synthetic Phospholipid-Protein Membrane: Calculation of Permeability Coefficient. R.H. Guy and R. Fleming. *Int. J. Pharmaceut.* **4**, 241-248 (1980).

(4) A Theoretical Description Relating Skin Penetration to the Thickness of the Applied Medicament. R.H. Guy, and J. Hadgraft. *Int. J. Pharmaceut.* **6**, 321-332 (1980).

(5) Diffusion Coefficient Determination Using a Filter-Paper Diaphragm Cell Technique. A.D. Cadman, R. Fleming, and R.H. Guy. *J. Pharm. Pharmacol.* **33**, 121-123 (1981).

(6) Capillary Diffusion and Interfacial Kinetics. R.H. Guy and J. Hadgraft. *J. Colloid Interface Sci.* **80**, 386-392 (1981).

(7) Interfacial Transport of Salicylic Acid. R.H. Guy and J. Hadgraft. *J. Colloid Interface Sci.* **81**, 69-74 (1981).

(8) Calculations of Drug Release Rates From Cylinders. R.H. Guy and J. Hadgraft. *Int. J. Pharmaceut.* **8**, 159-165 (1981).

(9) Transport Across a Phospholipid Barrier. R.H. Guy and R. Fleming. *J. Colloid Interface Sci.* **83**, 130-137 (1981).

(10) A Theoretical Comparison of Release Rates of Drugs Into Sink and Non-Sink Conditions. R.H. Guy and J. Hadgraft. *J. Pharm. Sci.* **70**, 1243-1245 (1981).

(11) Diffusion of Lysozyme Chloride in Water and Aqueous Potassium Chloride Solutions. A.D. Cadman, R. Fleming, and R.H. Guy. *Biophys. J.* **37**, 569-574 (1982).

(12) Kinetics of Solute Transfer Across Aqueous Phase- Liquid Hydrocarbon Interfaces. R.H. Guy, T.R. Aquino, and D.H. Honda. *J. Phys. Chem.* **86**, 280-283 (1982).

(13) The Influence of Urea on the Kinetics of Interfacial Transfer. R.H. Guy, D.H. Honda, and T.R. Aquino. *J. Colloid Interface Sci.* **87**, 107-114 (1982).

(14) Rapid Radial Transport of Methyl Nicotinate in the Dermis. R.H. Guy and H.I. Maibach. *Arch. Dermatol. Res.* **273**, 91-95 (1982).

(15) A Pharmacokinetic Model for Percutaneous Absorption. R.H. Guy, J. Hadgraft, and H.I. Maibach. *Int. J. Pharmaceut.* **11**, 119-129 (1982).

(16) Percutaneous Metabolism with Saturable Enzyme Kinetics. R.H. Guy and J.Hadgraft. *Int. J. Pharmaceut.* **11**, 187-197 (1982).

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(18) Solute Transfer Across Liquid-Liquid Interfaces. Kinetic and Thermodynamic Evaluation. R.H. Guy, T.R. Aquino III, and D.H. Honda. *J. Phys. Chem.* **86**, 2861-2866 (1982).

(19) Release of Non-Electrolytes from Liposomes. R.H. Guy, J. Hadgraft, M.J. Taylor, and I.W. Kellaway. *J. Pharm. Pharmacol.* **35**, 12-14 (1983).

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(25) A Physicochemical Interpretation of the Pharmacokinetics of Percutaneous Absorption. R.H. Guy and J. Hadgraft. *J. Pharmacokin. Biopharm.* **11**, 189-203 (1983).

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(57) Recent Advances in Transdermal Drug Delivery. R.H. Guy. *Ther. Res.* **3**, 69-80 (1985).

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(60) The Influence of Urea on Percutaneous Absorption. J. Beastall, R.H. Guy, J. Hadgraft, and I. Wilding. *Pharm. Res.* **3**, 294-297 (1986).

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(66) A Capillary Tube Method for the Measurement of Solute Transport Across Liquid-Liquid Interfaces. R.S. Hinz and R.H. Guy. *J. Phys. Chem.* **91**, 2915-2917 (1987).

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Absorption Studies: Relevance to Bioavailability and Bioequivalence. J.P. Skelly, V.P. Shah, H.I. Maibach, R.H. Guy, R.C. Wester, G. Flynn, and A. Yacobi. *Pharm. Res.* **4**, 265-267 (1987).

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(77) Percutaneous Absorption of Hydroquinone in Humans: Effect of 1-Dodecylaza-cycloheptan-2-one (Azone) and the 2-Ethylhexyl Ester of 4-(Dimethylamino)-Benzoic Acid (Escalol 507). D.A.W. Bucks, J.R. McMaster, R.H. Guy, and H.I. Maibach. *J. Tox. Environ. Health* **24**, 279-289 (1988).

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Publication metrics

A citation analysis of Dr. Guy's career-to-date peer-reviewed outputs (>370 in total as of 11-2016) shows that they have been cited over 15,000 occasions (average citations per article ~35) and that his Scopus h-index is 67.

In an editorial in *Pharmaceutical Research*, which is the official journal of the American Association of Pharmaceutical Scientists, marking the occasion of its 25th Anniversary at the end of 2008. (*Lee, VHL. Shaping the transformation of pharmaceutical science. Pharm Res 25, 2707-2712, 2009*), it was noted that Dr. Guy had co-authored more papers (72) than anyone else in *Pharmaceutical Research*, and that one of these publications was the fourth most cited in the journal (390 citations at the end of 2008, currently 689).

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in *Drinking Water Contamination and Health: Integration of Exposure Assessment, Toxicology and Risk Assessment,* pp. 347-373. Edited by R. Wang. New York: Marcel Dekker, 1994.

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Junginger, Paris: Editions de Santé, 1997.

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(69) Biological Models to Study Skin Permeation. N. Sekkat and R.H. Guy. Chapter in *Pharmacokinetic Optimization in Drug Research: Biological, Physicochemical and Computational Strategies*, pp. 155-172. Edited by B. Testa, H. van der Waterbeemd, G. Folkers and R.H. Guy. Lausanne: Wiley-VCH, 2001.

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(71) Feasibility Assessment in Topical and Transdermal Delivery: Mathematical Models and *In Vitro* Studies. J. Hadgraft and R.H. Guy. Chapter in *Transdermal Drug Delivery (2nd Edition, Revised and Expanded)*, pp. 1-23. Edited by R.H. Guy and J. Hadgraft. New York: Marcel Dekker, 2003.

(72) Iontophoresis: Applications in Drug Delivery and Noninvasive Monitoring. M.B. Delgado-Charro and R.H. Guy. Chapter in *Transdermal Drug Delivery (2nd Edition, Revised and Expanded)*, pp. 199-225. Edited by R.H. Guy and J.Hadgraft. New York: Marcel Dekker, 2003.

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Vivo. A.L. Bunge, G.D. Touraille, J.-P. Marty, and R.H. Guy, Chapter in *Dermal Absorption Models in Toxicology and Pharmacology*, pp. 191-212. Edited by J.E. Riviere, CRC Press, Boca Raton, FL, 2005.

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(80) Pharmacology of the Skin: Principles of Topical Drug Delivery. R.H. Guy. Chapter 13 in *Rook's Textbook of Dermatology, 9th Edition*. ISBN: 978-1-118-44119-0. Edited by C.E.M. Griffiths, J. Barker, R.J.G. Chalmers, T.O. Bleiker and D. Creamer, Wiley-Blackwell, Ltd., Chichester, U.K., 2016.

Research Awards, Fellowships and Extramural Grants (since 1994)

1994-96 U.S. Environmental Protection Agency, $183,074 TDC: Estimating the Absorbed Dose from Dermal Exposure to Environmental Pollutants: Development of Guidelines for Acquisition, Interpretation and Use of *In Vivo* and *In Vitro* Data (Co-Investigator; A.L. Bunge, Principal Investigator)

1994-98 U.S. Air Force, 94NL023, $433,293 TDC: Prediction and Assessment of Dermal Exposure

1994-98 National Institutes of Health, 1-R01-ES06825, $1,029,303 TDC: Dermal Absorption from Soils: Evaluation and Prediction (Co-Investigator; A.L. Bunge, Principal Investigator)

1995-98 National Institutes of Health, 1-R01-DA-09292, $95,658 TDC: Neonatal Skin: Barrier Function and Drug Delivery

U.S. Environmental Protection Agency, $245,268 TDC: Structure-Activity Relationships for Predicting Pesticide Dermal Absorption from Multimedia (Co-Investigator; A.L. Bunge, Principal Investigator)

1997-99 U.S. Air Force, 94NL023, $647,814 TDC: Dermal Absorption of Chemicals from Evaporating Vehicle Mixtures (Co-Investigator; A.L. Bunge, Principal Investigator)

1998-01 Fonds national suisse de la recherche scientifique, SFr 180,000: Mechanisms of Iontophoretic Drug Delivery Across Skin

1999-02 Programme Commun de Recherche en Génie Biomédical 1999-2002, SFr 374,000: Bioengineering for Transdermal Therapy and Diagnosis

2000-02 Fonds national suisse de la recherche scientifique, SFr 126,000: Prevention of Intravascular Device-Related Infections: Electrically-Mediated Skin Antisepsis [A. Naik, principal investigator]

2000-03 Fonds national suisse de la recherche scientifique, SFr 260,000: Reverse Iontophoresis: Noninvasive Drug Monitoring via the Skin [M.B. Delgado-Charro, principal investigator]

2003-04 U.S. Army Medical Research Acquisition Activity, $231,380: Skin Bioengineering – Noninvasive Transdermal Monitoring

U.S. Food & Drug Administration, $12,000: Dermatopharmacokinetics – Improvement of Methodology for Assessing Bioequivalence of Topical Dermatological Drug Products [A.L. Bunge, principal investigator; total budget $100,000]

2003-08 U.S. National Institutes of Health, 1-R01-EB-001420, $675,000 TDC: Skin Bioengineering – Noninvasive Transdermal Monitoring

2005-08 Parkinson's Disease Society, UK, £105,781 TDC: Optimizing the Pharmacological Treatment of Parkinson's Disease via Transdermal Iontophoresis [M.B. Delgado-Charro, principal investigator]

2005-09 European Commission 6th Framework, NMP3-CT-2005-011844, €244,952 TDC:

Nanostructured Waterborne Polymer Films with Outstanding Properties [J.M. Asua, Program Director]

2009-10 Department of the Environment, Food and Rural Affairs (Defra), PS2616, £91,800 FEC: Skin Uptake and Penetration of Pesticides

2009-11 Medical Research Council, G0802728, £242,172 FEC: Transdermal delivery of a Buprenorphine/Naltrexone Combination for the Treatment of Drug Abuse [S.M. Husbands, principal investigator]

2013-15 National Institute for Health Research (NIHR), £333,787 (Bath share £9,772): Choice of moisturiser in eczema treatment (COMET)

2013-18 U.S. Department of Health & Human Services; Food & Drug Administration, 1-U01-FD-004947-01, $2,499,989 (Bath share £434,779): Bioequivalence of topical drug products: in vitro - in vivo correlations [A.L. Stinchcomb, U. of Maryland, principal investigator]

2015-16 MRC Confidence-in-Concepts Scheme: £67,057 (100% FEC): "The 'Glucose Pathfinder': Noninvasive, transdermal, path-selective and highly specific glucose monitoring on a graphene platform" [A. Ilie, principal investigator]

2015-18 Sir Halley Stewart Trust: £50,000: New method for glucose monitoring in diabetics [A. Ilie, principal investigator]

2016-19 The Leo Foundation: DKK 3,564,000 (£309,514): Development and validation of physiologically-based pharmacokinetic model for dermal absorption [M.B. Delgado-Charro, principal investigator]

Participation in Other Sponsored Research Activity (since 1994)

1994-95 Becton Dickinson Transdermal Systems (USA), $35,000 TDC: Iontophoresis and the pH Profile of the Skin

1995-96 Becton Dickinson Transdermal Systems (USA), $35,000 TDC: Peptide Iontophoresis: Electrorepulsion *Versus* Electroosmosis

1997-98 Tilderm Systems (France), SFr67,000: Electroosmosis and Skin Impedance

Electricité de France, Institut Electricité Santé, FF300,000: Nouvelle Méthode non invasive de diagnostique et de suivi thérapeutique par ionophorèse inverse (ICI)

Cygnus, Inc. (USA), $55,482: Ultrasound-Enhanced Transport Across the Skin: Effect of Frequency?

1997-99 Novartis Pharma, Inc. (Switzerland), SFr215,250: Topical Drug Bioavailability: Evaluation and Optimisation

1998-2000 Novartis Pharma, Inc. (Switzerland), SFr 105,000: Supersaturation as a Method to Improve Topical Bioavailability of Lipophilic Drugs

Becton Dickinson Transdermal Systems (USA), $150,000 TDC: Peptide Iontophoresis:

	Electrorepulsion *Versus* Electroosmosis
1999-2001	Galderma (France), SFr410,000: Topical Dermatological Drug Product Bioavailability and Bioequivalence *in vivo*
2001-2002	Hisamitsu Pharmaceutical Co. Ltd. (Japan), SFr 70,000: Mechanisms of Iontophoresis
	Pierre-Fabre, Institut de Recherche (France), FF 120,000: L'Eau dans la Peau
	L'Oréal (France), SFr 121,000: Skin Absorption Databases
2001-2005	Leo Pharmaceutical Products, Inc. (Denmark), SFr 375,015: The Rational Design of Dermatological Products
2002	Power Paper (Israel), € 42,500: Iontophoresis of Cosmeceuticals
2002-2003	DPC Products, Inc. (USA), € 26,955: Skin Penetration Enhancement with Naturally-Occuring Oils
	Abbott Laboratories (USA), € 57,504: Transdermal Development of Mavik - Options and Strategies
2002-2005	Servier, Institut des recherches internationals (France), SFr 105,000: Development of a Transdermal 'Spray Patch' for the Systemic Administration of Testosterone
	Bracco Research S.A. (Switzerland), SFr 172,269: Sonoporation
2003	L'Oréal (France), € 14,600: Iontophoresis of Vitamin C
2003-2004	Novozymes A/S (Denmark), € 68,170: Hyaluronic Acid: Skin Penetration and Hydration
2003-2005	L'Oréal (France), $ 150,150: Skin Absorption Database Project
	Vyteris, Inc. (USA), SFr 463,000 "Vyteris Europe"
2003-2006	Vyteris, Inc. (USA), $ 147,000: Iontophoretic Drug Delivery: Increasing the Odds
2004	L'Oréal (France), € 15,000: Iontophoresis of Vitamin C
	L'Oréal (France), € 15,000: Skin Uptake of Nanoparticles
	Proctor & Gamble (UK), € 9,000: Reverse Iontophoresis and Skin Health
2005-2006	Vyteris, Inc. (USA), £26,500: Iontophoretic Drug Delivery: Increasing the Odds
	Ascend Therapeutics (USA), £37,170: Feasibility study for transdermal delivery of a group of related compounds
	Galderma Research & Development (France), £27,000: Iontophoretic Delivery of Amorolfine across the Nail
2006-2010	York Pharma/BBSRC Case Award, £67,500: Bioavailability of Topically Applied Drugs for the Treatment of Atopic Eczema and Other Related Diseases
2007-2008	EyeGate Pharmaceuticals, Inc. (USA), £36,791: Ocular Iontophoresis

	GlaxoSmithKline (USA), £15,000: Dermatopharmacokinetics of Docosanol *ex vivo*
2009-2010	Zealand Pharma (Denmark), £33,691: In vitro Assessment of Transdermal Peptide Delivery
2010	LSC, Inc. (USA), £25,066 TDC: Dermal delivery of an "active" from hydroxysomes.
2010-2013	Leo Pharma A/S (Denmark), £73,577 TDC: Dermal Controlled Release. 3-year PhD studentship.
	Leo Pharma A/S (Denmark), £232,011 TDC: Imaging drug disposition and pharmacokinetics in skin by stimulated Raman scattering microscopy. 2-year postdoctoral fellowship.
2011	Exchange Supplies, Ltd. (U.K.), £23,051 TDC: Alternative buffers: Identifying suitable alternatives or additives to citric and ascorbic acid as a harm reduction tool to reduce the risks associated with illicit heroin and crack cocaine injections. [J. Scott, principal investigator]
	Grünenthal GmbH (Germany), £12,999 TDC: Iontophoresis of tapentadol hydrochloride.
	L'Oréal (France), £13,851 TDC: Iontophoresis and electrical enhancement in the cosmetic and skin-care fields: a review.
	L'Oréal (France), £8.015 TDC: Iontophoresis and cosmetics [UnivMed].
2011-12	Orexo AB (Sweden), £140,708 TDC: Orexo facilities and partial secondment agreement.
2012-13	Orexo AB (Sweden), £140,708 TDC: Orexo facilities and partial secondment agreement.
2012-15	GlaxoSmithKline Research & Development (USA), £192,573 TDC: Examining formulation effects on drug-vehicle skin penetration enhancement.
2013	Reckitt Benkiser (U.K.) £38,110: Ibuprofen delivery across the skin.
2013-17	Syngenta Ltd./BBSRC Case Award, £123,520 TDC: Quantification of dermal absorption from pesticide residues from treated plant surfaces.
2014	Unilever, £16,344: S12 Delivery into and through mammalian skin.
2015	Benanova, Inc., £10,503: Skin penetration and distribution of polymeric nanoparticle formulations.

