IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Prior Appl. No.: 12/216,811

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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) (2 pages).

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

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

[**X**] Executed Declaration and Power of Attorney (3 pages).

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:

	Number Filed		**Included in Basic Fee**		**Extra**		Rate		Fee Totals
Basic Filing Fee							$380.00	=	$380.00
Search Fee							$620.00		$620.00
Examination Fee							$250.00		$250.00
Size Fee	21	-	100	= 0		x	$310.00		$0.00
Total Claims:	20	-	20	= 0		x	$60.00	=	$0.00
Independents:	4	-	3	= 1		x	$250.00	=	$250.00
If any Multiple Dependent Claim(s) present:						+	$450.00	=	$0.00
Surcharge under 37 CFR 1.16(e) for late payment of filing fee						+	$130.00	=	$130.00
							SUBTOTAL:	=	$1630.00
[ ]							Small Entity Fees Apply (subtract ½ of above):	=	0
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The required filing fees are not enclosed but will be submitted in response to the Notice to File Missing Parts of Application.

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Respectfully submitted,

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Application Data Sheet

Application Information

Application Type::	Regular
Subject Matter::	Utility
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Suggested Group Art Unit::	
CD-ROM or CD-R?::	None
Computer Readable Form (CRF)?::	No
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Request for Non-Publication?::	No
Suggested Drawing Figure::	1
Total Drawing Sheets::	1
Small Entity?::	No
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

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Representative Information

Representative Customer Number::	22428	

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	Continuation of	12/216,811	7/10/2008

Foreign Priority Information

Country::	Application number::	Filing Date::	Priority Claimed::

Assignee Information

Assignee Name::	NOVEN PHARMACEUTICALS, INC.

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 pharmacokinetic 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.

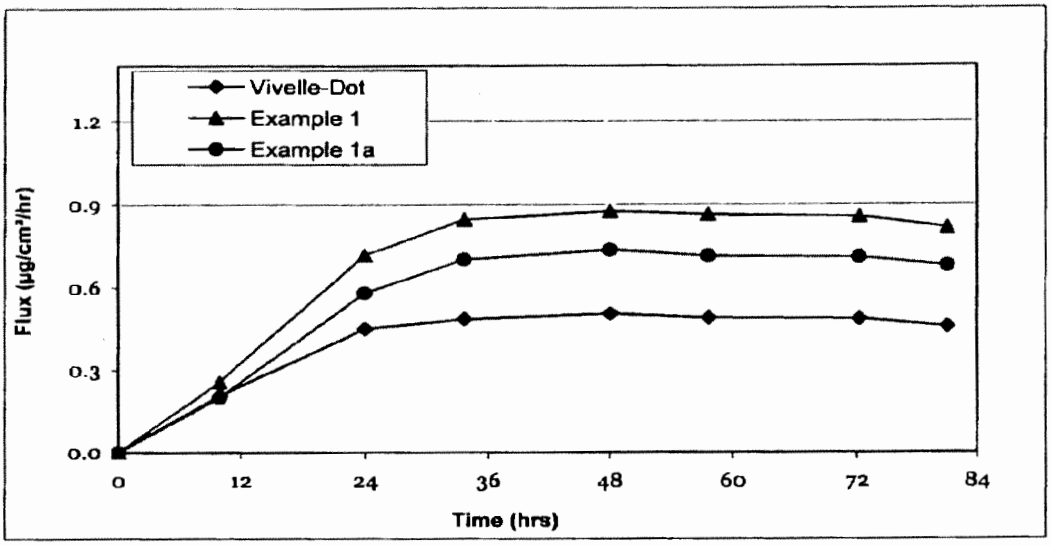
19. The method of claim 16, wherein the polymer matrix is applied to the support layer at a coat weight of greater than about 10 mg/cm^2.

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)
0.0
0.3
0.6
0.9
1.2
0
12
24
36
48
60
72
84
Time (hrs)

DECLARATION AND POWER OF ATTORNEY

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. 041457-0857)

the specification of which (check one)

___ is attached hereto.

_X_ was filed on July 10, 2008 as United States Application Number or PCT International Application Number 12/216,811 and was amended on _____ (if applicable).

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 specification, including the claim(s), as amended by any amendment specifically referred to above;

THAT I believe that the above-identified specification 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

I HEREBY APPOINT the registered attorneys and agents at Customer Number

22428

to have full power to prosecute this application and any continuations, divisions, reissues, and reexaminations thereof, to receive the patent, and to transact all business in the United States Patent and Trademark Office connected therewith.

I request that all correspondence be directed to:

Courtenay C. Brinckerhoff
FOLEY & LARDNER LLP
Customer Number: 22428

Telephone: (202) 295-4094
Facsimile: (202) 672-5399

I UNDERSTAND AND AGREE THAT the foregoing attorneys and agents appointed by me to prosecute this application do not personally represent me or my legal interests, but instead represent the interests of the legal owner(s) of the invention described in this application.

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 issuing thereon.

Name of first inventor	Juan Mantelle
Residence	Miami, Florida
Citizenship Country	U.S.A.
Post Office Address	10821 S.W. 92 Avenue Miami, Florida 33176
Inventor's signature	
Date	September 2, 2008

Electronic Acknowledgement Receipt

EFS ID:	13299649
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	20-JUL-2012
Filing Date:	
Time Stamp:	11:29:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		conapp.pdf	1719474 c347fa469c869054e4b0d01cd377ba6f68d90f7f	yes	36

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal of New Application	1	3
	Application Data Sheet	4	5
	Specification	6	28
	Claims	29	31
	Abstract	32	32
	Drawings-only black and white line drawings	33	33
	Oath or Declaration filed	34	36
Warnings:			
Information:			
	Total Files Size (in bytes):	1719474	

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/553,972	07/20/2012	1615	0.00	041457-0992	20	4

CONFIRMATION NO. 3635

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

FILING RECEIPT

OC00000055693744

Date Mailed: 08/01/2012

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**

Applicant(s)

Juan Mantelle, Miami, FL;

Assignment For Published Patent Application

NOVEN PHARMACEUTICALS, INC.

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

Domestic Priority data as claimed by applicant

This application is a CON of 12/216,811 07/10/2008 PAT 8231906

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 07/31/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/553,972**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

Preliminary Class

424

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 (1-866-999-4158).

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
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/553,972	07/20/2012	Juan Mantelle	041457-0992

CONFIRMATION NO. 3635

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

FORMALITIES LETTER

OC000000055693745

Date Mailed: 08/01/2012

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  *Applicant must submit $**380** to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of $**250** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- A surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**130** for a non-small entity, must be submitted.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of this Notice is $**1630** for a non-small entity

- $**380** Statutory basic filing fee.
- $**130** Surcharge.
- The application search fee has not been paid. Applicant must submit $**620** to complete the search fee.
- The application examination fee has not been paid. Applicant must submit $**250** to complete the examination fee for a non-small entity.
- Total additional claim fee(s) for this application is $**250**
  - $**250** for **1** independent claims over 3.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/fberhane/

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

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/553,972

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	380
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*			OR	x 60 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 250 =	250
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	1500

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(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($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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	

AMENDMENT B

	(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($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553972
Filing Date:	7/20/2012
Examiner:	Unassigned
Art Unit:	1615
Confirmation Number:	3635

TRANSMITTAL OF MISSING PARTS OF PATENT APPLICATION

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Notice to File Missing Parts of Application mailed 08/01/2012, in the above-identified patent application, transmitted herewith are the missing parts to complete the filing of the subject patent application.