Other Creative Activities and Accomplishments

1992 U.S. Patent # 5,115,805, "Ultrasound-Enhanced Delivery of Materials Into and Through the Skin." D. Bommannan, H. Okuyama, R.H. Guy, P. Stauffer, and G.L. Flynn

1993 U.S. Patent # 5,231,975, "Ultrasound-Enhanced Delivery of Materials Into and Through the Skin." D. Bommannan, H. Okuyama, R.H. Guy, P. Stauffer, and G.L. Flynn

1994 U.S. Patent # 5,279,543, "Device for Iontophoretic Non-Invasive Sampling or Delivery of Substances." P. Glikfeld, C. Cullander, R.S. Hinz, and R.H. Guy

1994 U.S. Patent # 5,323,769, "Ultrasound-Enhanced Delivery of Materials Into and Through the Skin." D. Bommannan, H. Okuyama, R.H. Guy, P. Stauffer, and G.L. Flynn

1994 U.S. Patent # 5,362,307, "Method for the Iontophoretic Non-Invasive Determination of the In Vivo Concentration Level of and Inorganic or Organic Substance." R.H. Guy, G. Rao, P. Glikfeld, C. Cullander and R.S. Hinz

1997 U.S. Patent # 5,636,632, "Ultrasound-Enhanced Sampling of Materials Through the Skin". D. Bommannan, H. Okuyama, R.H. Guy, P. Stauffer, and G.L. Flynn

1998 U.S. Patent # 5,730,714, "Method for the Iontophoretic Non-Invasive Determination of the In Vivo Concentration Level of Glucose." R.H. Guy, G. Rao, P. Glikfeld, C. Cullander and R.S. Hinz

1999 U.S. Patent # 5,911,223, "Introduction of Modifying Agents into Skin by Electroporation". J.C. Weaver, T.E. Zewert, U. Pliquett, R.Vanbever, M.R. Prausnitz, T. Chen, C. Cullander, R. Guy and R.S. Langer.

2000 Spanish 'Patente de Invención' #009602541, "Procedimiento de control por iontoforesis del paso a través de membranas de sustancias incluidas en microemulsiones". G. Iglesias Vilas, M.B. Delgado Charro, J. Blanco Mendéz, M.A. López Quintela and R.H. Guy.

2001/2 Patent Application EP1401532 (WO03000340), "Method for Noninvasively Determining the Relative Levels of Two Substances Present in a Biological System". M.B. Delgado-Charro and R.H. Guy.

2003 European Patent EP 673622B1, "Device for Iontophoretic Non-Invasive Sampling or Delivery of Substances." P. Glikfeld, C. Cullander, R.S. Hinz, and R.H. Guy

2003 U.S. Patent # 6,542,765 B1, "Method for the Iontophoretic Non-Invasive Determination of the In Vivo Concentration Level of and Inorganic or Organic Substance." R.H. Guy, G. Rao, P. Glikfeld, C. Cullander and R.S. Hinz

2004 U.S. Patent # 6,714,815 B2, "Method for the Iontophoretic Non-Invasive Determination of the In Vivo Concentration Level of and Inorganic or Organic Substance." R.H. Guy, G. Rao, P. Glikfeld, C. Cullander and R.S. Hinz

2009 U.S. Patent # 7,555,337 B2, "Method for Non-Invasively Determining the Relative Levels of Two Biological Substances." R.H. Guy and M.B. Delgado-Charro

2009 Canadian Patent # CA 2450965, "Method for Non-Invasively Determining the Relative Levels of Two Biological Substances." R.H. Guy and M.B. Delgado-Charro

2009 Patent application WO/2009/065787, "Use of Amorolfine for Treating a Nail Disease by Iontophoresis." R.H. Guy and M.B. Delgado-Charro

2010 U.S. Patent # 7,693,573 B2, "Method for Non-Invasively Determining the Relative Levels of Two Biological Substances." R.H. Guy and M.B. Delgado-Charro

2012 European Patent 1401532, "Device for Non-Invasively Determining the Relative Levels of Two Substances Present in a Biological System." R.H. Guy and M.B. Delgado-Charro

2014 European Patent Application WO2014012652 (A1), "Electric-field Assisted Administration of Tapentadol." I. Friedrich, M. Mikyna, S. Gedat and R.H. Guy

2016 GB Patent Application 1607265.4, "Multiplexed Transdermal Extraction and Detection Devices for Non-Invasive Monitoring of Substances and Methods of Use." A. Ilie, F. Dougmene, B. Dupont, R.H. Guy, L.Lupani, F. Merken and R.M. Tyrrell

Note: Italicised patents were initially licensed to Cygnus, Inc. (and are now licensed to Johnson & Johnson), and comprise integral intellectual property associated with a U.S. Food & Drug Administration and CE-mark approved device (the GlucoWatch® Biographer) for noninvasive glucose monitoring.

Graduated Ph.D. Students

1983-89 Daniel A.W. Bucks, Pharmaceutical Chemistry, University of California, San Francisco
Thesis: "Prediction of Percutaneous Absorption"
Current position: Dow Chemical, California, USA

1984-89 Victoria Knepp, Pharmaceutical Chemistry, University of California, San Francisco
Thesis: "Controlled Drug Release from a Novel Liposomal Delivery System"

Kathleen V. Roskos, Pharmaceutical Chemistry, University of California, San Francisco
Thesis: "The Effect of Skin Aging on the Percutaneous Penetration of Chemicals Through Human Skin"
Current position: Nektar, Inc., California, USA

1987-90 D. Bommannan, Bioengineering, University of California, San Francisco - University of California, Berkeley
Thesis: "Enhancement of Transdermal Drug Delivery: Mechanisms and Methodologies"
Current position: MaxVal California, USA

1991-96 Norris G. Turner, Pharmaceutical Chemistry, University of California, San Francisco
Thesis: "Mechanisms of Iontophoretic Drug Delivery"
Current position: Purdue Pharma, Connecticut, USA

1992-97 Lourdes Nonato, Bioengineering, University of California, San Francisco - University of California, Berkeley
Thesis: "Evolution of Skin Barrier Function in Premature Neonates"

1994-96 Fabrice Pirot, Faculté de Médicine et de Pharmacie de Besançon, Université de Franche-Comté
Thesis: "Analyse, Mesure et Prédiction de la Diffusion dans le Stratum Corneum Humain"
Current position: Université Claude-Bernard Lyon 1

1996-2000 Ingo Alberti, Pharmaceutical Sciences, University of Geneva
Thesis: "Local Bioavailability of Topical Dermatological Formulations *In Vivo* in Man"
Current position: University of Geneva, Switzerland

1997-2000 Katrin Moser, Pharmaceutical Sciences, University of Geneva
Thesis: "Supersaturation for the Enhanced Dermal Delivery of Lipophilic Drugs"

Diego Marro, Pharmaceutical Sciences, University of Geneva
Thesis: "Electromigration and Electroosmosis Contributions to iontophoretic Drug Delivery"
Current position: Pharmacist-Manager, Huesca, Spain

1997-2001 Catherine Curdy, Pharmaceutical Sciences, University of Geneva
Thesis: "Fonction Barrière du Stratum Corneum, chez l'Homme, *In Vivo*: Ionophorèse versus Diffusion Passive"
Current position: Novartis Consumer Health, Nyon, Switzerland

Gilles Touraille, Faculté de Pharmacie de Châtenay-Malabry, Université Paris XI
Thesis: "Modalités d'Absorption Percutanée à Partir de Terre Contaminée par une Substance Chimique" [co-advisor: Prof. Jean-Paul Marty]
Current position: EMEA, London, UK

1998-2001 Nabila Sekkat, Pharmaceutical Sciences, University of Geneva
Thesis: "A Model for Neonatal Skin: Barrier Function and Drug Delivery"

Current position: Novartis, Basel, Switzerland

1998-2002 Gustavo Merino, Pharmaceutical Sciences, University of Geneva
Thesis: "Mechanisms of Ultrasound-Enhanced Skin Penetration"
Current position: Carrefour Parapharmacie, Rennes, France

2000-2003 Rocio Alvarez-Román, Pharmaceutical Sciences, University of Geneva
Thesis: "Evaluation of Nanoparticle-Based Vehicles for (Trans)dermal Drug Delivery"
Current position: Universidad Nacional Autónoma de México, Mexico

2000-2004 Benoît Leboulanger, Pharmaceutical Sciences, University of Geneva
Thesis: "Evaluation de l'Ionophorèse Inversée comme Méthode Non-invasive pour le Monitoring Thérapeutique"
Current position: Novartis, Basel, Switzerland

Anke Sieg, Pharmaceutical Sciences, University of Geneva
Thesis: "The Internal Standard Concept for Non-Invasive Glucose Monitoring Using Reverse Iontophoresis"
Current position: Dow Corning, Belgium

2000-2005 Yannic Schuetz, Pharmaceutical Sciences, University of Geneva
Thesis: "Administration Transdermique des Peptides par Ionophorèse: Impact des Propriétés Moléculaires sur les Mécanismes de Transport et Applications Thérapeutiques"
Current position: Triskel Integrated Services, Geneva, Switzerland

Isabel Diaz del Consuelo, Pharmaceutical Sciences, University of Geneva
Thesis: " Evaluation de la Muqueuse Oesophagienne de Porc comme Modèle pour l'Etude in vitro de la Perméabilité Buccale "
Current position: Ipsen, SA, Barcelona, Spain

Nada Abla, Pharmaceutical Sciences, University of Geneva
Thesis: "Administration Transdermique par Ionophorèse: Effet de la Barrière Cutanée et Impact des Propriétés Physico-chimiques des Peptides sur leur Transport"
Current position: Ferring SA, Lausanne, Switzerland

Blaise Mudry, Pharmaceutical Sciences, University of Geneva
Thesis: "Prediction and Optimization of Iontophoretic Transport Across the Skin"
Current position: Ferring SA, Lausanne, Switzerland

Christophe Herkenne, Pharmaceutical Sciences, University of Geneva
Thesis: "Evaluation and Optimization of Topical Drug Bioavailability"
Current position: DebioPharm, Martigny, Switzerland

2001-2005 Sophie Mehier-Humbert, Pharmaceutical Sciences, University of Geneva
Thesis: "Mechanistic Investigation of Microbubble-Mediated Sonoporation for Intracellular Gene Delivery"
Current position: CEO, Cerma SA, Archamps, France (biotech start-up)

Marie-Laure Leichtnam, Pharmaceutical Sciences, University of Geneva
Thesis: "Mise au Point d'un Spray pour l'Administration Transdermique de Testostérone à Visée Systémique"

2003-2006 Sandra Wiedersberg, Faculty of Science, University of Bath
Thesis: "Dermatopharmacokinetics and Pharmacodynamics of Topical Glucocorticoids"
Current position: Research Scientist, LTS Lohmann Therapie-Systeme AG

2003-2007 Valentine Wascotte, Faculté de Pharmacie, Université catholique de Louvain, Belgium
Thesis:
Current position: Research Scientist, GSK, Belgium

2004-2007 Jean-Philippe Sylvestre
Thesis: "Applications of Iontophoresis in Sports Medicine"
Current position: University of Montreal, Canada

2005-2008 Xiao Wu
Thesis: "Characterisation and evaluation of novel nanoparticulate formulations for application to the skin"
Current position: Eli Lilly & Co.,Indianapolis, IN, U.S.A.

2005-2009 Lisa Russell
Thesis: "Dermatopharmacokinetics: an approach to evaluate topical bioavailability"
Current position: Consultant Pharmacist, Nottingham PCT

Asma Djabri
Thesis: "Iontophoresis in paediatric medicine: noninvasive drug delivery and monitoring applications"
Current position: Pharmacist

2006-2010 Manda Tsang
Thesis: "Formulation and delivery of topically applied drugs for the treatment of atopic eczema and other related diseases"
Current position:

2008-2011 Quan Yang
Thesis: "Application of Biophysics and Bioengineering to the Assessment of Skin Barrier Function"
Current position: MHRA, London, UK

2008-2013 Premrutai Thitilertdecha
Thesis: "Formulation optimization for the topical delivery of active agents in traditional medicines"
Current position: Centre for Thai Traditional Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

2010-2014 Kit Frederiksen
Thesis: "*In situ* polymeric film-forming systems for sustained topical delivery"
Current position: Novo Nordisk, Denmark

2011-2014 Hazel Garvie-Cook
Thesis: "Micro- and nano-scale assessment of novel (trans)dermal drug delivery strategies"
Current position: Postdoctoral Research Associate, University of Bath

Wing Chiu
Thesis: "Mechanism and optimisation of drug delivery into and through the nail"
Current position: Postdoctoral Research Associate, University of Bath

Professional Research Personnel, Postgraduate Personnel, and Postdoctoral Fellows

University of California, San Francisco

1982-83	Ethel Tur, M.D., Visiting Research Associate in Dermatology: Non-invasive monitoring of percutaneous absorption Current position: Ichilov Medical Center, Tel Aviv, Israel
	Michael Amantea, B.S., President's Undergraduate Fellow: The influence of alcohol at a model biomembrane interface Current position: UCSD School of Pharmacy, California, USA
1982–2001	Robert Hinz, Ph.D., Research Associate: Interfacial transport: Kinetics and perturbation
1983	Veronique Drouard, M.Pharm., Visiting Postgraduate Research Pharmacist: UV erythema Current position: Givaudan, Paris, France
	Charles Ryll, Pharm.D., M.S. Graduate Student: Pharmaceutical Chemistry
1983-84	Sharif Elamir, M.D., Visiting Research Associate in Dermatology: Quantification of irritation
	Larry Schall, M.D., Research Associate in Dermatology: Blood flow to the skin monitored by laser Doppler velocimetry
1983-89	Daniel A.W. Bucks, Graduate Student: Pharmaceutical Chemistry Current position: Dow Chemical, California, USA
1984	Eva M. Carlström, Postgraduate Research Chemist: *In vitro* skin penetration Current position: AstraZeneca, Sweden
1984-85	John M. Stevenson, B.S., Postgraduate Research Biologist: Skin irritancy studies
	Bruce A. Firestone, Graduate Student: Pharmaceutical Chemistry Current position: Allergan, California, USA
1984-88	Kathleen V. Roskos, Graduate Student: Pharmaceutical Chemistry Current position: Nektar, Inc., California, USA
1984-89	Victoria M. Knepp, Graduate Student: Pharmaceutical Chemistry Current position: Alza Corp., California, USA
1985	Kamaljit Ryatt, M.D., Visiting Lecturer in Dermatology: Skin blood flow Current position: Dermatologist, England
1985-86	GianCarlo Santus, Ph.D., Visiting Scientist (Sabbatical): Transdermal drug delivery and cutaneous metabolism Current position: NiCox, Sophia Antipolis, France
	Diana Villaflor, M.D., Visiting Postdoctoral Research Chemist: The influence of aging on the barrier function of skin
1985-	Cynthia Lorence, B.S., Research Associate: Percutaneous absorption of organic compounds *in vitro*