Enclosed are:

[X] Preliminary Amendment

[X] Return Copy of Notice to File Missing Parts

[X] Information Disclosure Statement

[X] Form PTO/SB/08 and 2 references

[**X**] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

[ ]	Extension for response filed within the first month
[ ]	Extension for response filed within the second month
[ ]	Extension for response filed within the third month
[ ]	Extension for response filed within the fourth month
[X]	Extension for response filed within the fifth month

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:

	Claims as Filed		Included in Basic Fee		Extra Claims		Rate		Fee Totals
Basic Filing Fee, Search Fee & Examination Fee							$1,260.00		$1,260.00
Size Fee	21	-	100	=	0	x	$320.00	=	$0.00
Total Claims:	16	-	20	=	0	x	$62.00	=	$0.00
Independents:	4	-	3	=	1	x	$250.00	=	$250.00
If any Multiple Dependent Claim(s) present:						+	$460.00	=	$0.00
Surcharge under 37 CFR 1.16(f) for late payment of filing fee						+	$130.00	=	$130.00
[X] Extension fee for response filed within the fifth month:						+	$2,730.00	=	$2,730.00
Non-electronic filing fee						+		=	$0.00
							SUBTOTAL:	=	$4,370.00
[ ] Small Entity Fees Apply (subtract ½ of above):								=	0
Basic Filing Fee Reduction for Filing via EFS-Web									$0.00
							TOTAL FILING FEE:	=	$4,370.00
Processing Fee under 37 CFR 1.17(i) for Late Filing of English Translation of Application:						+	$130.00	=	$0.00
							TOTAL FEE	=	$4,370.00
Difference to pay:						-	$0.00	-	$4,370.00

A credit card payment form in the amount of $4,370.00 is enclosed in payment of the required fees.

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 form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

Date Feb 28, 2013

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Appl. No.: 13/553,972

Filing Date: 7/20/2012

Examiner: Unassigned

Art Unit: 1615

Confirmation Number: 3635

PRELIMINARY AMENDMENT UNDER 37 CFR 1.115

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

Commissioner:

Applicant respectfully requests that the application be amended as follows prior to examination,:

Amendments to the Specification begin on page 2 of this document.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this document.

Remarks/Arguments begin on page 6 of this document.

Please amend the application as follows:

Amendments to the Specification:

Please add the following heading and paragraph after the title and before the heading FIELD OF THE INVENTION:

RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application 12/216,811, filed July 10, 2008 (now U.S. Patent No. 8,231,906), which is incorporated herein by reference in its entirety.

Amendments to the Claims:

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

Listing of Claims:

1. (Currently Amended) A monolithic transdermal drug delivery system for estradiol, comprising a single polymer matrix ~~drug-containing~~ layer defining an active surface area and comprising a polymer matrix comprising estradiol as the only drug, wherein the ~~system~~ polymer matrix layer 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. (Original) 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. (Original) 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. (Original) The transdermal drug delivery system of claim 3, wherein the penetration enhancer comprises oleyl alchol.

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

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

7. (Original) 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. (Original) 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. (Original) 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. (Canceled)

11. (Original) 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. (Canceled)

13. (Currently Amended) A monolithic transdermal drug delivery system for estradiol comprising a single polymer matrix layer comprising estradiol as the only drug, 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. (Currently Amended) A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system comprising a single ~~drug-containing~~ polymer matrix layer defining an active surface area and comprising a polymer matrix comprising estradiol as the only drug, wherein the ~~system~~ polymer matrix 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. (Original) 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. (Currently Amended) A method of making a monolithic transdermal drug delivery system for administering ~~estrogen~~ etradiol, comprising forming a polymer matrix comprising ~~estrogen~~ estradiol as the only drug and a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble PVP, and applying the polymer matrix to a support layer to form a single polymer matrix layer such that the ~~system~~ polymer matrix layer includes greater than 0.156 mg/cm^2 estradiol.

17. (Original) 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. (Canceled)

19. (Original) 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. (Canceled)

REMARKS

Applicant respectfully requests that the foregoing amendments be made prior to examination.

The specification is amended to add information regarding the parent application (now U.S. Patent No. 8,231,906).

The independent claims are amended to more closely conform to language of the granted claims of the parent application and claims 10, 12, 18 and 20 are canceled. These amendments are made without prejudice or disclaimer, and Applicant reserves the right to pursue any canceled subject matter in one or more continuing applications with the same rights of priority as the instant application

Upon entry of these amendments, claims 1-9, 11, 13-17, and 19 will be pending. These claims are presented for examination.

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

Respectfully submitted,

Date Feb 28, 2013

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/553,972	07/20/2012	Juan Mantelle	041457-0992

CONFIRMATION NO. 3635

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

FORMALITIES LETTER

OC000000055693745

Date Mailed: 08/01/2012

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  *Applicant must submit $**380** to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of $**250** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- A surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**130** for a non-small entity, must be submitted.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of this Notice is $**1630** for a non-small entity
- $**380** Statutory basic filing fee.
- $**130** Surcharge.
- The application search fee has not been paid. Applicant must submit $**620** to complete the search fee.
- The application examination fee has not been paid. Applicant must submit $**250** to complete the examination fee for a non-small entity.
- Total additional claim fee(s) for this application is $**250**
  - $**250** for **1** independent claims over 3.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/fberhane/

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Appl. No.: 13/553972

Filing Date: 7/20/2012

Examiner: Unassigned

Art Unit: 1615

Confirmation Number: 3635

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, 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), before the mailing date of the first Office Action on the merits.

RELEVANCE OF LISTED DOCUMENTS

Document A1 is the granted parent patent. Documents A2-A76 are Office Actions and references of record in the parent application.

Documents A2-A22 are also granted patents and co-pending applications with common or overlapping inventorship and/or ownership.

Documents A77 and A78 are Office Actions which were issued in Document A2.

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 Feb 28, 2013

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: February 28, 2013

(use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	13/553,972
Filing Date	07/20/2012
First Named Inventor	Juan Mantelle
Art Unit	1615
Examiner Name	Unassigned
Attorney Docket Number	041457-0992

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	8,231,906	07/31/2012	MANTELLE	
	A2	8,343,538	04/13/2006	KANIOS ET AL.	
	A3	5,446,070	08/29/1995	MANTELLE	
	A4	4,915,950	04/1990	MIRANDA ET AL.	
	A5	6,562,363	05/13/2003	MANTELLE ET AL.	
	A6	6,221,383	04/24/2001	MIRANDA ET AL.	
	A7	6,235,306	05/22/2001	MIRANDA ET AL.	
	A8	2005/0169977 A1	08/04/2005	KANIOS	
	A9	2005/0129749 A1	06/16/2005	STRAUSS	
	A10	2006/0240087 A1	10/26/2006	HOUZE ET AL.	
	A11	2006/0233870 A1	10/19/2006	HOUZE ET AL.	
	A12	4,994,278	02/19/1991	SABOLTSKY ET AL.	
	A13	4,494,278	2/19/1991	SABLOTSKY ET AL.	
	A14	5,300,291	4/5/1994	SABLOTSKY ET AL.	
	A15	5,958,446	9/28/1999	MIRANDA ET AL.	
	A16	5,474,783	12/12/1995	MIRANDA ET AL.	
	A17	4,814,168	3/21/1989	SABLOTSKY ET AL.	
	A18	4,994,267	2/19/1991	SABLOTSKY	
	A19	5,565,286	8/12/1997	MIRANDA ET AL.	
	A20	6,024,976	2/15/2000	MIRANDA ET AL.	
	A21	6,337,086	1/8/2002	KANIOS ET AL.	
	A22	6,638,528	10/2003	KANIOS	
	A23	RE 35,474	3/11/1997	WOODARD ET AL.	Reissue of USP 4,655,767
	A24	4,655,767	4/7/1987	WOODARD ET AL.	
	A25	2005/2022073	09/15/2005	JACKSON ET AL.	
	A26	2003/099695	05/29/2003	MUELLER	
	A27	4,591,622	5/27/1986	BLIZZARD ET AL.	
	A28	5,584,355	4/22/1986	BLIZZARD ET AL.	
	A29	4,585,836	4/29/1986	HOMAN ET AL.	
	A30	4,390,520	6/28/1983	NAGAI ET AL.	
	A31	5,665,377	09/1997	GONELLA	
	A32	2003/0228354	12/2003	MURAOKA ET AL.	
	A33	5,730,999	03/24/1998	LEHMANN ET AL.	
	A34	5,505,956	04/09/1996	KIM ET AL.	
	A35	5,350,581	09/27/1994	KOCHINKE	
	A36	4,983,395	01/08/1991	CHANG ET AL.	
	A37	4,559,222	12/17/1985	ENSCORE ET AL.	
	A38	5,762,952	06/09/1998	BARNHART ET AL.	
	A39	4,591,622	05/27/1986	BLIZZARD 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: February 28, 2013

(use as many sheets as necessary)

Sheet 2 of 4

Complete if Known	
Application Number	13/553,972
Filing Date	07/20/2012
First Named Inventor	Juan Mantelle
Art Unit	1615
Examiner Name	Unassigned
Attorney Docket Number	041457-0992

U.S. PATENT DOCUMENTS

		Document Number			
	A40	4,585,836	04/29/1986	HOMAN ET AL.	
	A41	5,474,787	12/12/1995	GRAY ET AL.	
	A42	2002/0100185 A1	08/01/2002	SITZ ET AL.	
	A43	6,808,739 B2	10/26/2004	SITZ ET AL.	
	A44	5,151,271	09/29/1992	OTSUKA ET AL.	
	A45	5,906,830	05/25/1999	FARINAS ET AL.	
	A46	5,902,603	05/11/1999	CHEN ET AL.	
	A47	5,837,280	11/17/1998	KENEALY ET AL.	
	A48	5,567,488	10/22/1996	ALLEN ET AL.	
	A49	5,271,940	12/21/1993	CLEARY ET AL.	
	A50	4,911,707	03/27/1990	HEIBER ET AL.	
	A51	4,746,515	05/24/1988	CHENG ET AL.	
	A52	5,904,931	05/1999	LIPP ET AL.	
	A53	4,938,759	07/1990	ENSCORE ET AL.	
	A54	5,928,666	07/1999	FARINAS ET AL.	
	A55	4,769,028	09/1998	HOFFMANN ET AL.	
	A56	4,624,665	11/1986	NUWAYESER	
	A57	6,156,335	12/2000	ROVATI 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]

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.

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: February 28, 2013

(use as many sheets as necessary)

Sheet 3 of 4

Complete if Known	
Application Number	13/553,972
Filing Date	07/20/2012
First Named Inventor	Juan Mantelle
Art Unit	1615
Examiner Name	Unassigned
Attorney Docket Number	041457-0992

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]
	A58	VAUGHAN, "Using Solubility Parameters in Cosmetics Formulation," *J. Soc. Cosmet. Chem.*, Vol. 36, pp. 319-333 (1985).	
	A59	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).	
	A60	"Acrylic Adhesives," *Handbook of Pressure-Sensitive Adhesive Technology*, 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, N.Y. (1989)	
	A61	International Preliminary Report on Patentability and Written Opinion issued April, 19, 2007.	
	A62	International Search Report issued on 04/06/2005 in application number PCT/US2004/029789.	
	A63	International Search Report issued on 02/24/2011 in application number PCT/US2009/050069.	
	A64	"Acrylic and Methacrylic Ester Polymers," *Polymer Science and Engineering*, Vol. 1, 2nd ed., pp. 234-269, John Wiley & Sons (1984).	
	A65	Office Action issued on 09/09/2010 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A66	Office Action issued on 01/20/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A67	Office Action issued on 06/30/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A68	Office Action issued on 09/13/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A69	Office Action issued on 11/08/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A70	Office Action issued on 05/29/2012 by the Examiner in application number 12/216,811 (US 8,231,906)	

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: February 28, 2013

(use as many sheets as necessary)

Sheet 4 of 4

Complete if Known	
Application Number	13/553,972
Filing Date	07/20/2012
First Named Inventor	Juan Mantelle
Art Unit	1615
Examiner Name	Unassigned
Attorney Docket Number	041457-0992

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]
	A71	Notice of Allowance issued on 06/19/2012 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A72	Office Action issued on 12/29/2010 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A73	Office Action issued on 04/14/2010 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A74	Office Action issued on 06/10/2009 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A75	Office Action issued on 10/26/2011 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A76	Office Action issued on 05/13/2011 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A77	Office Action issued on 06/13/2012 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A78	Notice of Allowance issued on 08/22/2012 by the Examiner in application number 11/245,084 (US 8,343,538)	

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.

Electronic Patent Application Fee Transmittal

Application Number:	13553972
Filing Date:	20-Jul-2012
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-0992

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	390	390
Utility Search Fee	1111	1	620	620
Utility Examination Fee	1311	1	250	250
Pages:				
Claims:				
Independent claims in excess of 3	1201	1	250	250
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	1051	1	130	130

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 5 months with $0 paid	1255	1	2730	2730
Miscellaneous:				
		Total in USD ($)		**4370**

Electronic Acknowledgement Receipt

EFS ID:	15079112
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	28-FEB-2013
Filing Date:	20-JUL-2012
Time Stamp:	15:10:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$4370
RAM confirmation Number	2211
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		missparts.pdf	974225 b8afdd470858d2aa31b9f534efa6b1c761c8e792	yes	17

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Applicant Response to Pre-Exam Formalities Notice	1	3
Preliminary Amendment	4	9
Miscellaneous Incoming Letter	10	11
Transmittal Letter	12	13
Information Disclosure Statement (IDS) Form (SB08)	14	17

Warnings:

Information:

2		npl.pdf	1557703 9cc23ab97aff8713a94cad5c287cdc50bc60c357	yes	37

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Non Patent Literature	1	31
Non Patent Literature	32	37

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	39986 7100572958c1dd6d8fb324beae75faeb42549bfb	no	2

Warnings:

Information:

Total Files Size (in bytes):	2571914

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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/553,972

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	390
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	16 minus 20 =	*			OR	x 62 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 250 =	250
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	1510

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(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($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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	

AMENDMENT B

	(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($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/553,972	07/20/2012	1615	1640	041457-0992	16	4

CONFIRMATION NO. 3635

UPDATED FILING RECEIPT

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

Date Mailed: 03/08/2013

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.

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

Domestic Priority data as claimed by applicant

This application 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.

If Required, Foreign Filing License Granted: 07/31/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/553,972**

Projected Publication Date: 06/20/2013

Non-Publication Request: No

Early Publication Request: No

Title

TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

Preliminary Class

424

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 (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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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.

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NOT GRANTED

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 04/12/2013

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
JAVIER, MELISSA L	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
04/12/2013	PAPER

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.

Office Action Summary	Application No. 13/553,972	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 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *28 February 2013*.

☐ 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) *1-9,11,13-17, and 19* 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) *1-9, 11, 13-17, and 19* 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.