1985-89 Joy Houk, M.S., Graduate Student: Pharmaceutical Chemistry

1986-88 Geoffrey Ridout, Ph.D., Postdoctoral Research Chemist: Models for percutaneous absorption

Katherine L. Kendrick, Ph.D., Postdoctoral Research Chemist: Interfacial transfer kinetics

Peretz Glikfeld, Dip. Chem. Eng., Postdoctoral Research Chemical Engineer: Transdermal drug delivery by iontophoresis
Current position: Israel Institute for Biological Research, Ness-Ziona, Israel

1987-88 C. Hodson, B.A., Research Associate: *In vitro* skin absorption

1987-90 D. Bommannan, M.S., Graduate Student: Bioengineering
Current position: CEO, Maxval Group, California, USA

Christopher Cullander, Ph.D., Postdoctoral Research Biophysicist: Electrical properties of skin
Current position: University of California – San Francisco, USA

1987-89 Takashi Kai, M.S., Postgraduate Research Chemist: Percutaneous penetration enhancement
Current position: Nippon Shokubai Co. Ltd., Japan

Vivien Mak, Ph.D., Postdoctoral Research Chemist: Spectroscopic investigations of skin barrier function
Current position: Independent consultant

1988-90 Naruhito Higo, B.S., Postgraduate Research Chemist: Transdermal drug delivery and cutaneous metabolism
Current position: Hisamitsu Pharmaceutical Co. Ltd, Tsukuba, Japan

Philip G. Green, Ph.D., Postdoctoral Research Chemist: Iontophoretic delivery of peptides across the skin
Current position: Merck Bioventures, New Jersey, USA

1989-90 Daniel A.W. Bucks, Ph.D.: Assistant Research Chemist: Percutaneous absorption
Current position: Dow Chemical, California, USA

Hirohito Okuyama, M.S.: Postgraduate Research Chemist: Effects of ultrasound on transdermal drug delivery
Current position: Boehringer Ingelheim, Narita, Japan

1990-92 Carol L. Gay, Ph.D.: Postdoctoral Research Chemist: Enhancement of Transdermal Delivery
Current position: GlaxoSmithKiline Consumer Health, Weybridge, England

1990-93 Girish Rao, Ph.D.: Postdoctoral Research Chemist: Transdermal Sampling of Blood Glucose by Iontophoresis
Current position: Unilever, India

1990-94 Christopher Cullander, Ph.D.: Assistant Research Biophysicist: Electrophysiological and Microscopic Evaluations of Skin Barrier Function
Current position: Adjunct Associate Professor, University of California – San Francisco

1990-96 Jurij J. Hostynek, Ph.D.: Visiting Scientist: Prediction of Risk Following Dermal Exposure to Toxic Chemicals
Current position: Research scientist, University of California, San Francisco

1991-92 Jens Brange, M.Sc.: Visiting Professor of Pharmacy: Iontophoretic Delivery of Insulin Analogs Across the Skin

Liselotte Langkjaer, M.Sc.: Visiting Assistant Professor of Pharmacy: Iontophoretic Delivery of Insulin Analogs Across the Skin
Current position: Novo Nordisk, Bagsværd, Denmark

Ronald van der Geest, B.S.: Postgraduate Research Student: Transdermal Delivery of Oligonucleotides
Current position: Tibotec-Virco Co., VA, Belgium

1991-93 Aeri Kim, Ph.D.: Postdoctoral Research Chemist: Iontophoretic Delivery of Insulin Analogs Across the Skin
Current position: LG, Inc., Korea

Rhonda Brand, Ph.D.: Postdoctoral Research Bioengineer: Biophysical Analysis of the Effect of Iontophoresis on Skin Barrier Function
Current position: NorthWestern University, Illinois, USA

M. Begoña Delgado Charro, Ph.D.: Visiting Assistant Professor: Iontophoretic Delivery of LHRH Analogs and Antagonists
Current position: University of Bath, UK, Senior Lecturer in Pharmaceutical Sciences

Seaung Oh, Ph.D.: Postdoctoral Research Chemist: Skin Impedance, Electroporation, and Transdermal Drug Delivery
Current position: Sookmyung Women's University, Seoul, Korea

1991-94 Aarti Naik, Ph.D.: Postdoctoral Research Chemist: IR Spectroscopic Investigations of Skin Barrier Function
Current position: Triskel SA, Geneva, Switzerland

1991-96 Norris Turner, Pharm.D.: Graduate Student: Pharmaceutical Chemistry
Current position: Pfizer, Connecticut, USA

1992-93 Frédérique Hueber, Ph.D.: Postdoctoral Research Chemist: Iontophoresis of Oligonucleotides
Current position: L'Oréal Research, Paris, France

Amalia Rodriguez-Bayon, Ph.D.: Postdoctoral Research Chemist: Iontophoretic Delivery of LHRH Analogs and Antagonists.
Current position: Associate Professor, Complutense University, Madrid, Spain

Karine Buffard, B.S.: Postgraduate Research Student: Measurement of Skin Permeability *In Vivo*

1992-94 Elena Aspe-Carranza, M.S.: Postgraduate Research Student: Transdermal Delivery of an Antiviral Drug

1992-97 Lourdes Nonato, M.S.: Graduate Student: Bioengineering

1994 Patrizia Santi, Ph.D.: Visiting Assistant Professor of Pharmacy: Mechanisms of Iontophoretic Transport
Current position: Professor, University of Parma, Italy

1994-96 Jouni Hirvonen, Ph.D.: Postdoctoral Research Chemist: Noninvasive Biological Monitoring via the Skin
Current position: Professor and Dean, University of Helsinki, Finland

1994-96 Yogeshvar Kalia, Ph.D.: Postdoctoral Research Chemist: Theoretical and Experimental Modeling of Iontophoretic Drug Delivery
Current position: Associate Professor, University of Geneva, Switzerland

Fabrice Pirot, Pharm.D.: Postgraduate Research Pharmacist: Assessment of Dermal Exposure *in vivo*
Current position: Associate Professsor, Université Claude-Bernard Lyon 1

1995-96 Audra Stinchcomb, Ph.D.: Postgraduate Research Chemist: Chemical Absorption Across Human Skin *in vivo* - Effect of Vehicle
Current position: Professor, University of Kentucky, USA

1995- Gilles Touraille, Pharm.D.: Postgraduate Research Pharmacist: Assessment of Dermal Exposure *in vivo* - Vehicle Effects
Current position: EMEA, London, U.K.

1996 Monica Rodríguez-Fernandez: Postgraduate Research Student: Isoelectric Point of the Skin

University of Geneva - Centre Interuniversitaire de Recherche et d'Enseignement, Archamps

1996 Virginia Merino-Sanjuan, Ph.D.: Visiting Professor: Reverse Iontophoresis
Current position: Associate Professor, University of Valencia, Spain

1996, 1999 Alicia Lopéz, Ph.D. Visiting Postdoctoral Fellow: Reverse Iontophoresis; pI of Skin
Current position: Associate Professor, University Cardenal Herrera, Valencia, Spain

1996-2000 Ingo Alberti, Dip. Pharm.: Doctorant: Evaluation and Optimisation of Topical Drug Bioavailability
Current position: Swiss Medical Authority, Basel, Switzerland

1996-2001 Yogeshvar Kalia, Ph.D.: Maître Assistant: Theoretical and Experimental Modeling of Iontophoretic Drug Delivery
Current position: Associate Professor, University of Geneva, Switzerland

1996-2003 M. Begoña Delgado-Charro, Ph.D.: Maître Assistante: Iontophoresis, Sonophoresis and Novel Topical Formulations
Current position: Senior Lecturer in Pharmaceutical Sciences, University of Bath, UK

1996-2004 Aarti Naik, Ph.D. Visiting Postdoctoral Fellow, Maître Assistante: Mechanism and Enhancement of Transdermal Drug Delivery
Current position: Triskel, SA, Geneva, Switzerland

1997	Asteria Luzardo-Alvarez, Dip. Pharm.: Visiting Graduate Student: Iontophoresis and Isoelectric Point of Skin Current position: University of Santiago de Compostela, Spain
	Antonella Casiraghi, Pharm.D.: Visiting Graduate Student: Infrared spectroscopy and Skin Current position: University of Milan, Italy
1997-2000	Diego Marro, Dip. Pharm.: Doctorant: Electrorepulsion and Electroosmosis in the Iontophoretic Delivery of Peptides Current position: Visiting Professor, University Cardenal Herrera, Valencia, Spain
	Katrin Moser, Dip. Pharm.: Doctorante: Supersaturation and Topical Drug Delivery Current position: MIT, Boston, USA
1997-2001	Catherine Curdy, Dipl. Pharm.: Doctorante: Skin Barrier Function Current position: Novatris Consumer Health, Nyon, Switzerland
	Gilles Touraille, Pharm. D.: Doctorant: Skin Penetration of Toxic Compounds Following Exposure to Contaminated Soil Current position: EMEA, London
1998-2000	Renata F.V. Lopez, Dipl. Pharm.: Visiting Graduate Student: Iontophoresis and Photodynamic Therapy Current position: Professor, University of São Paulo, Ribeirão Preto, Brazil
1998-2001	Nabila Sekkat, Dipl. Pharm.: Doctorante: A Model for Neonatal Skin Barrier Function Current position: Ferring, Lausanne, Switzerland
1998-2002	Gustavo Merino, Dipl. Pharm.: Doctorant: Ultrasound-Enhanced Transport Across the Skin Current position: Carrefour pharmacie, France
1999	Monica Dias, Ph.D.: Visiting Postdoctoral Scientist: Infrared spectroscopy and Skin Current position: EMEA, London, England
2000	Nathalie Dujardin, Pharm.D.: Visiting Graduate Student: Electroporation of the Skin
	Peretz Glikfeld, Dipl. Chem. Eng.: Visiting Scientist: Drug Delivery to the Nail Current position: Israel Institute for Biological Research, Ness-Ziona, Israel
2000-01	Hirotoshi Adachi, Ph.D.: Visiting Postdoctoral Scientist: Prevention of Intravascular Device-Related Infections - Electrically-Mediated Skin Antisepsis Current position: Hisamitsu Pharmaceutical Co. Ltd, San Diego, CA
2000-04	Rocio Alvarez-Román, Pharm.D.: Doctorante: Particulate Formulations for Topical Drug Delivery to the Skin Current position: Associate Professor, Universidad Autónoma de Nuevo León, Mexico
	Benoît Leboulanger, M.S.: Doctorant: Noninvasive Therapeutic Drug Monitoring by Reverse Iontophoresis Current position: Novartis, Basel, Switzerland
	Anke Sieg, Pharm.D.: Doctorante: Noninvasive Glucose Monitoring by Reverse Iontophoresis

Current position: Dow-Corning, Brussels, Belgium

2000-05 Yannic Schütz, Dipl. Pharm.: Doctorante: Iontophoretic Delivery of peptides Across the Skin
Current position: DebioPharm, Martigny, Switzerland

Nada Abla, Dipl. Pharm.: Doctorante: Structure-Activity Relationships for peptide Iontophoresis
Current position: Merck Serono, Geneva, Switzerland

2001-05 Christophe Herkenne, Dipl. Pharm.: Doctorant: Rational Design of Topical Formulations
Current position: DebioPharm, Martigny, Switzerland

Blaise Mudry, Dipl. Pharm.: Doctorant: Structure-Transport Relationships for Iontophoretic Drug Delivery Across the Skin
Current position: Ferring, Lausanne, Switzerland

Sophie Mehier, M.S.: Doctorante: Sonoporation – Ultrasound-Mediated Gene Delivery
Current position: Managing Director, Cerma, SA, Archamps, France

Isabel Diaz, Pharm.D.: Doctorante: Transmucosal Drug Delivery
Current position: Ipsen SA, Barcelona, Spain

Marie-Laure Leichtnam, M.S.: Doctorante: Development of a Transdermal 'Spray Patch' for the Systemic Administration of Testosterone

2002-04 Emmanuelle Sublet, M.S.: Staff Research Associate: Topical and Transdermal Drug Delivery
Current position: Staff Research Associate, University of Geneva

Danielle Masuelle, M.S.: Staff Research Associate: Topical and Transdermal Drug Delivery
Current position: Staff Research Associate, University of Geneva

Yves Jacques, Ph.D.: Senior Scientist: Transmucosal Drug Delivery
Current position: Independent consultant

2002 Valentine Wascotte, B.S.: Visiting Erasmus Student: Novel Formulations for Application in Reverse Iontophoresis
Current position: GSK, Belgium

Nuria Uson, M.S.: Visiting Graduate Student: Microemulsions as Topical Vehicles
Current position: CSIC, Barcelona, Spain

2003-04 M. Begoña Delgado-Charro, Ph.D.: Collaboratrice Scientifique: Reverse Iontophoresis and Prediction of Skin Permeability
Current position: Senior Lecturer in Pharmaceutical Sciences, University of Bath, UK

Susan Nixon, Pharm.D.: Doctorante: Noninvasive Monitoring of Lactate by Reverse Iontophoresis
Current position: Novartis Consumer Health, Nyon, Switzerland

2004 Rocio Alvarez-Román, Ph.D.: Postdoctoral Scientist: Particulate Formulations for Topical Drug Delivery to the Skin
Current position: Associate Professor, Universidad Autónoma de Nuevo León, Mexico