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

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

I. Claims 1-9, 11, and 13, drawn to a monolithic transdermal drug delivery system, classified in class 424, subclass 449.

II. Claims 14 and 15, drawn to a method for administering estradiol, classified in class 604, subclass 290.

III. Claims 16, 17, and 19, drawn to a method of making a monolithic transdermal drug delivery system, classified in class 424, subclass 487.

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 these 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 at least **one of** the following reason(s) 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 a 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(a) of the other invention.

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, Daniel Sullivan can be reached on 571-272-0779. 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

/CHERIE M STANFIELD/
Primary Examiner, Art Unit 1647

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

RESPONSE TO RESTRICTION REQUIREMENT
AND PRELIMINARY AMENDMENT

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

Commissioner:

The is a response to the Restriction Requirement mailed April 12, 2013.

Applicant also requests that the following amendments be made prior to examination:

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

Remarks/Arguments begin on page 6 of this document.

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

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

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

7. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) 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. (Canceled)

11. (Withdrawn) 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. (Canceled)

13. (Withdrawn) A monolithic transdermal drug delivery system for estradiol comprising a single polymer matrix layer comprising estradiol as the only drug, 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. (Previously Presented) A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system 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 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. (Original) 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. (Withdrawn) A method of making a monolithic transdermal drug delivery system for administering etradiol, comprising forming a 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 polymer matrix to a support layer to form a single polymer matrix layer such that the polymer matrix layer includes greater than 0.156 mg/cm^2 estradiol.

17. (Withdrawn) 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. (Canceled)

19. (Withdrawn) 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. (Canceled)

21. (New) The method of claim 14, wherein the polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble polyvinylpyrrolidone (PVP).

22. (New) The method of claim 14, 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.

23. (New) The method of claim 22, wherein the penetration enhancer comprises oleyl alchol.

24. (New) The method of claim 22, wherein the penetration enhancer comprises dipropylene glycol.

25. (New) The method of claim 22, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

26. (New) The method of claim 22, 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.

27. (New) The method of claim 3, wherein the polymer matrix has a coat weight of greater than about 10 mg/cm^2.

28. (New) The method of claim 14, 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.

29. (New) The method of claim 14, 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.

30. (New) A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system for estradiol comprising a single polymer matrix layer comprising estradiol as the only drug, 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.

REMARKS

In response to the Restriction Requirement, Applicant hereby provisionally elects the subject matter of **Group II**, drawn to methods for administering estradiol. This election is made **with traverse** at least with respect to Group I and Group II, because examining the subject matter of these groups of claims would not impose a serious burden on the Examiner. In this regard, Applicant notes that the claims of both Group I and Group II recite monolithic transdermal drug delivery systems 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 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 (claim 1; claim 14) or monolithic transdermal drug delivery systems comprising a single polymer matrix layer comprising estradiol as the only drug, 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 (claim 13; claim 30). Although Group I is directed to monolithic transdermal drug delivery systems *per se* while Group II is directed to methods using them, this difference does not give rise to a significant examination burden. Applicant therefore respectfully urges reconsideration and withdrawal of the Restriction Requirement at least with respect to Group I and Group II.

Claims 21-30 are added to recite specific embodiments of the subject matter of Group II. These claims parallel claims 2-9, 11 and 13. Thus, no new matter is introduced by these amendments.

Upon entry of these amendments, claims 1-9, 11, 13-17, 19 and 21-30 will be pending, with claims 14, 15 and 21-30 being drawn to elected subject matter. These claims are presented for examination.

If there are any questions regarding this submission, or if any issues remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

Respectfully submitted,

Date May 9, 2023

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

Electronic Acknowledgement Receipt

EFS ID:	15735113
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	09-MAY-2013
Filing Date:	20-JUL-2012
Time Stamp:	15:03:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		resp.pdf	370965 3720cdae460d433d6daa9cdd21442a3e9544449b	yes	10

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	1	3
	Response to Election / Restriction Filed	4	10
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<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Appl. No.: 13/553972

Filing Date: 7/20/2012

Examiner: Melissa L. Javier

Art Unit: 1611

Confirmation Number: 3635

AMENDMENT TRANSMITTAL

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

Commissioner:

Transmitted herewith is an amendment in the above-identified application.

[ ] Small Entity status under 37 C.F.R. § 1.9 and § 1.27 has been established by a previous assertion of Small Entity status.

[ ] Assertion of Small Entity status is enclosed.

[**X**] The fee required for additional claims is calculated below:

	Claims As Amended		Previously Paid For		Extra Claims Present		Rate		Additional Claims Fee
Total Claims:	26	-	20	=	6	x	$80.00	=	$480.00
Independent Claims:	5	-	4	=	1	x	$420.00	=	$420.00
First presentation of any Multiple Dependent Claims:						+	$780.00	=	$0.00
							CLAIMS FEE TOTAL	=	$900.00

[ ] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

[ ] Extension for response filed within the first month:	$200.00	$0.00
[ ] Extension for response filed within the second month:	$600.00	$0.00
[ ] Extension for response filed within the third month:	$1,400.00	$0.00
[ ] Extension for response filed within the fourth month:	$2,200.00	$0.00
[ ] Extension for response filed within the fifth month:	$3,000.00	$0.00
	EXTENSION FEE TOTAL:	$0.00
[ ] Statutory Disclaimer Fee under 37 C.F.R. 1.20(d):	$160.00	$0.00
	CLAIMS, EXTENSION AND DISCLAIMER FEE TOTAL:	$900.00
	Extension Fees Previously Paid:	$0.00
	TOTAL FEE:	$900.00

A credit card payment form in the amount of $900.00 is enclosed.

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 form being unsigned, providing incorrect information resulting in a rejected credit

card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

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

Respectfully submitted,

Date May 9, 2013

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
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Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/553,972	Filing Date 07/20/2012	☐ 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 **05/09/2013**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 26	Minus	** 20	= 6	X $80 =	480
Independent (37 CFR 1.16(h))	* 5	Minus	***4	= 1	X $420 =	420
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	**900**

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	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.

LIE
/WANDA ANTHONY/

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 05/13/2013

WANTHONY	SALE	#00000001	Mailroom Dt:	05/09/2013	190741	13553972	
	01	FC : 1201		420.00	DA		
	02	FC : 1202		480.00	DA		

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/553,972	07/20/2012	Juan Mantelle	041457-0992

CONFIRMATION NO. 3635

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

PUBLICATION NOTICE

OC000000062096251

Title:TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

Publication No.US-2013-0156815-A1
Publication Date:06/20/2013

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 09/04/2013

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
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EXAMINER	
JAVIER, MELISSA L	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
09/04/2013	PAPER

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.

Office Action Summary	Application No. 13/553,972	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 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *9 May 2013*.

☐ 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) *1-9,11,13-17,19 and 21-30* is/are pending in the application.

5a) Of the above claim(s) *1-9,11,13,16,17 and 19* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *14,15 and 21-30* 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 *20 July 2012* 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/08) Paper No(s)/Mail Date *2/28/2013*.

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

4) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the invention of Group II, claims 14, 15, and newly added claims 21-30, submitted 5/9/2013 is acknowledged.

The traversal is on the ground(s) that no undue burden is placed upon the Office to search and examine the claims of Group I and II together. This is not found persuasive because the invention of Group I is drawn to a monolithic transdermal drug delivery system whereas Group II is drawn to a method for administering estradiol. The inventions of Group I and II are separate and distinct, related as product and process of use, as discussed in the Requirement for Restriction mailed 4/12/2013. See the restriction Requirement page 2. As noted in 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. Therefore, the inventions of Groups I and II are seen to be separate and distinct inventions properly restricted from each other. Further, the search for the inventions of both Groups I and II would place an undue burden on the Office. Note regarding the classification of the inventions herein that the search is not limited to the patent files.

Moreover, the search field for a composition is non-coextensive with the search field for a method of treating a patient employing the same composition. A reference to the composition herein would not necessarily be a reference to the method of treatment herein under 35 USC 103 because a search indicating the process or method is novel

or unobvious would not extend to a holding that the product itself is novel or unobvious whereas a search indicating that the product is known or would have been obvious would not extend to a holding that the process or method is known or would have been obvious. Note that the search is not limited to patent files.

Thus, an undue burden on the Office is seen for the search all inventions herein, as discussed in the Requirement for Restriction and above.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14, 15, and 21-30 will be examined on the merits herein.

Claims 1-9, 11, 13, 16, 17, and 19 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. Applicant timely traversed the restriction (election) requirement.

Information Disclosure Statement

The Information Disclosure Statement (IDS) filed 2/28/2013 has been considered by the examiner.

Claim Rejections - 35 USC § 112

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.

Claim 27 is 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 27 recites "[t]he method of claim 3". However, claim 3 is drawn to a transdermal drug delivery system (i.e. a product not a method). Further, in the response filed 5/9/2013 applicant argues that all newly added claims, including claim 27, recite specific embodiments of the subject matter of Group II (drawn to a method for administering estradiol). For the purposes of examination and to promote compact prosecution, claim 27 will be interpreted to depend from claim 22, which recites the same limitations as claim 3 in a method of administering estradiol.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14, 21, and 27-29 are rejected under pre-AIA 35 U.S.C. 102b as being anticipated by Kanios et al. (US2006/0078601).

Regarding claim 13, Kanios et al. discloses a transdermal drug delivery system in which the drug is delivered from the pressure-sensitive adhesive composition and through dermis when the pressure-sensitive adhesive composition is in contact with human skin (see abstract). Kanios et al. discloses an active agent carrier layer comprising a pressure-sensitive adhesive composition and a drug incorporated therein and that the agent-carrier composition may comprise one layer (see [0014]) (i.e. a monolithic transdermal drug delivery system). Kanios et al. discloses the use of estradiol at a coat weight of about 5mg/cm2 (see [0117]), meeting the limitation recited by the instant claim of wherein the amount of estradiol in the polymer matrix and the coat weight thereof are such that the system includes greater than 0.156 mg/cm2 estradiol. In Figure 4, the flux of the disclosed system is 0.4mg/cm2/hr (9.6um/cm2/day or 0.096 mg/cm2/day), meeting the limitation recited by the instant claim of a flux that is greater than 0.01 mg/cm2/day. Further, Kanios et al. discloses examples with estradiol as the only drug (see [0117]). Kanios et al. discloses the attachment to the skin or mucosa of the user (see [0015]).

Regarding claim 21, Kanios et al. discloses that the carrier composition is a blend an acrylic-based polymer and at least one polymer selected from a group that includes silicone-based polymers and polyvinylpyrrolidone (see claim 5). Although Kanios et al. does not explicitly recite that the PVP is soluble; the solubility of the material is an inherent property.

Regarding claim 27, Kanios et al. discloses that the polymeric coating has a coat weight from about 2.5mg/cm2 to about 15mg/cm2 (see [0090]).

Regarding claim 28, Kanios et al. discloses amounts of estradiol delivered over a period of 84 hours (3.5 days) (see Figure 4).

Regarding claim 29, Kanios et al. discloses in Figure 4, the flux of the disclosed system is 0.4mg/hr (9.6um/day or 0.096 mg/day), meeting the limitation recited by the instant claim of a flux that is about 0.1 mg/day.

Claim Rejections - 35 USC § 103

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 of this title, 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.

Claims 14 and 21-29 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Kanios et al. (US2006/0078601) in view of Kanios (US 6638528, referred to as Kanios II).

The teachings of Kanios et al. have been set forth above. Additionally, Kanios et al. teaches an example with a dry weight of 20% acrylic adhesive, 56% silicone adhesive, 6% oleyl alcohol (a penetration enhancer), 8% dipropylene glycol (a penetration enhancer), and 2% estradiol (see [0117]) and suggestes the use of polyvinylpyrrolidone (see claim 5).

Kanios et al. does not teach that the polymer matrix comprises about 2-25% by weight soluble PVP.

Kanios II teaches compositions and methods for the transdermal delivery of active agents (see abstract). Kanios II 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 II teaches an example with 48.6% polysiloxane 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).

Regarding claim 22, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to utilize the concentration of PVP taught by

Kanios II in a monolithic transdermal drug delivery system. One would be motivated to do so because Kanios et al. teaches the use of PVP (see claim 5) in the polymer blend and Kanios II teaches a similar composition utilizing PVP which was successfully used for the transdermal delivery of estradiol.

Regarding claims 23-25, Kanios et al. teaches an example with a dry weight of 20% acrylic adhesive, 56% silicone adhesive, 6% oleyl alcohol (a penetration enhancer), 8% dipropylene glycol (a penetration enhancer), and 2% estradiol (see [0117]).

Regarding claim 26, Kanios et al. teaches an example with a dry weight of 20% acrylic adhesive and 56% silicone adhesive (see [0117]). MPEP 2144.05 states that "[i]n the case where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a prima facie case of obviousness exists" quoting *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976).

Claims 14, 15, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kanios et al. (US2006/0078601) in view of Nuwayser (US4624665).

The teachings of Kanios et al. have been set forth above.

Kanios et al. does not teach a surface area that is about 60% of a size selected from the group consisting of 2.5, 3.75, 5.0, 7.5, and 10cm^2.

Nuwayser teaches a transdermal drug delivery system (see abstract). 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.

A person of ordinary skill in the art at the time that the invention was made would utilize the size of the patch taught by Nuwayser in the system taught by Kanios et al. One would be motivated to do so as the transdermal patches with the surface area taught by Nuwayser were successfully used for the transdermal delivery of estradiol.

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 claims at issue 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); and *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 a nonstatutory

double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form 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 http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 14, 15, and 30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 11 and 12 of U.S. Patent No. 8,231,906. Although the claims at issue are not identical, they are not patentably distinct from each other because U.S. Patent No. 8,231,906 is drawn to a method for administering estradiol, con to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system 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.

Conclusion

No claims are allowed.

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, Daniel Sullivan can be reached on 571-272-0779. 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

/Cherie M Stanfield/
Primary Examiner, Art Unit 1647

Notice of References Cited	Application/Control No. 13/553,972	Applicant(s)/Patent Under Reexamination MANTELLE, JUAN	
	Examiner Melissa Javier	Art Unit 1611	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2006/0078601	04-2006	Kanios et al.	424/449
*	B	US-6,638,528	10-2003	Kanios, David	424/449
*	C	US-4,624,665	11-1986	Nuwayser, Elie S.	604/307
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
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	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
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NON-PATENT DOCUMENTS

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	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.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13553972	MANTELLE, JUAN
	Examiner	Art Unit
	MELISSA JAVIER	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 history)	8/25/2013	MJ
Inventor search in EAST	8/25/2013	MJ
Google Scholar search (keywords used: transdermal monolithic estradiol)	8/25/2013	MJ

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/M.J./ Examiner.Art Unit 1611	

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
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: February 28, 2013

(use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	13/553,972
Filing Date	07/20/2012
First Named Inventor	Juan Mantelle
Art Unit	1615
Examiner Name	Unassigned
Attorney Docket Number	041457-0992