University of Bath, Department of Pharmacy & Pharmacology

2004-06	Sandra Weidersberg, Pharm.D.: Ph.D. student: Dermatopharmacokinetics of Topical Steroids Current position: Lohmann LTS, Neuwid, Germany
	Sara Nicoli, Ph.D.: Visiting Scientist: Evaluation of Topical Drug Bioavailability in the Skin Current position: Associate Professor, University of Parma, Italy
2004-07	Jean-Philippe Sylvestre, M.S.: Ph.D. student: Applications of Iontophoresis in Sports Medicine Current position: Postdoctoral scientist, University of Montreal, Canada
2005-08	Xiao Wu, M.Pharm.: Ph.D. student: Interactions of Nanoparticles with Skin Current position: Postdoctoral scientist, University of Kentucky, U.S.A.
2005-09	Lisa Russell, M.Pharm.: Ph.D. student: Dermatopharmacokinetics Current position: Pharmacist, Bristol PCT
	Asma Djabri, M.Pharm.: Ph.D. student: Applications of Iontophoresis in Pediatrics Current position: Pharmacist
2006-07	Camille Bouissou, Ph.D.: Postdoctoral Scientist: Reverse Iontophoresis as a Tool to Characterize "Skin Health".
2006-08	Sevgi Gungor, Ph.D.: Visiting Scientist: Transdermal Delivery of Anti-Cancer Drugs Current position: Associate Professor, Istanbul University, Turkey
2006-10	Manda Tsang, B.Sc.: Ph.D. student: Bioavailability of Topically Applied Drugs for Eczema
2006-16	Sarah Cordery, B.Sc.: Research Associate: Skin Research; Ph.D. student: Transdermal Treatment of Drug Abuse
2008-11	Quan Yang, M.Pharm.: Ph.D. student: Application of Biophysics and Bioengineering to the Assessment of Skin Barrier Function
2008-13	Premrutai Thitilertdecha, B.Sc.: Ph.D. student: Topical delivery of active agents in traditional medicines
2009-10	Christopher Campbell, Ph.D.: Postdoctoral Scientist: Disposition of nanoparticles on the skin
	Ian Benzeval, Ph.D.: Postdoctoral Scientist: Drug delivery to the nail
	Natalie Belsey, Ph.D.: Postdoctoral Scientist: Skin uptake and penetration of pesticides
2010-12	Natalie Belsey, Ph.D.: Postdoctoral Scientist: Imaging drug disposition and pharmacokinetics in skin by stimulated Raman scattering microscopy.
2009-	Luis Rodrigo Contreras-Rojas, M.Pharm.: Ph.D. student: Disposition of nanoparticles on the skin

2010-14	Kit Frederiksen, M.Sc.: Ph.D. student: Controlled drug delivery to the skin.
2011-14	Hazel Garvie-Cook, M.Phys.: Ph.D. student: Atomic Force Microscopy Investigations of the Nanomechanical Properties of Skin and Nail
	Wing Sin Chiu, M.Pharm.: Ph.D. student: Drug Delivery to the Skin and Nail
2011-15	Bertrand Dupont, M.Eng.: Ph.D. student: Novel Applications of Graphene-Based Biosensors to the Skin
	Duygu Celebi, M.Chem.: Ph.D. student: Novel, sustainable gel materials for topical drug delivery
2013-14	Leila Leal, Ph.D.: Visiting Professor: *In vivo-in vitro* correlations for topical bioavailability
2013-	James Clarke, B.Sc.: Ph.D. student: Quantification of dermal absorption from pesticide residues from treated plant surfaces
	Simon Vanstone, M.Phys.: Ph.D. student: Atomic Force Microscopy Investigations of the Nanomechanical Properties of Skin and Nail
2014-15	Hazel Garvie-Cook, Ph.D.: Postdoctoral Scientist: Imaging drug disposition and pharmacokinetics in skin.
	Wing Sin Chiu, Ph.D.: Postdoctoral Scientist: *In vivo-in vitro* correlations for topical bioavailability
	Mohammed Zaher Shehab, Ph.D.: Postdoctoral Scientist: *In vivo-in vitro* correlations for topical bioavailability
2014-	M. Alice Naciel Tabosa, Pharm.D.: Ph.D. student: Development and validation of a pharmacokinetic model for dermal absorption
2015-	Magdalena Hoppel, Pharm.D., Ph.D.: Postdoctoral Scientist: Development and validation of a pharmacokinetic model for dermal absorption
	Andrea Pensado-Lopez, Pharm.D., Ph.D.: Postdoctoral Scientist: *In vivo-in vitro* correlations for topical bioavailability
	Luca Lupani, Pharm.D.: Ph.D. student: Novel Applications of Graphene-Based Biosensors to the Skin
	Floriant Doungmene, Ph.D.: Postdoctoral Scientists: Novel Applications of Graphene-Based Biosensors to the Skin

Doctoral Dissertation Committees

1982-84	Ming-Zong Lai, Pharmaceutical Chemistry, University of California - San Francisco
1986-88	Kathleen V. Roskos, Pharmaceutical Chemistry, University of California - San Francisco
1986-89	Victoria M. Knepp, Pharmaceutical Chemistry, University of California - San Francisco Daniel A.W. Bucks, Pharmaceutical Chemistry, University of California - San Francisco
1988-90	Aeri Kim, Pharmaceutical Chemistry, University of California - San Francisco Seaung Oh, Pharmaceutical Chemistry, University of California - San Francisco D. Bommannan, Bioengineering, University of California - San Francisco - , University of California - Berkeley
1989-92	José M. Cornejo-Bravo, Pharmaceutical Sciences, University of California - San Francisco
1991-94	Marcello Gutierrez, Pharmaceutical Chemistry, University of California - San Francisco Murali Ramanathan, Bioengineering, University of California - San Francisco, University of California - Berkeley
1992	Tamie Minami, Pharmaceutical Sciences, University of Sydney, Australia
1993	Nagahiro Yoshida, Pharmaceutical Sciences, University of Queensland, Australia
1993-95	Sarah Noonberg, Bioengineering, University of California - San Francisco, University of California - Berkeley
1994	Uwe Rohr, Habilitationsschrift, Pharmaceutical Technology, Rheinische Friedrich-Wilhelms-Universität, Bonn, Germany Lucas Ferreira, Groupe de Formation Doctorale Biologie et Pharmacologie Cutanées, Université de Paris-Sud, Châtenay-Malabry, France
1995	Malua de Carvalho Bouton, Diplôme de Doctorat, L'Université Claude Bernard-Lyon 1, Lyon, France Fernando Guerra Domínguez, Facultad de Farmacía,Universidad de La Laguna, Tenerife, Spain
1996	Vikram K. Ramanathan, Pharmaceutical Chemistry, University of California - San Francisco Norris G. Turner, Pharmaceutical Chemistry, University of California - San Francisco Bernard Neau, Groupe de Formation Doctorale Biologie et Pharmacologie Cutanées, Université de Paris-Sud, Châtenay-Malabry, France Abdou E. Said, Faculté de Médicine et de Pharmacie de Besançon, Université de Franche-Comté Fabrice Pirot, Faculté de Médicine et de Pharmacie de Besançon, Université de Franche-Comté Christain Surber, Ph.D., Faculty of Medicine, University of Basel, Switzerland (Habilitation)

1997	Gabriela Marginean-Lazar, Groupe de Formation Doctorale Biologie et Pharmacologie Cutanées, Université de Paris-Sud, Châtenay-Malabry, France
	Anne Jadoul, Université catholique de Louvain, Ecole de Pharmacie, Unité de Pharmacie Galénique, Industrielle et Officinale
	Claudia Witschi, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Sophie Chesnoy, Groupe de Formation Doctorale Pharmacotechnie et Biopharmacie, Université de Paris-Sud, Châtenay-Malabry, France
	Adriana Ganem-Quintanar, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Jacques Bailly, Groupe de Formation Doctorale Biologie et Pharmacologie Cutanées, Université de Paris-Sud, Châtenay-Malabry, France
1998	Peter Boderke, Swiss Federal Institute of Technology, Zürich (ETH-Z)
	Ronald van der Geest, Leiden University, The Netherlands
1999	Laure Brinon, Groupe de Formation Doctorale Pharmacotechnie et Biopharmacie, Université de Paris-Sud, Châtenay-Malabry, France
2000	Gwénaëlle Potard, Groupe de Formation Doctorale Pharmacologie Expérimentale et Clinique, Université de Paris-Sud, Châtenay-Malabry, France
	Nicole Wyttenbach, Swiss Federal Institute of Technology, Zürich (ETH-Z)
	Ingo Alberti, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Katrin Moser, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Diego Marro, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Claudia Valenta, Ph.D., University of Vienna, Austria (Habilitation)
	Alain Boucaud, Université de Tours, France
2001	Pascale Clement, Groupe de Formation Doctorale Pharmacologie Expérimentale et Clinique, Université de Paris-Sud, Châtenay-Malabry, France
	Véronique Gobry, Swiss Federal Institute of Technology, Lausanne (EPFL)
	Catherine Curdy, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Nabila Sekkat, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Gilles Touraille, Groupe de Formation Doctorale Pharmacologie Expérimentale et Clinique, Université de Paris-Sud, Châtenay-Malabry, France
2002	Nathalie Dujardin, Faculty of Medicine, Université catholique de Louvain, Belgium
	Christain Tran, Faculty of Pharmacy, Université Claude-Bernard – Lyon 1, France
	Ignacio de Miguel Clave, Université Paul Sabatier de Toulouse, France
	Gustavo Merino, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Sandrine Geinoz, Université de Lausanne, Faculté des Sciences
2003	Rocio Alvarez-Román, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Anne-Rose Denet, Faculty of Medicine, Université catholique de Louvain, Belgium
2004	Benoît Leboulanger, Université de Genève, Faculté des Sciences, Section de Pharmacie

	Nuria Usón Sanchiz, Universitat de Barcelona, Spain
	Anke Sieg, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Fabienne Jeanneret, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Brigette Traversa, Victoria College of Pharmacy, Monash University, Australia
2005	Laïla Boulmedarat, Ecole doctorale 'Innovation thérapeutique: du fondamental a l'appliqué', Université de Paris-Sud, Châtenay-Malabry, France
	Yannic Schuetz, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Sophie Mehier-Humbert, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Nada Abla, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Marie-Laure Leichtnam, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Isabel Diaz de Consuelo, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Blaise Mudry, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Christophe Herkenne, Université de Genève, Faculté des Sciences, Section de Pharmacie
	Yingxin Cui, London South Bank University
	Rebecca Watkinson, University of Greenwich
2006	Paul Prentice, University of Dundee
	Delphine Soury, Ecole doctorale 'Innovation thérapeutique: du fondamental a l'appliqué', Université de Paris-Sud, Châtenay-Malabry, France
	Giorgio Ottoviani, Faculté des sciences, Université de Genève, Switzerland
2007	Valentine Wascotte, Université catholique de Louvain, Brussels, Belgium
	Andrés Femenía Font, Universidad CEU Cardenal Herrera, Valencia, Spain
2008	Corinne Eenschooten, Danish Technical University, Lyngby, Denmark
	Virginie Vallet, Faculty of Pharmacy, Université Claude-Bernard – Lyon 1, France
2009	Yanjun Zhao, King's College, London
2010	Kent Wooi Ng, Cardiff University, Cardiff
	Oliver Ackaert, Leiden University, Leiden, The Netherlands
	Carine Jacques, Université Paul Sabatier – Toulouse III, Toulouse, France
2011	Harshal Kubavat, University of Bath
	Marina Krämer, University of Bath
	Marta Jorge Cabral Machado, University of London
2014	Xueqin Chen, Ecole Centrale, Marseille, France
	Vikas Hegde, University of Dundee
2015	Martin Rowland, University of Bath
	Clemence Chenevas-Paule, University of Sunderland

Masters Examinations or Theses Committees

1984 Chairman, Masters Degree Committee, Charles Ryll, Pharmaceutical Chemistry
1993 Masters Degree Committee, Karine Buffard, Pharmacy, Université de Paris-sud
1997 Docteur en Pharmacie Degree Committee, Gilles Touraille, Pharmacy, Université de Paris-sud

UNIVERSITY AND PUBLIC SERVICE

University Service

1998-2004	Faculty search committees, University of Geneva
2001-2003	Director, Ecole romande de pharmacie, Universities of Geneva and Lausanne
2004-2006	Executive Committee, Department of Pharmacy & Pharmacology, University of Bath Research Committee, Department of Pharmacy & Pharmacology, University of Bath
2004-	Professorial promotion/appointment committees, University of Bath
2006-2008	Executive Committee, Faculty of Sciences, University of Bath Head of Department of Pharmacy & Pharmacology, University of Bath
2005-2009	External examiner, The Welsh School of Pharmacy, Cardiff University
2006-2008	Board of Studies, Faculty of Sciences, University of Bath Biosciences Services Management Committee, University of Bath Chair, Strategy Committee, Department of Pharmacy & Pharmacology, University of Bath Chair, Operating Committee, Department of Pharmacy & Pharmacology, University of Bath Chair, Safety Committee, Department of Pharmacy & Pharmacology, University of Bath Chair, ETG Committee, Department of Pharmacy & Pharmacology, University of Bath Chair, Board of Studies, M.Pharm. degree, Department of Pharmacy & Pharmacology, University of Bath Chair, Board of Studies, M.Pharmacol. and B.Pharmacol. degrees, Department of Pharmacy & Pharmacology, University of Bath
2008-11	University of Bath Research Committee
2008-10	University Research Students Committee, University of Bath Chair, University of Bath Research Information Group University Research Advisor, University of Bath
2009-10	Chair, Research Information Advisory Group, University of Bath
2009-	University of Bath Senate
2010-12	Chair, Research Staff Working Group, University of Bath Impact Sub-Group, REF 2014, Unversity of Bath
2010-13	Chair, Research Committee, Department of Pharmacy & Pharmacology, University of Bath Research Committee, Faculty of Science, University of Bath Unit of Assessment Leader, REF 2014, University of Bath
2011-12	Academic Staff Development Steering Committee, University of Bath
2013-	Disciplinary Committee of Senate, University of Bath
2014	Academic Staff Appeal Committee, University of Bath

2015 Member, External Assessment Panel, B.Sc. programme in Cosmetic Science, University of Sunderland

2015-16 Member, "Partridge Group", responsible for new M.Pharm. curriculum development and GPhC reaccreditation, Department of Pharmacy & Pharmacology, University of Bath.

2016- Metrics in Research Assessment and Management Working Group, University of Bath

Service to Educational, Governmental, and Other Agencies

1998- Referee, Engineering and Physical Sciences Research Council, U.K.

2002 External Referee, Upjohn Research Award, University of Michigan, Ann Arbor, Michigan
External Reviewer, Foundation for Research & Development, South Africa
Reviewer, American Diabetes Association

2004- External Reviewer, Biotechnology and Biological Sciences Research Council, U.K.
Referee, Medical Research Council, U.K.
Referee, Science Foundation Ireland
External Reviewer, U.S. National Institutes of Health
Expert Reviewer, Cosmetics, Toiletries and Fragrance Association, New York, USA

2005-6 Member, Expert Group on the application of the Threshold of Toxicological Concern (TTC) to the safety evaluation of cosmetic ingredients and end products, COLIPA (The European Cosmetic, Toiletry and Perfumery Association), Brussels, Belgium
Member, Scientific Committee on Consumer Products, Working Group on 'Nanotechnology', European Commission, Health & Consumer Protection Directorate-General, Brussels, Belgium.

2006 External Reviewer, Foundation for Research & Development, South Africa
Referee, Israel Science Foundation

2007 Contributor to European Commission, Health & Consumer Protection Directorate-General, Scientific Committee on Consumer Products "Opinion on Safety of Nanomaterials in Cosmetic Products", adopted December 18, 2007.
http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_123.pdf

2009 Expert, European Medicines Evaluation Agency, London, U.K.
Panel member, Research Councils for Health and Natural Sciences and Engineering of the Academy of Finland
Expert, Federal Trade Commission, Washington, DC, USA
Reviewer, Diabetes U.K.

2010	Expert witness on behalf of the Minister for Health & Ageing, Australia (Therapeutic Goods Administration), Administrative Appeals Tribunal, Sydney
	External Reviewer, National Research Foundation, South Africa
	External Assessor for the internal review of the University of Nottingham's School of Pharmacy
2010-	Member, Expert Advisory Panel for Pharmaceutical Science, Royal Pharmaceutical Society of Great Britain
2011	Member, The Danish Council for Independent Research, Danish Agency for Science, Technology & Innovation, Medical Bio-Pharma grants review panel
	External Reviewer, British Skin Foundation
	External Reviewer, SPARKS
	External Reviewer, Wellcome Trust
2012	External Panel Member, Appointment committee for the Norbrook Chair in Pharmaceutical Sciences, University of Ulster
	External Assessor, Chair in Pharmaceutical Sciences, Welsh School of Pharmacy, Cardiff University
	External Member, Professors interview panel, University of the Arts London
	External Reviewer, ETH Zurich Research Commission
2013-14	Assessor for the REF Sub-panel 3: Allied Health Professions, Dentistry, Nursing and Pharmacy.
2013	External Reviewer, National Institute of Health Research
2014	External Reviewer, Czech Research Foundation
	External Reviewer (Stage 1 panel), Science Foundation Ireland
	Panel Member, International Life Sciences Research Announcement (ILSRA) Physiology, Monitoring and Pharmacology, NASA (Washington, D.C., USA)
2015	External Reviewer, Hadwen Trust
	External Reviewer, Queen's University, Belfast, MRC Confidence-in-Concepts grant applications
	External Reviewer, National Research, Development and Innovation Office, Hungary
2015-16	Panel Member, NC3Rs CRACK-IT Challenge Review Panel – Metaboderm, Wellcome Trust, U.K.

PROFESSIONAL ACTIVITIES

Service to Scholarly and Professional Societies (since 1994)

1994	Co-Director (with Professeur Jean-Paul Marty), "Administration Transdermique de Médicaments," a 3-day course covering all aspects of the transdermal administration of drugs. Marne la Vallée, France
	Co-Chairman (with Professeur Jean-Paul Marty), 21st International Symposium on Controlled Release of Bioactive Materials, Controlled Release Society. Nice, France
1994-95	Member, Organizing Committee, "Prediction of Percutaneous Penetration: Methods, Measurements, Modeling." International Conference. Montpellier, France
1994-97	Member, Electorate Nominating Committee, AAAS Section on Pharmaceutical Sciences. American Academy for the Advancement of Science. Washington, DC
1998-2001	Vice-President, President-Elect and President, Controlled Release Society, Deerfield, Illinois
2002-2006	Member, Høst-Madsen Award Committee, Fédération internationale de pharmacie (F.I.P.), The Hague, Netherlands
2003	Discussion Leader, Gordon Research Conference on 'Barrier function of mammalian skin', Roger Williams University, Rhode Island, USA
2003-	Member, Executive Committee, Skin Forum
2005	Discussion Leader, Gordon Research Conference on 'Barrier function of mammalian skin', Mount Holyoke College, Massachusetts, USA
2008	Co-Chair, Lohmann LTS Academy Symposium on "Unmet Needs in Transdermal Drug Delivery", Königswinter, Germany
2009	Debate Leader, Gordon Research Conference on 'Barrier function of mammalian skin', Waterville Valley, New Hampshire, USA
2011	Discussion Leader, Gordon Research Conference on 'Barrier function of mammalian skin', Waterville Valley, New Hampshire, USA
	Conference Scientific Chair, Academy of Pharmaceutical Sciences, Great Britain, PharmSci 2011, Nottingham, UK
2011-	Member of, now Advisor to, the Board of the Academy of Pharmaceutical Sciences, Great Britain
	Member, Expert Working Group on the 'evaluation of oral-to-dermal extrapolation', European Commission Project 'Integrated In Silico Models for the Prediction of Human repeated Dose Toxicity of COSMetics to Optimise Safety' (COSMOS).
2014	Co-author, "New Medicines, Better Medicines, Better Use of Medicines", a guide to the science underpinning pharmaceutical practice, Royal Pharmaceutical Society, London, May 2014.

Service to Scholarly and Professional Journals

1981 –	Referee, International Journal of Pharmaceutics Referee, Journal of Physical Chemistry Referee, Canadian Journal of Chemical Engineering
1982 –	Referee, Journal of Pharmaceutical Sciences
1983 –	Referee, Journal of Investigative Dermatology Referee, Pharmaceutical Research
1984 –	Referee, Journal of Controlled Release Referee, Journal of Pharmacokinetics and Biopharmaceutics Referee, Chemical Reviews
1985 –	Referee, Archives of Dermatology Referee, Microvascular Research Referee, Life Sciences
1986 –	Referee, Science
1986 –	Referee, Journal of the American Chemical Society Referee, Mathematical Biosciences
1987 –	Referee, S. African Journal of Science Referee, Drug Design and Delivery Referee, Skin Pharmacology
1987-2008	Member, Editorial Advisory Board, Skin Pharmacology
1988 –	Referee, Plastic and Reconstructive Surgery Referee, Toxicology and Applied Pharmacology Referee, Industrial and Chemical Engineering Research
1990 –	Referee, Diabetes Care Referee, Chest
1992-2003	Member, Editorial Advisory Board, Advanced Drug Delivery Reviews Referee, American Institute of Chemical Engineers Journal Referee, Toxicology and Applied Pharmacology
1993–4	Member, Editorial Advisory Board, Pharmaceutical Research
1993 –	Referee, European Journal of Pharmaceutical Sciences Referee, Journal of Pharmacology and Experimental Therapeutics Referee, European Journal of Pharmaceutics and Biopharmaceutics Referee, Journal of Drug Targeting Referee, Bioorganic & Medicinal Chemistry

1994 –	Referee, Journal of Exposure Analysis and Environmental Epidemiology
1995 –	Referee, S.T.P. Pharma Sciences (Editions de Santé)
1996 –	Member, Editorial Advisory Board, European Journal of Pharmaceutics and Biopharmaceutics
1997-2000	Member, Editorial Advisory Board, Journal of Controlled Release
1997-2003	Member, Editorial Advisory Board, Journal of Pharmacy & Pharmacology
2000-16	Member, Editorial Advisory Board, Diabetes, Technology & Therapeutics Referee, Diabetes, Technology & Therapeutics
2001-02	Member, Editorial Advisory Board, Drug Discovery Today
2002-07	Associate Editor, Journal of Pharmaceutical Sciences Referee, Photochemistry & Photobiology
2003-	Referee, Bioelectrochemistry Referee, Nature Reviews, Drug Discovery
2003-	Member, Editorial Advisory Board, European Journal of Pharmaceutical Sciences
2004-	Referee, Sensors and Actuators, B Referee, Environmental Science & Technology
2005-	Referee, Journal of Drug Delivery Science & Technology Referee, Nature Reviews Immunology Referee, Skin Pharmacology & Physiology
2006-	Referee, Pharm. Biochem. Behaviour Referee, Proceedings of the National Academy of Sciences, USA Referee, Journal of Medicinal Chemistry Referee, Expert Opinion in Drug Delivery Referee, American Journal of Drug Delivery
2008-	Member, Editorial Advisory Board, Skin Pharmacology & Physiology Member, Editorial Advisory Board, Journal of Pharmaceutical Sciences Referee, Journal of Pharmacokinetics and Pharmacodynamics Referee, Biophysical Journal
2009-	Referee, Nature Nanotechnology Referee, Journal of Drug Targeting
2010-	Referee, Toxicology Letters Referee, ACS Nano

2011-	Referee, Molecular Pharmaceutics Referee, AAPS J. Referee, Nanomedicine
2012-	Referee, International Journal of Cosmetic Science
2014-	Referee, Chemical Research in Toxicology Referee, PLoS One
2015-	Referee, Nature Protocols Referee, Environmental Science & Technology Referee, Lab on a Chip Referee, Annals of Otology, Rhinology & Laryngology
2016-	Referee, Clinical Pharmacokinetics Referee, J. Appl. Toxicol. Referee, J. Exposure Sci. Environ. Epidemiol. Referee, Nature Nanotechnology
2017-	Member, Editorial Advisory Board, International Journal of Pharmaceutics

Consultant or Service as a Professional Expert (since 1994; active in green)

1994-5	Co-Founder and Member, Board of Directors, De Novo, Inc., Menlo Park, California Member, Scientific Advisory Board, De Novo, Inc., Menlo Park, California
1994-9	Consultant, Becton Dickinson Transdermal Systems, Franklin Lakes, New Jersey: Iontophoresis and Formulation Member, Scientific Advisory Board, Advanced Polymer Systems, Redwood City, California
1994-2001	Consultant, Unilever Research, Port Sunlight, England: Skin/hair care
1995-6	Consultant, Tilderm Systems, Laboratoires Fournier, Chenôve, France: Iontophoresis Member, Scientific Advisory Board, Advanced Therapies Inc., Novato, California
1996	Consultant, Searle, Skokie, Illinois: Transdermal drug delivery Consultant, Zyma SA, Nyon, Switzerland: Topical and transdermal drug delivery
1996-9	Consultant, Novo Nordisk, Denmark: Iontophoresis and drug delivery Consultant, Novartis, Basel, Switzerland: Optimization of topical drug delivery
1996-8	Member, Scientific Advisory Board, EKOS LLC, Seattle, Washington Consultant, Cellegy, Inc., Foster City, California: Topical drug delivery
1997-8	Consultant, CIRD-Galderma, Sophia Antipolis, France: Topical drug delivery Consultant, Institut de Recherche Pierre Fabre, Castanet Tolosan, France

1997-8	Member, Scientific Advisory Board, Biovector, Toulouse, France
1998-9	Member, Scientific Advisory Board, Cellegy, Inc., Foster City, California
1999-2000	Consultant, *éthymed*, Paris, France Consultant, Innothera, Paris, France
1999-2002	Consultant, Pacific Corporation, Seoul, Korea
2001-2013	Consultant, L'Oréal, Paris, France
2001-2003	Member, Scientific Advisory Board, LSC, Inc., Burlingame, California
2001-2004	Consultant, OM Pharma, Geneva, Switzerland
2001-2006	Member, Scientific Advisory Board, Vyteris, Inc., Fair Lawn, New Jersey
2002-2007	Member, Scientific Advisory Board, TransPharma, Inc., Israel
2002-2004	Consultant, GSK Consumer Health, Weybridge, England Consultant, Abbott Laboratories, Abbott Park, Illinois
2003	Consultant, Laboratoires Besins
2003-2004	Consultant, Galderma SA, Sophia Antipolis, France
2004-2005	Consultant, Shire Pharmaceuticals, PLC, Basingstoke, UK
2004-2006	Consultant; Member, Scientific Advisory Board, PowerPaper, Inc., Israel Consultant, Firmenich, SA, Geneva, Switzerland
2005	Consultant, Amgen, Inc., Cambridge, UK
2005-2009	Consultant, York Pharma, Sheffield, UK
2005-2010	Member, Scientific Advisory Board, Acrux, Ltd., Melbourne, Australia
2006	Member, Scientific Advisory Board, Connetics, Inc., Palo Alto, CA, USA
2006-2008	Consultant, Shire Pharmaceuticals, PLC, Basingstoke, UK
2006-2010	Member, Scientific Advisory Board, DBV Technologies, Paris, France
2006-2013	Member, Scientific Advisory Board, EyeGate Pharmaceuticals, Inc., Waltham, MA, USA
2007	Consultant, GSK, Parsippany, NJ, USA Consultant, Unilever, Trumbull, CT, USA
2007-2008	Consultant, Altea Therapeutics, Atlanta, GA, USA

	Consultant, Pharmakodex, Chippenham, U.K.
2008-2011	Member, Scientific Advisory Board, Vyteris, Inc., Fair Lawn, New Jersey, USA Chair, Scientific Advisory Board, Altea Therapeutics, Atlanta, GA, USA
2008	Consultant, Acclarent, Inc., Palo Alto, CA, USA Consultant, Serentis, Ltd., Cambridge, U.K. Consultant, TPG Partners, Fort Worth, TX, USA Consultant, Rader, Fishman & Grauer PLLC, Bloomfield Hills, Michigan, USA
2008-09	Consultant, OBJ, Ltd., Leederville, WA, Australia
2009	Consultant, Bristol Myers Squibb, Moreton, Wirral, U.K.
2009-2010	Consultant, Therapeutic Goods Administration, Canberra, Australia
2009-	Consultant, PMIC, Anthony, France
2010-	Consultant, Grunenthal GmbH, Germany Consultant, Leo Pharma A/S, Denmark
1997	Consultant, Novartis Pharma, Basel, Switzerland Consultant, Isdin S.A., Spain
2011-	Consultant, Nemaura Pharma, Loughborough, U.K.
2012	Consultant, Genentech, South San Francisco, CA, USA Consultant, GSK Consumer Health, Parsippany, NJ, USA Consultant, Sanofi Recherche, Montpellier, France
2012-	Consultant, Delenex AG, Zurich, Switzerland
2013-	Consultant, Dermira, Inc., Redwood City, CA, USA Consultant, Nitto Denko Technical Corporation, Oceanside, CA, USA
2013-14	Chair, Expert Panel Meeting on Topical Ketoprofen, Hisamitsu Pharmaceutical Co., Ltd., Japan
2014-	Consultant, GSK Consumer Health, Singapore Consultant, Medivation, Inc., San Francisco, CA, USA Consultant, Mundipharma Research Ltd., Cambridge, U.K.
2016-	Member, Scientific Advisory Board, Almirall S.A., Barcelona, Spain Member, Scientific Advisory Board, Pierre-Fabre, Toulouse, France Consultant, L'Oréal, Paris, France

Invited Lectures and Seminars (since 2005)

2005 Mechanisms of Iontophoretic and Sonophoretic Drug Delivery Across the Skin. United Kingdom and Ireland Controlled Release Society, 11th Annual Symposium, Aston University, Birmingham, UK (January 6)

Recent Advances in Transdermal Administration. Plenary Lecture. VII Congreso de la Sociedad Española de Farmacia Industrial y Galénica. Salamanca, Spain (February 8)

Science Meets the Skin: Delivering Drugs Legally. Inaugural lecture. University of Bath, Bath, UK (February 23)

Physical Delivery Methods: Iontophoresis and Beyond. Skin Science and Advances in Aesthetic Therapies Symposium, 39th Annual Conference of the Australian Society of Cosmetic Chemists. Brisbane, Australia (March 16)

Following Substances Into (and Through) the Skin by Tape-Stripping. 39th Annual Conference of the Australian Society of Cosmetic Chemists. Brisbane, Australia (March 17)

Biophysical Techniques in Skin Research: Infrared (IR) Spectroscopy. 39th Annual Conference of the Australian Society of Cosmetic Chemists. Brisbane, Australia (March 20)

Following Substances Into (and Through) the Skin by Tape-Stripping. Acrux, Inc. Melbourne, Australia (March 22)

(Trans)dermal Technologies. Hud och Läkemedel («Skin and Drugs»), University of Göteborg, Gothenburg, Sweden (May 18)

Method Development and Modeling to Characterize Penetration, Absorption, Dose, and Local Effects Resulting from Dermal Exposures. Plenary lecture, Occupational and Environmental Exposures of the Skin to Chemicals, Karolinska Institute, Stockholm, Sweden (June 12)

Closing the Loop: Noninvasive Drug Delivery and Clinical Monitoring via the Skin. Invited Lecture, 32nd Annual Meeting & Exposition of the Controlled Release Society, Miami Beach, Florida, USA (June 20)

Novel Transdermal Technologies to Control, Manipulate and Optimize Drug Input Across the Skin. Sanofi-Aventis, Paris, France (June 28)

Dermatopharmacokinetics: Opportunities and Limitations for Assessment of Topical Bioavailability. Invited speaker, 6th Annual Meeting of Skin Forum, University College, Winchester, UK (June 30)

(Trans)Dermal Technologies for Delivery and Diagnosis. Proctor & Gamble, Egham, UK (July 10)

Dermatopharmacokinetics: Opportunities and Limitations for Assessment of Topical Bioavailability. York Pharma, Sheffield, UK (July 12)

Latest Developments in Iontophoresis. PowerPaper Scientific Advisory Board meeting, Paris, France (September 2)

Dermatopharmacokinetics: A Tool for Determining Bioequivalence between Topical Formulations. Invited speaker, "Biointernational 2005: Towards Resolution of Complex BE Issues", Royal Pharmaceutical Society, London, UK (October 24)