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	8,231,906	07/31/2012	MANTELLE	
	A2	8,343,538	04/13/2006	KANIOS ET AL.	
	A3	5,446,070	08/29/1995	MANTELLE	
	A4	4,915,950	04/1990	MIRANDA ET AL.	
	A5	6,562,363	05/13/2003	MANTELLE ET AL.	
	A6	6,221,383	04/24/2001	MIRANDA ET AL.	
	A7	6,235,306	05/22/2001	MIRANDA ET AL.	
	A8	2005/0169977 A1	08/04/2005	KANIOS	
	A9	2005/0129749 A1	06/16/2005	STRAUSS	
	A10	2006/0240087 A1	10/26/2006	HOUZE ET AL.	
	A11	2006/0233870 A1	10/19/2006	HOUZE ET AL.	
	A12	4,994,278	02/19/1991	SABOLTSKY ET AL.	
	A13	4,494,278	2/19/1991	SABLOTSKY ET AL.	
	A14	5,300,291	4/5/1994	SABLOTSKY ET AL.	
	A15	5,958,446	9/28/1999	MIRANDA ET AL.	
	A16	5,474,783	12/12/1995	MIRANDA ET AL.	
	A17	4,814,168	3/21/1989	SABLOTSKY ET AL.	
	A18	4,994,267	2/19/1991	SABLOTSKY	
	A19	5,565,286	8/12/1997	MIRANDA ET AL.	
	A20	6,024,976	2/15/2000	MIRANDA ET AL.	
	A21	6,337,086	1/8/2002	KANIOS ET AL.	
	A22	6,638,528	10/2003	KANIOS	
	A23	RE 35,474	3/11/1997	WOODARD ET AL.	Reissue of USP 4,655,767
	A24	4,655,767	4/7/1987	WOODARD ET AL.	
	A25	2005/2022073	09/15/2005	JACKSON ET AL.	
	A26	2003/099695	05/29/2003	MUELLER	
	A27	4,591,622	5/27/1986	BLIZZARD ET AL.	
	A28	5,584,355	4/22/1986	BLIZZARD ET AL.	
	A29	4,585,836	4/29/1986	HOMAN ET AL.	
	A30	4,390,520	6/28/1983	NAGAI ET AL.	
	A31	5,665,377	09/1997	GONELLA	
	A32	2003/0228354	12/2003	MURAOKA ET AL.	
	A33	5,730,999	03/24/1998	LEHMANN ET AL.	
	A34	5,505,956	04/09/1996	KIM ET AL.	
	A35	5,350,581	09/27/1994	KOCHINKE	
	A36	4,983,395	01/08/1991	CHANG ET AL.	
	A37	4,559,222	12/17/1985	ENSCORE ET AL.	
	A38	5,762,952	06/09/1998	BARNHART ET AL.	
	A39	4,591,622	05/27/1986	BLIZZARD 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.

4850-7355-3427.1 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J./

PTO/SB/08 (09-06)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: February 28, 2013

(use as many sheets as necessary)

Sheet 2 of 4

Complete if Known	
Application Number	13/553,972
Filing Date	07/20/2012
First Named Inventor	Juan Mantelle
Art Unit	1615
Examiner Name	Unassigned
Attorney Docket Number	041457-0992

U.S. PATENT DOCUMENTS

		Document Number			
	A40	4,585,836	04/29/1986	HOMAN ET AL.	
	A41	5,474,787	12/12/1995	GRAY ET AL.	
	A42	2002/0100185 A1	08/01/2002	SITZ ET AL.	
	A43	6,808,739 B2	10/26/2004	SITZ ET AL.	
	A44	5,151,271	09/29/1992	OTSUKA ET AL.	
	A45	5,906,830	05/25/1999	FARINAS ET AL.	
	A46	5,902,603	05/11/1999	CHEN ET AL.	
	A47	5,837,280	11/17/1998	KENEALY ET AL.	
	A48	5,567,488	10/22/1996	ALLEN ET AL.	
	A49	5,271,940	12/21/1993	CLEARY ET AL.	
	A50	4,911,707	03/27/1990	HEIBER ET AL.	
	A51	4,746,515	05/24/1988	CHENG ET AL.	
	A52	5,904,931	05/1999	LIPP ET AL.	
	A53	4,938,759	07/1990	ENSCORE ET AL.	
	A54	5,928,666	07/1999	FARINAS ET AL.	
	A55	4,769,028	09/1998	HOFFMANN ET AL.	
	A56	4,624,665	11/1986	NUWAYESER	
	A57	6,156,335	12/2000	ROVATI 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]

Examiner Signature		Date Considered	

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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

4850-7355-3427.1 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J./

PTO/SB/08 (09-06)
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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/553,972
Date Submitted: February 28, 2013				**Filing Date**	07/20/2012
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	1615
				Examiner Name	Unassigned
Sheet	3	of	4	Attorney Docket Number	041457-0992

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]
	A58	VAUGHAN, "Using Solubility Parameters in Cosmetics Formulation," *J. Soc. Cosmet. Chem.*, Vol. 36, pp. 319-333 (1985).	
	A59	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).	
	A60	"Acrylic Adhesives," *Handbook of Pressure-Sensitive Adhesive Technology*, 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, N.Y. (1989)	
	A61	International Preliminary Report on Patentability and Written Opinion issued April, 19, 2007.	
	A62	International Search Report issued on 04/06/2005 in application number PCT/US2004/029789.	
	A63	International Search Report issued on 02/24/2011 in application number PCT/US2009/050069.	
	A64	"Acrylic and Methacrylic Ester Polymers," *Polymer Science and Engineering*, Vol. 1, 2nd ed., pp. 234-269, John Wiley & Sons (1984).	
	A65	Office Action issued on 09/09/2010 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A66	Office Action issued on 01/20/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A67	Office Action issued on 06/30/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A68	Office Action issued on 09/13/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A69	Office Action issued on 11/08/2011 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A70	Office Action issued on 05/29/2012 by the Examiner in application number 12/216,811 (US 8,231,906)	

Examiner Signature		Date Considered	

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4850-7355-3427.1 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J./

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: February 28, 2013

(use as many sheets as necessary)

Sheet 4 of 4

Complete if Known	
Application Number	13/553,972
Filing Date	07/20/2012
First Named Inventor	Juan Mantelle
Art Unit	1615
Examiner Name	Unassigned
Attorney Docket Number	041457-0992

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]
	A71	Notice of Allowance issued on 06/19/2012 by the Examiner in application number 12/216,811 (US 8,231,906)	
	A72	Office Action issued on 12/29/2010 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A73	Office Action issued on 04/14/2010 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A74	Office Action issued on 06/10/2009 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A75	Office Action issued on 10/26/2011 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A76	Office Action issued on 05/13/2011 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A77	Office Action issued on 06/13/2012 by the Examiner in application number 11/245,084 (US 8,343,538)	
	A78	Notice of Allowance issued on 08/22/2012 by the Examiner in application number 11/245,084 (US 8,343,538)	

Examiner Signature	/Melissa Javier/	Date Considered	08/25/2013

*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.