Measurement and Prediction of the Rate and Extent of Drug Delivery into and through the Skin. Invited speaker, 2nd EUFEPS Conference on "Optimizing Drug Delivery and Formulation", Versailles, France (November 23)

2006 Penetration of Molecules and Particles (?) into and through the Skin. Nanotoxicology Symposium: Toxicology and Technology of Nanoparticles. Centre for Xenobiotic and Environmental Risk Research, University of Zurich, Zurich, Switzerland (January 11)

Drug Delivery into and through the Skin: Quantification, Enhancement and Optimization. Connetics Visiting Lecture Series, Palo Alto, CA, USA (April 19)

Novel Transdermal Technologies to Control, Manipulate and Optimize Drug Input across the Skin. L'Oréal Research, Aulnay-sous-Bois, France (May 22)

Novel Transdermal Technologies to Control, Manipulate and Optimize Drug Input across the Skin. Galderma Research & Development, Sophia Antipolis, France (July 10)

Drug Delivery into and through the Skin: Quantification, Enhancement and Optimization. Galderma Research & Development, Sophia Antipolis, France (July 11)

Science Meets the Skin: Delivering Drugs Legally. U3A, Warminster (July 19)

Transdermal Science and Technology in the New Millenium. Invited speaker, Teikoku Seiyaku Reception, 33rd Annual Meeting & Exposition of the Controlled Release Society, Vienna, Austria (July 23)

Closing the Loop: Noninvasive Drug Delivery and Clinical Chemistry via the Skin. Invited speaker, British Pharmaceutical Conference, Manchester, UK (September 6)

Estimating the Percutaneous Absorption of Fragrance Materials. Expert panel meeting of the Research Institute of Fragrance Materials, Berlin, Germany (September 11)

Topical Bioavailability: Stripping and Science. Invited speaker, 2nd APGI Symposium: Skin & Formulation. Versailles, France (October 10)

Chemical Enhancement of Transdermal Drug Delivery. Corium, Inc. Redwood City, CA, USA (October 23)

Novel Transdermal Technologies to Control, Manipulate and Optimize Drug Input across the Skin. Connetics, Inc., Palo Alto, CA, USA (October 24)

Topical Bioavailability: Quantification and Optimization. Invited speaker, 2nd International Meeting of the Society for Skin Pharmacology and Physiology: *Skin Physiology: Irritation and Penetration Pathways*. Rome, Italy (November 6)

Electrotransport Across the Skin: Physical Chemistry, Bioengineering and Clinical Application. Physical & Theoretical Chemistry Laboratory, Department of Chemistry, Oxford University, Oxford (November 13)

2007 Closing the Loop: Noninvasive Drug Delivery and Clinical Monitoring via the Skin. The Strathclyde Institute of Pharmacy & Biomedical Sciences, University of Strathclyde, Galsgow, Scotland (January 30)

Skin Barrier Function: Biophysics, Models and Measurements. Conopco, Inc., (Unilever), Trumbull, CT, USA (March 15)

Iontophoresis: Basic Principles and Potential Applications. Eyegate Pharmaceuticals, Waltham, MA, USA (March 16)

Topical Bioavailability: Stripping and Science. Invited speaker, 8th Skin Forum, London (April 4)

Opportunities and Limitations for Assessment of Topical Bioavailability. Chulalongkorn University, Faculty of Pharmaceutical Sciences, Bangkok, Thailand (May 14)

Electrotransport Across the Skin: Physical Chemistry, Bioengineering and Clinical Application. Chulalongkorn University, Faculty of Pharmaceutical Sciences, Bangkok, Thailand (May 14)

Transdermal Science and Technology in the New Millenium. Altea Therapeutics, Atlanta, GA, USA (June 14)

Drug Delivery: Hits, Hype and Hope for the 21st Century. Dept. of Pharmacy & Pharmacology, Centenary Science Day Celebration, University of Bath (July 5)

Assessment of Topical Drug Delivery and Bioavailability. Invited speaker. Gordon Research Conference on "Barrier Function of Mammalian Skin", Newport, RI, USA (August 6)

New Technologies in the Evolution of Transdermal Drug Delivery. Plenary speaker. 5th International Postgraduate Research Symposium on Pharmaceutics. Istanbul, Turkey (September 14)

New Aspects of Cutaneous Drug Penetration. Invited speaker. World Congress of Dermatology, Buenos Aires, Argentina (October 4)

Predicting the Rate and Extent of Chemical Absorption into and through the Skin. Invited speaker. American College of Toxicology, 28th Annual Meeting, Charlotte, NC, USA (November 13)

Transdermal Drug Delivery: Principles, Practice and Promise. Hisamitsu Pharmaceutical Co., Ltd., 160th Anniversary Symposium. Plenary speaker. Tokyo, Japan (December 1)

Assessment of Topical Drug Delivery and Bioavailability. Hisamitsu Pharmaceutical Co., Ltd., Tosu, Kyushu, Japan (December 3)

2008 Iontophoresis, Electroporation and Other Techniques to Overcome the Skin's Barrier. L'Oréal (Cosmétique Active), Asnières, Paris, France (January 9)

Electrotransport Across the Skin: Physical Chemistry, Bioengineering and Clinical Application. Plenary speaker, "Perspectives in Percutaneous Penetration", 11th International Conference, La Grande Motte, France (March 26)

Dermatopharmacokinetics. Invited speaker, "Perspectives in Percutaneous Penetration", 11th International Conference, La Grande Motte, France (March 27)

Topical Drug Bioavailability: Dermatopharmacokinetics. Invited speaker, "Topical and Transdermal Drugs – Challenges and Opportunities", Swedish Academy of Pharmaceutical Sciences, Stockholm, Sweden (April 23)

Dermatopharmacokinetics: Assessment of Topical Drug Bioavailability. Galderma S.A., Sophia Antipolis, France (June 16)

Topical Drug Bioavailability and Dermatopharmacokinetics. Invited speaker, 4th Skin Focus Meeting, Cardiff (June 18)

Topical Drug Bioavailability and Dermatopharmacokinetics. Invited speaker, L'Oréal Research, Aulnay-sous-Bois, France (October 13)

Iontophoretic Drug Delivery. Invited speaker. Lohmann LTS Academy Symposium on "Unmet Needs in Transdermal Drug Delivery", Königswinter, Germany (October 16)

Disposition of Nanoparticles Contacting the Skin. 1st International Conference on Dermatotoxicology, Vaals, The Netherlands (October 25)

Bioengineering and the Skin: Transdermal technologies for Drug Delivery and Clinical Monitoring. Department of Chemical Engineering, University of Cambridge, Cambridge (November 26)

2009 Bilateral Collaboration on Education and Research. UKIERI Awards Symposium. New Delhi, India (March 23)

Assessment of Topical Bioavailability. Invited speaker. Annual meeting of the British Society for Investigative Dermatology, Royal Agricultural College, Cirencester (March 30)

Transdermal Drug Delivery for Children. Invited speaker. Pharmaceutical Translational Research Conference. Medicines for Children Research Network. The School of Pharmacy, University of London, London (April 2)

Transdermal Drug Delivery. Invited speaker. 5th GPA/UKCPA Joint Annual National Conference. Leicester (May 16)

Transdermal Delivery Techniques. Invited speaker. Joint Conference in Medical Sciences 2009. Mahidol-Chulalongkorn Universities. Bangkok, Thailand (June 23)

Bioavailability of Actives Applied Topically to the Skin. Invited speaker. Joint Conference in Medical Sciences 2009. Mahidol-Chulalongkorn Universities. Bangkok, Thailand (June 23)

Non-Invasive Monitoring Across the Skin. Bath Biosensor Network, 1st Bath Interdisciplinary Meeting on Biosensors. Bath (September 23)

The Stratum Corneum as a Pharmacokinetic Compartment. Invited speaker. "StratumCorneum VI", International Society of Stratum Corneum Research. Boston, MA, USA (October 1)

Disposition of Nanoparticles Contacting the Skin: a Reality Check… Invited speaker.

Dermatopharmaceutics Focus Group Meeting, Annual Meeting of the American Association of Pharmaceutical Scientists. Los Angeles, CA, USA (November 11)

Microdialysis and Stratum Corneum Tape-Stripping for Dermatopharmacokinetics. Invited speaker. Annual Meeting of the American Association of Pharmaceutical Scientists. Los Angeles, CA, USA (November 11)

Fonction Barrière de la Peau. Les Matinees Scientifiques de Cosmétique Active. L'Oréal. Asnières-sur-Seine, France (December 4)

Research Study Options in the U.K. and at the University of Bath. Ph.D. Workshop China 2009. Beijing, China (December 12)

2010 Transdermal Drug Delivery. Department of Bioengineering & Therapeutic Sciences, University of California – San Francisco, San Francisco, CA, USA (January 25)

Optimising Topical Formulations for Drug Delivery into the Skin: Mechanisms and Methodologies. Leo Pharma A/S, Ballerup, Denmark (March 4)

Transdermal Drug Delivery Technologies. School of Pharmacy, Queen's University Belfast. Belfast, N. Ireland (March 10)

Topical Bioavailablity and Formulation Optimisation. Invited speaker. 8th International Conference & Workshop on Biological Barriers. Saarland University, Saarbrücken, Germany (March 29)

Dermatopharmacokinetics: Assessment of Topical Drug Bioavailability. Leiden-Amsterdam Centre for Drug Research. Leiden University, Leiden, The Netherlands (April 28)

Dermatopharmacokinetics: Clinical Perspectives. University of Valencia. Valencia, Spain (June 1)

Predicting the Rate and Extent of Chemical Absorption Into and Through the Skin. Dermal Exposure Working Group, International Life Sciences Institute (ILSI) Research Foundation & U.S. Environmental Protection Agency, Washington, DC, USA (June 21)

Probing Drug Delivery to the Skin Using Stimulated Raman Scattering Microscopy. Invited speaker. 7th Annual Coherent Raman Microscopy Workshop, Harvard University, Cambridge, MA, USA (June 25)

Les Systèmes Iontophorétiques. L'Oréal. Asnières-sur-Seine, France (July 12)

Bioavailability Issues in Dermal Delivery – In Vivo Methods. Invited speaker. Academy of Pharmaceutical Sciences G.B., UK PharmSci 2010, University of Nottingham (September 1)

Optimising Topical Formulations to Deliver Actives into the Skin: Mechanisms and Methodologies. Unilever. Trumbull, CT, USA (December 14)

Skin – "That Unfakeable Young Surface". Invited speaker. Festschrift for Prof. Jonathan Hadgraft. The School of Pharmacy, University of London (December 16)

2011 Optimising Topical Formulations to Deliver Actives into the Skin: Mechanisms and Methodologies. L'Oréal. Aulnay-sous-Bois, France (March 4)

Measuring Drug Permeation and Penetration into and through Skin Using Coherent Raman Microscopy. Invited speaker. Skin Forum 12th Annual Meeting (with APV). Frankfurt, Germany (March 29)

Imaging Drug Delivery to Skin with Stimulated Raman Scattering Microscopy. Invited speaker. 39th Interpharm Research Conference. Brockenhurst, UK (May 13)

Transdermal Technology for Drug Delivery. Invited speaker. 3rd PharmSciFair. Prague, Czech Republic (June 15)

Measuring Drug Permeation and Penetration into and through Skin Using Coherent Raman Microscopy. Invited speaker. CARS Explorer Symposium: Optical Solutions to Biomedical Problems. Marseille, France (June 20)

Imaging Drug Delivery to Skin with Stimulated Raman Scattering Microscopy. Leo Pharma A/S, Ballerup, Denmark (June 23)

Electrotransport Across the Skin – Delivery and Sampling. Invited speaker. Skin Trailblazer, 2nd Workshop. Boston, MA, USA (August 7)

Is There a Future for (Transdermal) Drug Delivery? Conference Scientific Chair's Address. PharmSci 2011, Academy of Pharmaceutical Sciences, Great Britain. Nottingham (August 31)

Imaging Drug Delivery to Skin Using Coherent Raman Scattering Microscopy. Invited speaker. PharmSci 2011, Academy of Pharmaceutical Sciences, Great Britain. Nottingham (August 31)

Predicting the Rate and Extent of Chemical Absorption through the Skin. International Life Sciences Institute (ILSI), COSMOS expert group 2, Brussels, Belgium (September 13)

Formulation Chemistry and (Trans)Dermal Drug Delivery. [in French] D.Young & Co., London (September 27)

Is There a Future for Transdermal Drug Delivery? Invited speaker. LTS Academy 8th Symposium "New Horizons in Drug Delivery: 35 years on". Bonn, Germany (September 29)

A Tiered Approach to Dermal Exposure Assessment for Anti-Microbial Pesticides. Speaker. Society for Risk Analysis 2011 Annual Meeting, Charleston, SC, USA (December 6)

A Tiered Approach to Dermal Exposure Assessment for Anti-Microbial Pesticides. U.S. Environmental Protection Agency, Crystal City, VA, USA (December 8)

1998 Predicting the Flux of Cosmetic Ingredients across the Skin. International Life Sciences Institute (ILSI), COSMOS expert group 2, Brussels, Belgium (March 19)

Transdermal Drug Delivery from Gels. Invited speaker, "Perspectives in Percutaneous Penetration", 13th International Conference, La Grande Motte, France (April 12)

Skin Biophysics and Transdermal Technologies for Drug Delivery and Clinical Monitoring. Department of Physics, University of Exeter, Exeter (April 23)

Imaging Drug Delivery to Skin Using Coherent Raman Scattering Microscopy. Invited speaker. Workshop on Applications of Coherent Raman Scattering Microscpy. University of Exeter, Exeter (April 23).