4850-7355-3427.1 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J./

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BIB DATA SHEET

CONFIRMATION NO. 3635

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/553,972	07/20/2012	424	1611	041457-0992

APPLICANTS
Juan Mantelle, Miami, FL;

**** CONTINUING DATA ***************************
This application is a CON of 12/216,811 07/10/2008 PAT 8231906

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
07/31/2012

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /MELISSA L JAVIER/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		FL	1	16	4

ADDRESS

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007
UNITED STATES

TITLE

TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

FILING FEE RECEIVED		
2540	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	11231	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/08/25 13:42
L2	4027	L1 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/08/25 13:42
L3	616	L2 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/08/25 13:42
L4	30	L3 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/08/25 13:42
L5	204	L3 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/08/25 13:42
L6	43	L3 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/08/25 13:42
L7	78	L1 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/08/25 13:42
L8	65	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/08/25 13:42
L9	27	L8 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/08/25 13:42
L10	53	L8 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/08/25 13:42
L11	49	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/08/25 13:42
L12	12	L11 NOT L8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/08/25 13:42
L13	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2013/08/25 13:42
L14	451	L1 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2013/08/25 13:42
L15	81	L3 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2013/08/25 13:42

EAST Search History (Interference)

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8/25/2013 1:44:00 PM

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 11/05/2013

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
JAVIER, MELISSA L	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
11/05/2013	PAPER

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.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/553,972	MANTELLE, JUAN	
	Examiner	Art Unit	
	Melissa Javier	1611	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Melissa Javier*.

(2) *Kevin Orwig*.

(3) *Courtenay Brinkerhoff*.

(4) _____.

Date of Interview: *31 October 2013*.

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: _____.

Identification of prior art discussed: *Kanios et al. (US 2006/0078601)*.

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 interpretation of the Kanios teaching in [0117] with regards to the amount of estradiol (i.e. 5mg/cm2 vs. two percent of 5mg/cm2). Applicant's representative took the position that the Kanios reference was teaching two percent of 5mg/cm2. Applicant's representative pointed to [0126] and [0122] in support of this position. Examiners suggested that this position should be clearly set forth in the record.

Discussed Applicant's position that Kanios teaches a two layer system, with a non-drug contain layer to control delivery, vs. the instantly claimed patch. Discussed claim language to clarify the single layer system of the instant invention, including "consisting of" and a possible negative limitation.

Discussed that amendments would require further search and consideration.

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

/Kevin S. Orwig/ Primary Examiner, Art Unit 1611	/Melissa Javier/ 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

AMENDMENT AND RESPONSE UNDER 37 CFR 1.111

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

Commissioner:

This is a response to the non-final Office Action mailed September 4, 2013.

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

Remarks/Arguments begin on page 7 of this document.

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. (Withdrawn-Currently Amended) A monolithic transdermal drug delivery system for estradiol, ~~comprising~~ consisting of (i) a backing layer, (ii) a single polymer matrix layer defining an active surface area and, optionally, (iii) a release liner, wherein the single polymer matrix layer ~~comprising~~ comprises a polymer matrix comprising estradiol as the only drug, wherein the polymer matrix layer 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. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The transdermal drug delivery system of claim 3, wherein the penetration enhancer comprises oleyl alchol.

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

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

7. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) 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. (Canceled)

11. (Withdrawn) 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. (Canceled)

13. (Withdrawn—Currently Amended) A monolithic transdermal drug delivery system for estradiol ~~comprising~~ consisting of (i) a backing layer, (ii) a single polymer matrix layer and, optionally, (iii) a release liner, wherein the single polymer matrix layer ~~comprising~~ comprises estradiol as the only drug, 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. (Currently Amended) A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system ~~comprising~~ consisting of (i) a backing layer and (ii) 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 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. (Original) 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. (Withdrawn—Currently Amended) A method of making a monolithic transdermal drug delivery system for administering ~~estradiol~~ estradiol consisting of (i) a backing layer, (ii) a single polymer matrix layer and, optionally, (iii) a release liner, comprising forming a 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 polymer matrix to a support layer to form a single polymer matrix layer such that the polymer matrix layer includes greater than 0.156 mg/cm^2 estradiol.

17. (Withdrawn) 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. (Canceled)

19. (Withdrawn) 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. (Canceled)

21. (Previously Presented) The method of claim 14, wherein the polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble polyvinylpyrrolidone (PVP).

22. (Previously Presented) The method of claim 14, 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.

23. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alchol.

24. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises dipropylene glycol.

25. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

26. (Previously Presented) The method of claim 22, 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.

27. (Currently Amended) The method of claim [[3]] 22, wherein the polymer matrix has a coat weight of greater than about 10 mg/cm^2.

28. (Previously Presented) The method of claim 14, 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.

29. (Previously Presented) The method of claim 14, 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.

30. (Currently Amended) A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system for

estradiol ~~comprising~~ consisting of (i) a backing layer and (ii) a single polymer matrix layer comprising estradiol as the only drug, 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.

REMARKS

Applicant respectfully requests reconsideration of the application in view of the foregoing claim amendments and the reasons that follow.

Claim Amendments

The claims are amended to clarify the nature of the recited monolithic transdermal drug delivery systems, e.g., to recite that the monolithic transdermal drug delivery systems consist of a backing layer, a single polymer matrix layer comprising estradiol as the only drug, and, optionally, a release liner. Support for these amendments is found throughout the specification as filed, including in paragraphs [0034] and [0037]. Claim 27 also is amended to correct a clerical error in its dependency.

These amendments are made without prejudice or disclaimer and Applicant reserves the right to pursue any canceled subject matter in one or more continuing applications with the same rights of priority as the instant application.

Upon entry of these amendments, claims 1-9, 11, 13-17, 19 and 21-30 will remain pending, with claims 14, 15 and 21-30 being drawn to elected subject matter. These claims are presented for reconsideration.

Telephonic Interview

Applicant thanks Examiner Javier and Supervisory Examiner Orwig for the courtesies extended during the Telephone Interview on October 31, 2013. Applicant's Statement of the Substance of the Interviews is provided here, in accordance with MPEP 713.04. As reflected on the Examiner's Interview Summary, Applicant's representative explained that Kanios I (US 2006/0078601) does not teach a system with the recited amount of estradiol per unit area, and is directed to multilayer systems in contrast to the recited monolithic systems. The Examiners proposed amending the claims to further clarify the structure of the recited systems. These amendments are reflected in the claim amendments presented above.

Restriction Requirement

Applicant again asks for reconsideration of the Restriction Requirement, at least with respect to Group I and elected Group II, because examining the subject matter of these groups of claims would not impose a serious burden on the Examiner. Although Group I is directed to monolithic transdermal drug delivery systems *per se* while Group II is directed to methods using them, this difference does not give rise to a significant examination burden. In this regard, Applicant notes that the mere possibility of using different search terms or identifying different references does not amount to a "significant examination burden," where the overwhelming majority of relevant prior art will be coextensive. Applicant also notes that both product claims and method claims were granted in the parent patent, further showing that no significant examination burden is required to examine both types of claims in a single application. Applicant therefore respectfully urges reconsideration and withdrawal of the Restriction Requirement at least with respect to Group I and Group II.

Indefiniteness Rejection

Claim 27 was rejected for depending from product claim 3. Applicant has amended this claim to depend from claim 22, in accordance with the comments at page 4 of the Office Action. Thus, this issue is believed to be overcome.

§ 102 Rejection

Claims 14, 21 and 27-29 are rejected as allegedly anticipated by Kanios I (US 2006/0078601). Applicant traverses this rejection in as much as it may be applied to the instant claims.

As reflected in independent claim 14, the method claims under examination are directed to methods 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 polymer matrix layer defining an active surface area and comprising a polymer

matrix comprising estradiol as the only drug, wherein the polymer matrix 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. Kanios I does not teach or suggest such systems.