Disposition of Nanomaterials Applied to the Skin: Assessment and Imaging. Invited speaker. International Meeting: The Fundamental Pillars of Nanotechnology for the Cosmetic Industry. São Paulo, Brazil (May 18)

Delivering Actives into the Skin: Separating Fact from Fiction. Invited speaker. 5th Society of Cosmetic Scientists Annual Scientific Symposium, "Cosmetic Science: The Good, The Bad and The Beautiful", Trinity College, Dublin, Ireland (May 31)

Administration transdermique des médicaments: la technologie de pointe. [in French] Invited speaker. Académie galénique Michel Lanquetin: Sciences pharmaceutiques. Monte Carlo, Monaco (June 1)

Dermatopharmacokinetics: Assessing Bioavailability of Topically Applied "Actives". L'Oréal Research, Aulnay-sous-Bois, France (June 6)

Delivery of Ketoprofen from a Topical Patch Product: a Benefit/Risk Analysis. Invited speaker. 11th Congress of The European Society of Contact Dermatitis. Malmö, Sweden (June 13)

Improving the Bioavailability of Topically and Transdermally Administered Drugs. Invited speaker. 39th Annual Meeting of the Controlled Release Society. Quebec City, Canada (July 17)

Transdermal Drug Delivery - Past, Present and Future: Basic Science, Regulatory Challenges and New Technologies. GlaxoSmithKline Consumer Health. Parsippany, NJ, USA (July 19)

Technologies for Drug Delivery into and through the Skin. Reckitt Benkiser. Hull (July 27)

Noninvasive Sensing of Glucose and Other Analytes Across the Skin. Invited speaker. International Mini-Symposium on Sensing and Drug Delivery Systems. University of Bath (August 6)

Improving the Bioavailability of Topically and Transdermally Administered Drugs. Centre for Dermatology and Genetic Medicine, University of Dundee (October 9)

Transdermal Drug Delivery and Associated Pathology. Invited speaker. 27th Annual Scientific Meeting of the British Society of Toxicological Pathology. Astra Zeneca, Alderley Edge (November 16)

Predicting Chemical Uptake into Skin. Invited speaker. Society for Chemical Industry, Symposium: "Uptake across the leaf cuticle and skin", London (November 22)

Predicting and Measuring Drug Delivery into and through the Skin. Invited speaker. Sanofi-Aventis, Symposium: "Biopharmaceutical aspects of specific administration routes: Ocular, Otic and Cutaneous", Montpellier, France (November 29)

Imaging Drug Delivery to Skin Using Coherent Raman Scattering Microscopy. L'Oréal Research, Aulnay-sous-Bois, France (December 4)

Transdermal Drug Delivery Technology. "Drug Delivery Strategies for Biologics", Knowledge Transfer Network – Healthtech and Medicines, BioCity – Nottingham, (December 13)

2013 Topical and Transdermal Drug Delivery: Rules, Tools and Nanoparticles. National Institute for Pharmaceutical Education & Research, Mohali (Punjab), India (January 21)

Topical and Transdermal Drug Delivery: Rules, Tools and Nanoparticles. Invited speaker. Controlled Release Society Indian Chapter, 13th International Symposium. Mumbai, India (January 22)

Transdermal Drug Delivery. Department of Bioengineering & Therapeutic Sciences, University of California – San Francisco, San Francisco, CA, USA (January 24)

Topical Drug Delivery: Rules, Tools and Nanoparticles. Stiefel, a GSK company. Research Triangle Park, NC, USA (March 14)

Modélisation de la Barrière et du Passage Transcutané. Invited speaker. 20ème Cours francophone de Biologie de la Peau (CoBiP 2013). Lyon, France (March 22)

Predicting and Measuring Drug Delivery into and through the Skin. University of Maryland, School of Pharmacy, Baltimore, MD, USA (May 20)

Dermatopharmacokinetics and Tape Stripping the Stratum Corneum: Origins and Problems. Invited speaker. Topical Drug Bioavailability/Bioequivalence Summit. University of Maryland, School of Pharmacy, Baltimore, MD, USA (May 21)

Decision Framework for Data Needs to Estimate Dermal Exposure. Invited speaker. Webinar - Thresholds of Toxicological Concern: An Example of Integrated Approaches to Testing and Assessment. U.S. Environmental Protection Agency, Washington, DC, USA (June 11)

Topical and Transdermal Drug Delivery: Rules, Tools and Nanoparticles. Invited speaker. Skin Forum 12th Annual Meeting, UCL School of Pharmacy, London (June 26)

Skin – "The Finest Clothing Ever Made". Founders Award address, 40th Annual Meeting of the Controlled Release Society. Honolulu, HI, USA (July 22)

Probing the Skin-Drug Delivery Platform Interface. Invited speaker. Gordon Conference on "Barrier Function of Mammalian Skin". Waterville Valley, NH, USA (August 21)

Predicting and Measuring Drug Delivery into and through the Skin. Invited speaker. 28ème seminaire de 3ème cycle en sciences pharmaceutiques, "Innovation in Medicinal Chemistry". Zermatt, Switzerland (September 11)

Drug Delivery and Targeting to Appendageal Structures in the Skin. Dermira, Inc. Redwood City, CA, USA (October 11)

Predicting, Measuring and Optimising Drug Delivery to the Skin. Invited speaker. 4th Annual Symposium of the Pan Asian Pacific Skin Barrier Research Society. Seoul, Korea (October 15)

Stratum Corneum et Imagerie. Invited speaker. Société Francophone d'Ingénierie et d'Imagerie Cutanée. Paris, France (October 24)

L'Absorption Cutanée – Théorie et Practique. Invited short-course lecturer. L'Oréal Research. Chevilly-Larue, Paris, France (November 5-6)

Dermatopharmacokinetics (DPK): Potential and Limitations of Stratum Corneum Tape-Stripping. Invited speaker. Topical Bioequivalence Symposium. UCL School of Pharmacy. London (December 19)

2014 Optimisation and Quantification of Topical Drug Delivery to the Skin. National Skin Centre, Singapore (March 3)

Optimisation and Quantification of Topical Drug Delivery to the Skin. British High Commission Sponsored Lecturer, Singapore International Conference on Skin Research, Singapore (March 4)

Bioequivalence of Topical Drug Products: Development of *in vitro-in vivo* Correlations. Stiefel, a GSK company. Research Triangle Park, NC, USA (March 28)

Drug Delivery into and through the Skin. Invited speaker. 9th World Congress on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology. Lisbon, Portugal (April 3)

Nanoparticles and Skin: Unmoveable Objects and Irresistible Barrier. Invited speaker. 5th FIP Pharmaceutical Sciences World Congress. Melbourne, Australia (April 16)

Imaging Drug Delivery to Skin and Nail with Microspectroscopic Techniques. National Physical Laboratory. Teddington, U.K. (May 28)

Topical Bioavailability/Bioequivalence – Product Development and Regulatory Science. Stiefel, a GSK company. Webinar (June 2)

Transdermal Drug Delivery: Assessment and Evaluation of Feasibility. Tesa-Labtec GmbH, Langenfeld, Germany (July 3)

Technology is not Always Enough – a Lesson from Glucose Monitoring. PROSense (Marie-Curie ITN) Workshop on "Clinical perspectives and commercial forces on biosensor devices". University of Bath (September 18)

Predicting, Measuring and Optimising Drug Delivery to the Skin. Pfizer, Inc., Cambridge, MA, USA (October 30)

Applying Advanced Spectroscopic and Imaging Techniques to Optimize Lipid-Based (Trans)dermal Drug Formulations. Invited speaker. American Association of Pharmaceutical Scientists, 2014 Annual Meeting & Exposition. San Diego, CA, USA (November 5)

Imaging the Disposition of Topical Drug Formulations Applied to the Skin. Invited speaker. Gattefossé Formulation Masterclass 2014. St. Priest, Lyon, France (November 24)

2015 Drug Delivery into and through the Skin. Almirall, S.A. Barcelona, Spain (February 9)

Application of Coherent Raman Scattering Microscopy to Topical Product Design and Development. Almirall, S.A. Barcelona, Spain (February 9)

Non-invasive, Reverse Iontophoretic Glucose Monitoring across the Skin. Physical &

Theoretical Chemistry Laboratory, Oxford University, Oxford (March 2)

Transdermal Drug Delivery: a Mature and Evolving Technology. Invited speaker. 1st European Conference on Pharmaceutics: Drug Delivery. Reims, France (April 13)

Imaging Drug Delivery to Skin and Nail with Microspectroscopic Techniques. Institut Fresnel, UMR 7249, Marseille, France (April 15)

Predicting, Measuring and Optimising the Delivery of Actives into the Skin. Unilever Research, Trumbull, CT, USA (April 27)

Imaging Drug Delivery to Skin and Nail with Micro(spectro)scopic Techniques. Oxford Institute of Biomedical Engineering, Oxford University, Oxford (June 2)

Predicting, Measuring and Optimising Drug Delivery to the Skin. Invited speaker. 6th Dermatological Product Development Workshop. Association for Applied Human Pharmacology. London (June 23)

In vivo Skin Stripping Studies to Evaluate Bioequivalence of Topical Drug Products. Invited speaker. FDA workshop: "Bioequivalence Testing of Topical Drug Products". Silver Spring, MD, USA (July 15)

Imaging Drug Delivery to Skin and Nail with Micro(spectro)scopic Techniques. Keynote speaker. Gordon Conference on "Barrier Function of Mammalian Skin". Waterville Valley, NH, USA (August 16)

Assessment and Optimisation of Drug Delivery to the Skin. Invited speaker. 39th Annual Meeting of the Spanish Society of Pharmacology. Valencia, Spain (September 16)

Imaging Drug Delivery to Skin and Nail with Micro(spectro)scopic Techniques. Hisamitsu Pharmaceutical Co. Ltd. Tsukuba, Japan (September 24)

Transdermal Drug Delivery: Scientific Ingenuity *versus* Skin Barrier Function. Keynote speaker. Transdermal Drug Delivery System World Symposium 2015. Tokyo, Japan (September 26)

2016 Imaging Drug Delivery to Skin and Nail with Micro(spectro)scopic Techniques. University of Bath, Department of Pharmacy & Pharmacology, Bath (March 9)

La pénétration des médicaments à travers l'ongle. Invited speaker. 11ème Colloque Francophone Thématique de Biologie Cutanée. Lyon, France (March 16).

Assessing Topical Bioavailability and Bioequivalence. Universidade Federal de Pernambuco, Department of Pharmaceutical Sciences, Recife, Brazil (March 29)

Transdermal Technologies for Drug Delivery and Clinical Monitoring. Universidade Federal de Pernambuco, Centre for Health Sciences, Recife, Brazil (March 30)

I've Got You Under My Skin. Maurice-Marie Janot Award Lecture, 10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Glasgow (April 4)

Imaging Drug Delivery to Skin and Nail with Micro(spectro)scopic Techniques. Plenary speaker. International Society for Biophysics & Imaging of the Skin, Lisbon, Portugal (June

2)

Skin Pharmacokinetics: Modelling, Assessment and Manipulation. L'Oréal Research, Aulnay-sous-Bois, France (June 17).

Transdermal Technologies for Drug Delivery and Clinical Monitoring. University of Bath, Centre for Sustainable Chemical Technologies, Bath (July 12)

Drug Delivery to Targets in the Skin and Nail: Measurement and Optimisation. Plenary speaker. 4th Conference on Innovation in Drug Delivery, Antibes, France (September 26)

Optimisation and Evaluation of Topical Drug Bioavailability in the Skin. Pierre-Fabre, R&D Pharma, Toulouse, France (October 3)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Application No.:	14/870,574
Filing Date:	9/30/2015
Examiner:	FISHER
Art Unit:	1611
Confirmation No.:	5148

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that the listed documents be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicant does not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(c), before the mailing date of any of a final action under 37 CFR §1.113, a notice of allowance under 37 CFR §1.311, or an action that otherwise closes prosecution in the application.

RELEVANCE OF LISTED DOCUMENT

Documents A1 and A2 are parent patents granted from applications already of record.

Document A3 is discussed in the Rule 132 Declaration of Dr. Richard H. Guy submitted herewith. The other references discussed in the Declaration are already of record.

Documents A4-A7 are Office Actions issued in the parent applications.

FEE

Fees in the amount of $180.00 to cover the fee associated with an information disclosure statement are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required to support this submission to Deposit Account Number 19-0741.

Respectfully submitted,

Date Dec 27, 2007

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/870,574
Date Submitted: August 29, 2017				**Filing Date**	9/30/2015
				First Named Inventor	Juan Mantelle
				Art Unit	1611
(use as many sheets as necessary)				Examiner Name	Melissa L. Fisher
Sheet	1	of	1	Attorney Docket Number	041457-1160

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	9,730,900-B2	08-15-2017	Mantelle	
	A2	9,724,310-B2	08-08-2017	Mantelle	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A3	MANTELLE ET AL., "Effect of Silicone/Acrylic PSA Blends on Skin Permation," Proceed. Int'l. Symp. Control. Rel. Bioact. Mater., June 20-23, 1999	
	A4	Notice of Allowance issued on 03/23/2017 in application number 13/553,972 (US 2013/0156815)	
	A5	Notice of Allowance issued on 04/26/2017 in application number 14/024,985 (US 2014/0200530)	
	A6	Notice of Allowance issued on 06/27/2017 in application number 13/553,972 (US 2013/0156815)	
	A7	Notice of Allowance issued on 06/27/2017 in application number 14/024,985 (US 2014/0200530)	

Examiner Signature		Date Considered	

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/25 PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION AND TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	14870574
Filing Date	30-Sep-2015
First Named Inventor	Juan Mantelle
Attorney Docket Number	041457-1160
Title of Invention	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
NOVEN PHARMACEUTICALS, INC.	100 %

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

14738255 filed on 06/12/2015

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

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9724310

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicants claims the following fee status:

○ Small Entity

○ Micro Entity

◉ Regular Undiscounted

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

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 37288

○ A sole inventor

○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

○ A joint inventor; all of whom are signing this request

Signature	/Courtenay C Brinckerhoff/
Name	Courtenay C. Brinckerhoff

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	14870574
Filing Date:	30-Sep-2015
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff/Katie Newcomb
Attorney Docket Number:	041457-1160

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 14870574

Filing Date: 30-Sep-2015

Applicant/Patent under Reexamination: Mantelle

Electronic Terminal Disclaimer filed on August 29, 2017

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	30208128
Application Number:	14870574
International Application Number:	
Confirmation Number:	5148
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Customer Number:	22428
Filer:	Courtenay C. Brinckerhoff/Katie Newcomb
Filer Authorized By:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-1160
Receipt Date:	29-AUG-2017
Filing Date:	30-SEP-2015
Time Stamp:	16:21:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$160
RAM confirmation Number	083017INTEFSW16211800
Deposit Account	190741
Authorized User	Katie Newcomb

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

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	36305 731d00a85de44e5aac9cad761bfc039c67fe79fd	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30855 fca8841fbadfea06d37923009351dd1baaefbfb7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	67160		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

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

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/870,574	Filing Date 09/30/2015	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $80 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $420 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	08/29/2017	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 15	Minus	** 20	= 0		x $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

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

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

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NOTICE OF ALLOWANCE AND FEE(S) DUE

22428 7590 10/03/2017

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WASHINGTON, DC 20007-5109

EXAMINER
FISHER, MELISSA L

ART UNIT	PAPER NUMBER
1611	

DATE MAILED: 10/03/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/870,574	09/30/2015	Juan Mantelle	041457-1160	5148

TITLE OF INVENTION: TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	01/03/2018

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

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

HOW TO REPLY TO THIS NOTICE:

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

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

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

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

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

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

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

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

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

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

22428 7590 10/03/2017
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

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

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

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/870,574	09/30/2015	Juan Mantelle	041457-1160	5148

TITLE OF INVENTION: TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	01/03/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
FISHER, MELISSA L	1611	424-487000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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

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

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

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

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

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

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

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14/870,574	09/30/2015	Juan Mantelle	041457-1160	5148

22428 7590 10/03/2017

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	
FISHER, MELISSA L	

ART UNIT	PAPER NUMBER
1611	

DATE MAILED: 10/03/2017

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

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

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

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

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

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

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

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

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

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

Notice of Allowability	Application No. 14/870,574	Applicant(s) MANTELLE, JUAN	
	Examiner Melissa Fisher	Art Unit 1611	AIA (First Inventor to File) Status No

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

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

1. ☒ This communication is responsive to *8/29/2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *36-50*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

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

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

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

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

/Melissa Fisher/
Primary Examiner, Art Unit 1611

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Information Disclosure Statement

The Information Disclosure Statement (IDS) filed 6/15/2017 has been considered by the examiner.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: The prior art does not teach nor reasonably suggest the claimed monolithic transdermal drug delivery system. Additionally, Applicant's arguments of unexpected results based on the coat weight of the polymer to achieve the claimed flux of drug delivery are persuasive. Applicant has additionally filed a Declaration on 8/29/2017 providing further support of the unexpected results.

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

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Fisher whose telephone number is (571)270-7430. The examiner can normally be reached on Monday-Friday, 8am-5pm.

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

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bethany Barham can be reached on 571-272-6175. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Melissa Fisher/
Primary Examiner, Art Unit 1611

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14870574	MANTELLE, JUAN
	Examiner	**Art Unit**
	MELISSA FISHER	1611

CPC						
Symbol					**Type**	**Version**
A61K		9	/	7069	F	2013-01-01
A61K		9	/	7061	I	2013-01-01
A61K		31	/	565	I	2013-01-01
A61K		47	/	10	I	2013-01-01
A61K		47	/	32	I	2013-01-01
A61K		9	/	0014	I	2013-01-01
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CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	15	
/MELISSA FISHER/ Primary Examiner.Art Unit 1611	09/26/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14870574	MANTELLE, JUAN
	Examiner	**Art Unit**
	MELISSA FISHER	1611

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
		A	6	1	K	9 / 70 (2006.01.01)						
CROSS REFERENCE(S)		A	6	1	K	31 / 565 (2006.01.01)						
		A	6	1	K	9 / 00 (2006.01.01)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	15	
/MELISSA FISHER/ Primary Examiner.Art Unit 1611	09/26/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14870574	MANTELLE, JUAN
	Examiner	**Art Unit**
	MELISSA FISHER	1611

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

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

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 15	
/MELISSA FISHER/ Primary Examiner.Art Unit 1611 (Primary Examiner)	09/26/2017 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

UNITED STATES PATENT AND TRADEMARK OFFICE

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

BIB DATA SHEET

CONFIRMATION NO. 5148

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/870,574	09/30/2015	424	1611	041457-1160

APPLICANTS
NOVEN PHARMACEUTICALS, INC., Miami, FL

INVENTORS
Juan Mantelle, Miami, FL;

**** CONTINUING DATA ***************************
This application is a CON of 14/738,255 06/12/2015
which is a CON of 14/024,985 09/12/2013 PAT 9724310
which is a CON of 13/553,972 07/20/2012 PAT 9730900
which is a CON of 12/216,811 07/10/2008 PAT 8231906

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
10/14/2015

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ Yes ☑ No	☐ Yes ☑ No	/MELISSA L FISHER/ Examiner's Signature	☐ Initials	FL	1	20	4

ADDRESS
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109
UNITED STATES

TITLE
TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

FILING FEE RECEIVED		
2020	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	16424	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L2	5653	L1 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L3	970	L2 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L4	35	L3 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L5	270	L3 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L6	53	L3 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L7	92	L1 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L8	264	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L9	44	L8 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L10	157	L8 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L11	188	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L12	41	L11 NOT L8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L13	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L14	755	L1 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L15	142	L3 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L16	16424	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L17	5653	L16 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO;	OR	OFF	2017/09/26 11:57

			JPO; DERWENT			
L18	970	L17 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L19	35	L18 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L20	270	L18 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L21	53	L18 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L22	92	L16 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L23	264	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L24	44	L23 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L25	157	L23 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L26	188	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L27	41	L26 NOT L23	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L28	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L29	755	L16 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L30	142	L18 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L31	2	"6638528".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L32	4	"4624665".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L33	3	"20090041831".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L34	16424	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L35	5653	L34 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L36	970	L35 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L37	35	L36 and estradiol.ab.	US-PGPUB; USPAT;	OR	OFF	2017/09/26

			USOCR; FPRS; EPO; JPO; DERWENT			11:57
L38	270	L36 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L39	53	L36 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L40	92	L34 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L41	264	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L42	44	L41 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L43	157	L41 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L44	188	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L45	41	L44 NOT L41	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L46	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L47	755	L34 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L48	142	L36 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L49	16424	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L50	5653	L49 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L51	970	L50 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L52	35	L51 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L53	270	L51 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L54	53	L51 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L55	92	L49 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L56	264	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57

L57	44	L56 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L58	157	L56 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L59	188	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L60	41	L59 NOT L56	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L61	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L62	755	L49 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L63	142	L51 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L64	16424	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L65	5653	L64 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L66	970	L65 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L67	35	L66 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L68	270	L66 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L69	53	L66 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L70	92	L64 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L71	264	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L72	44	L71 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L73	157	L71 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L74	188	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L75	41	L74 NOT L71	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L76	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2017/09/26 11:57

L77	755	L64 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L78	142	L66 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L79	16424	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L80	5653	L79 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L81	970	L80 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L82	35	L81 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L83	270	L81 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L84	53	L81 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L85	92	L79 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L86	264	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L87	44	L86 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L88	157	L86 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L89	188	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L90	41	L89 NOT L86	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L91	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L92	755	L79 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L93	142	L81 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L94	2	"6638528".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L95	4	"4624665".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L96	3	"20090041831".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L97	16424	estradiol and transdermal	US-PGPUB; USPAT;	OR	OFF	2017/09/26

			USOCR; FPRS; EPO; JPO; DERWENT			11:57
L98	5653	L97 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L99	970	L98 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L100	35	L99 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L101	270	L99 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L102	53	L99 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L103	92	L97 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L104	264	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L105	44	L104 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L106	157	L104 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L107	188	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L108	41	L107 NOT L104	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L109	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L110	755	L97 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L111	142	L99 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L112	16424	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L113	5653	L112 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L114	970	L113 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L115	35	L114 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L116	270	L114 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57

L117	53	L114 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L118	92	L112 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L119	264	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L120	44	L119 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L121	157	L119 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L122	188	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L123	41	L122 NOT L119	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57
L124	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L125	755	L112 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L126	142	L114 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2017/09/26 11:57
L127	1286566	(monolith$2 estradiol transdermal adhesive coat weight flux).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2017/09/26 11:57

9/ 26/ 2017 12:02:36 PM
C:\ Users\ mjavier\ Documents\ EAST\ Workspaces\ 14870574.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14870574	MANTELLE, JUAN
	Examiner	Art Unit
	MELISSA FISHER	1611

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

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

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search (see attached search history)	6/11/2017	MF
Inventor search in EAST	6/11/2017	MF
Google Scholar search (keywords used: monolithic transdermal estradiol)	6/11/2017	MF
Updated EAST search	9/26/2017	MF
Updated Google Scholar search	9/26/2017	MF

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
	(monolithic transdermal drug estradiol adhesive polymer matrix active surface area release liner coat weight flux).clm.	9/26/2017	MF

	/M.F./ Primary Examiner.Art Unit 1611

PTO/SB/08 (modified)

Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/870,574
Date Submitted: August 29, 2017				**Filing Date**	9/30/2015
				First Named Inventor	Juan Mantelle
				Art Unit	1611
(use as many sheets as necessary)				Examiner Name	Melissa L. Fisher
Sheet	1	of	1	Attorney Docket Number	041457-1160

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	9,730,900-B2	08-15-2017	Mantelle	
	A2	9,724,310-B2	08-08-2017	Mantelle	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A3	MANTELLE ET AL., "Effect of Silicone/Acrylic PSA Blends on Skin Permation," Proceed. Int'l. Symp. Control. Rel. Bioact. Mater., June 20-23, 1999	
	A4	Notice of Allowance issued on 03/23/2017 in application number 13/553,972 (US 2013/0156815)	
	A5	Notice of Allowance issued on 04/26/2017 in application number 14/024,985 (US 2014/0200530)	
	A6	Notice of Allowance issued on 06/27/2017 in application number 13/553,972 (US 2013/0156815)	
	A7	Notice of Allowance issued on 06/27/2017 in application number 14/024,985 (US 2014/0200530)	

Examiner Signature	/Melissa L Fisher/	Date Considered	09/26/2017

4833-7087-9562.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.L.F./

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

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

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

22428 7590 10/03/2017
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

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

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

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/870,574	09/30/2015	Juan Mantelle	041457-1160	5148

TITLE OF INVENTION: TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	01/03/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
FISHER, MELISSA L	1611	424-487000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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

1 FOLEY & LARDNER LLP
2
3

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

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

(A) NAME OF ASSIGNEE: NOVEN PHARMACEUTICALS, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Miami, Florida

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

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☒ Payment by credit card. Form PTO-2038 is attached.
- ☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 19-0741 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☐ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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

Authorized Signature /Courtenay C. Brinckerhoff/ Date October 27, 2017

Typed or printed name Courtenay C. Brinckerhoff Registration No. 37,288

Electronic Patent Application Fee Transmittal

Application Number:	14870574
Filing Date:	30-Sep-2015
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff/Kandie Predmore
Attorney Docket Number:	041457-1160

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt

EFS ID:	30788538
Application Number:	14870574
International Application Number:	
Confirmation Number:	5148
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Customer Number:	22428
Filer:	Courtenay C. Brinckerhoff/Kandie Predmore
Filer Authorized By:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-1160
Receipt Date:	27-OCT-2017
Filing Date:	30-SEP-2015
Time Stamp:	18:03:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$960
RAM confirmation Number	103017INTEFSW18045301
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	Issue-Fee-Transmittal.pdf	102975 b450ee6563af3fd7ad43d01f5d8461b7a3ee26e1	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30963 ba0b6ed27e071b69bbb490775f50530138635fe3	no	2
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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: April 22, 2016

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Sheet 1 of 6

Complete if Known	
Application Number	14/870,574
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First Named Inventor	Juan Mantelle
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	041457-1160

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	A2	2014/0200530	07/17/2014	MANTELLE	
	A3	2013/0156815	06/20/2013	MANTELLE	
	A4	8,231,906	07/31/2012	MANTELLE	
	A5	8,343,538	~~04/13/2006~~ 01/2013	KANIOS ET AL.	
	A6	5,446,070	08/29/1995	MANTELLE	
	A7	4,915,950	04/1990	MIRANDA ET AL.	
	A8	6,562,363	05/13/2003	MANTELLE ET AL.	
	A9	6,221,383	04/24/2001	MIRANDA ET AL.	
	A10	6,235,306	05/22/2001	MIRANDA ET AL.	
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	A13	2006/0240087 A1	10/26/2006	HOUZE ET AL.	
	A14	2006/0233870 A1	10/19/2006	HOUZE ET AL.	
	A15	2006/0078602 A1	04/13/2006	KANIOS	
	A16	4,994,278	02/19/1991	SABOLTSKY ET AL.	
	A17	4,494,278	~~2/19/1991~~ 01/1985	~~SABLOTSKY ET AL.~~ Kroyer,	et al.
	A18	5,300,291	4/5/1994	SABLOTSKY ET AL.	
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	A26	6,638,528	10/2003	KANIOS	
	A27	7,456,159 B2	11/25/2008	HOUZE ET AL.	
	A28	RE 35,474	3/11/1997	WOODARD ET AL.	Reissue of USP 4,655,767
	A29	4,655,767	4/7/1987	WOODARD ET AL.	
	A30	2005/2022073	09/15/2005	JACKSON ET AL.	
	A31	2003/099695	05/29/2003	MUELLER	
	A32	4,591,622	5/27/1986	BLIZZARD ET AL.	
	A33	5,584,355	~~4/22/1986~~ 12/1996	~~BLIZZARD ET AL.~~ Burns	
	A34	4,585,836	4/29/1986	HOMAN ET AL.	
	A35	4,390,520	6/28/1983	NAGAI ET AL.	
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	A37	2003/0228354	12/2003	MURAOKA ET AL.	
	A38	5,730,999	03/24/1998	LEHMANN ET AL.	
	A39	5,505,956	04/09/1996	KIM ET AL.	

Change(s) applied to document, /N.W.S./ 10/13/2017

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Sheet 1 of 6

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First Named Inventor	Juan Mantelle
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	041457-1160

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	A8	6,562,363	05/13/2003	MANTELLE ET AL.	
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	A24	6,024,976	2/15/2000	MIRANDA ET AL.	
	A25	6,337,086	1/8/2002	KANIOS ET AL.	
	A26	6,638,528	10/2003	KANIOS	
	A27	7,456,159 B2	11/25/2008	HOUZE ET AL.	
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	A29	4,655,767	4/7/1987	WOODARD ET AL.	
	A30	~~2005/2022073~~	09/15/2005	JACKSON ET AL.	2005/0202073
	A31	~~2003/099695~~	05/29/2003	MUELLER	2003/0099695
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	A34	4,585,836	4/29/1986	HOMAN ET AL.	
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: April 22, 2016

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Sheet 2 of 6

Complete if Known	
Application Number	14/870,574
Filing Date	09/30/2015
First Named Inventor	Juan Mantelle
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	041457-1160

U.S. PATENT DOCUMENTS

Examiner	Cite No.[1]	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant
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UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

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FOREIGN PATENT DOCUMENTS

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	A64	EP 0 887 075 A2	12/30/1998	BERTEK, INC.		

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/870,574
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				First Named Inventor	Juan Mantelle
				Art Unit	Unassigned
(use as many sheets as necessary)				Examiner Name	Unassigned
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NON PATENT LITERATURE DOCUMENTS

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	A65	VAUGHAN, "Using Solubility Parameters in Cosmetics Formulation," *J. Soc. Cosmet. Chem.*, Vol. 36, pp. 319-333 (1985).	
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	A68	NAGAI ET AL., "New Drug Delivery Systems," Kurashiki Printing Co. Ltd., Academic Document 2009-00984-005, published January 31, 2000.	
	A69	SEKINE ET AL., "New Cosmetic Handbook," Nikko Chemical Co. Ltd., et al., Academic Documents 2008-02180-001, published October 30, 2006.	
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	A72	FELDMANN ET AL., "Percutaneous Penetration of Steroids in Man," The Journal of Investigative Dermatology, Vol. 52, No. 1, pp. 89-94, 1969.	
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Sheet 4 of 6

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	A78	Office Action issued on 09/09/2010 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A79	Office Action issued on 01/20/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A80	Office Action issued on 06/30/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
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	A84	Notice of Allowance issued on 06/19/2012 by the Examiner in application number 12/216,811 (US 8,231,906)	
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	A86	Office Action issued on 04/14/2010 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A87	Office Action issued on 06/10/2009 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A88	Office Action issued on 10/26/2011 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A89	Office Action issued on 05/13/2011 by the Examiner in application number 11/245,084 (US 8,343,538)	
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Sheet 5 of 6

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	A93	Office Action issued on 09/04/2013 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A94	Office Action issued on 03/05/2014 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A95	Office Action issued on 05/05/2015 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A96	Notice of Allowance issued on 10/02/2015 by the Examiner in application number 13/553,972 (US 2013/0156815)	
	A97	Office Action issued on 05/20/2015 by the Examiner in application number 14/024,985 (US 2014/0200530)	
	A98	Notice of Allowance issued on 10/02/2015 by the Examiner in application number 14/024,985 (US 2014/0200530)	
	A99	Office Action issued on 08/12/2015 by the Examiner in application 14/738,255 (US 2015/0272905)	
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	A101	RIETSCHEL ET AL., "Effects of harvesting techniques on hydration dynamics: gravimetric studies of stratum corneum," J. Soc. Cosmet. Chem., Vol. 29, pp. 777-782, December 1978.	
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	A103	PFISTER, "Transdermal and Dermal Therapeutic Systems: Current Status," Transdermal and Topical Drug Delivery Systems, Ghosh et al., eds., Chapter 2, pp. 33-112, 1997.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: April 22, 2016

(use as many sheets as necessary)

Sheet 6 of 6

Complete if Known	
Application Number	14/870,574
Filing Date	09/30/2015
First Named Inventor	Juan Mantelle
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	041457-1160

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A104	Dow Corning, :"Dow Corning® BIO-PSA Standard Silicone Adhesives," Product Information, 07/28/2008.	
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	A107	Noven Pharmaceuticals, Inc., Response filed in European application number 09790211.8 on 12/19/2014.	

Examiner Signature	/Melissa L Fisher/	Date Considered	11/08/2017

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/870,574	09/30/2015	Juan Mantelle	041457-1160	5148

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FISHER, MELISSA L	

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14/870,574	09/30/2015	Mantelle, Juan	041457-1160

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The information Disclosure STatement (IDS) filed 4/26/2016 has been considered by the Examiner.

/Melissa L Fisher/
Primary Examiner, Art Unit 1611

PTO-90C (Rev.04-03)

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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 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

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

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

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

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

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