As discussed during the October 31, 2013, Patent Office Interview, Kanios I is directed to ***multilayer*** transdermal systems formed with two polymeric layers, (i) a polymeric drug-loaded carrier layer and (ii) a polymeric non-drug containing coating layer (in addition to a backing layer and/or release liner), while the instant claims recite ***monolithic*** transdermal drug delivery systems consisting of a backing layer and a single polymer matrix layer (and, in some claims, optionally, a release liner). Kanios I does not teach or suggest a monolithic transdermal drug delivery system comprising a single polymer matrix layer as recited in the instant claims. As discussed during the October 31, 2013 Telephonic Interview, it is believed that the foregoing claims amendments further distinguish Kanios I in this regard, such that the § 102 rejection will be withdrawn.

Moreover, although the Office Action cites paragraph [0117] of Kanios I as disclosing an estradiol system that includes greater than 0.156 mg/cm^2 estradiol as recited in the instant claims, that is not the case. As discussed during the October 31, 2013 Telephonic Interview, when paragraph [0117] refers to a coat weight of 5 mg/cm^2, the stated coat weight relates to the drug-loaded carrier composition ***as a whole***. This is shown by reading the full sentence at issue, which lists other components of the drug-loaded carrier composition. This also is shown by paragraph [0120], which states that for Examples 1-3 the "drug-in-adhesive matrix" had a "coat weight of 5.0 mg/cm^2." Similarly, paragraph [0122] states that for Examples 4-6 the drug-in-adhesive matrix had a "coat weight of 5.0 mg/cm^2." Based on the stated 2% estradiol content of the drug-loaded carrier of its examples, Kanios uses estradiol in an amount of 0.1 mg/cm^2 (2% of 5 mg/cm^2 = 0.1 mg/cm^2), which is lower than the amount recited in the claims. (Applicant notes that the "control" used for the examples of Kanios is the prior art Vivelle-Dot ® product discussed in the instant application, which also is outside the scope of the claims.)

For at least these reasons, the § 102 rejection based on Kanios I should be withdrawn.

§ 103 Rejections

Claims 14 and 21-29 are rejected as allegedly obvious in view of Kanios I and Kanios II (US 6,638,528). Claims 14, 15, and 30 are rejected as allegedly obvious in view of Kanios I and Nuwayser (US 4,624,665). Applicant traverses these rejections in as much as they may be applied to the instant claims.

The obviousness rejections rely on Kanios I for allegedly teaching the subject matter of the independent claims, which it does not, as shown above. Combining Kanios I with Kanios II and/or Nuwayser does not overcome this deficiency, as no combination of the cited references teaches or suggests a monolithic transdermal drug delivery systems for estradiol consisting of (i) a backing layer and (ii) a single polymer matrix layer comprising greater than 0.156 mg/cm^2 estradiol that achieves an estradiol flux that is greater than 0.01 mg/cm^2/day. Based on the discussions during the October 31, 2013 Telephone Interview, it is believed that the foregoing claims amendments further distinguish the cited references, such that the § 103 rejections will be withdrawn.

Applicant therefore respectfully urges reconsideration and withdrawal of the prior art rejections based on Kanios I and Kanios II and/or Nuwayser.

Obviousness-Type Double Patenting Rejection

Claims 14, 15 and 30 are rejected for alleged obviousness-type double patenting over claims 11 and 12 of parent patent U.S. Patent 8,231,906. Applicant submits herewith a Terminal Disclaimer that obviates this issue.

Conclusion

The application is believed to be in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

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 a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date November 14, 2013

By _____

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

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

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**	13/553972
Date Submitted: November 12, 2013				**Filing Date**	7/20/2012
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	1611
				Examiner Name	Melissa L. Javier
Sheet	1	of	1	Attorney Docket Number	041457-0992

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	2006/0078602	04/13/2006	KANIOS ET AL.	
	A2	2012/0258942	10/11/2012	KANIOS 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]

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	NOVARTIS PHARMACUETICALS CORPORTION, "Vivelle-Dot® (estradiol transdermal system)," prescripton labeling, August 2004.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP . if possible. and . 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 . This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Patent Application Fee Transmittal

Application Number:	13553972
Filing Date:	20-Jul-2012
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-0992

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
Statutory or Terminal Disclaimer	1814	1	160	160
		Total in USD ($)		**340**

Electronic Acknowledgement Receipt

EFS ID:	17404338
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	14-NOV-2013
Filing Date:	20-JUL-2012
Time Stamp:	15:41:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$340
RAM confirmation Number	2417
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		resp.pdf	1763739 e8d3da4b8aecb472103892b103b90a97a1fca27c	yes	18

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	11
Terminal Disclaimer Filed	12	12
Assignee showing of ownership per 37 CFR 3.73.	13	13
Power of Attorney	14	14
Transmittal Letter	15	17
Information Disclosure Statement (IDS) Form (SB08)	18	18

Warnings:					
Information:					
2	Non Patent Literature	ref.pdf	1206821 de8c55d2289ca2ef0607c579760e7c1b3b3e3049	no	4
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	31796 35454b28d425d5fda82f3c02cc16068a6a354bd1	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3002356		

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/80 (12-03)
Approved for use through 11/30/2005. OMB 0651-0035
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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

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(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 DOCUMENTS

Documents A1 and A3 were cited during prosecution of the corresponding European application.

Document A2 is a continuation of Document A1, and is a co-pending application with common or overlapping inventorship and/or ownership.

FEE

A credit card payment form in the amount of $180.00 is enclosed to cover the fee associated with an information disclosure statement under 37 CFR §1.97(c).

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this submission 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 form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

Date NOV 14, 2013

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/SB/26 (08-11)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 041457-0992

In re Application of: Juan Mantelle

Application No.: 13/553972

Filed: 7/20/2012

For: Transdermal Estrogen Device and Delivery

The owner*, NOVEN PHARMACEUTICALS, INC., of 100 percent interest 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** No. 8,231,906 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.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

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.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 37,288

Courtney C Brinckerhoff — Signature
11/14/2013 — Date

Courtenay C. Brinckerhoff
Typed or printed name

(202) 295-4094
Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

*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.

PTO/SB/96 (07-09)
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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Juan Mantelle

Application No./Patent No.: 13/553972 Filed/Issue Date: 7/20/2012

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 it is:

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

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

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

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

OR

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

1. From: _____ To: _____

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

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

2. 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.

3. 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.

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

☒ As required by 37 CFR 3.73(b)(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 — 11/14/2013

Signature — Date

Courtney C. Brinckerhoff — Attorney for Applicant

Printed or Typed Name — Title

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/553,972	Filing Date 07/20/2012	☐ 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 **11/14/2013**

	(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))	* 26	Minus	** 26	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 5	Minus	***5	= 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.

LIE
/ANTHONY TYSON/

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/553,972	07/20/2012	Juan Mantelle	041457-0992

CONFIRMATION NO. 3635

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

POA ACCEPTANCE LETTER

OC000000065022001

Date Mailed: 11/19/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/14/2013.

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.

/hsarwari/

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

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/553,972	MANTELLE, JUAN	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 11/14/13	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

Angie Walker

U.S. Patent and Trademark Office

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 03/05/2014

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
JAVIER, MELISSA L	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
03/05/2014	PAPER

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.

Office Action Summary	Application No. 13/553,972	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 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *9 May 2013*.

☐ 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) *1-9,11,13-17,19 and 21-30* is/are pending in the application.

5a) Of the above claim(s) *1-9,11,13,16 and 17* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *14,15 and 21-30* 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/08) Paper No(s)/Mail Date *11/14/2013*.

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

4) ☐ Other: _____.

DETAILED ACTION

Status of Claims

The amendments and arguments filed on 11/14/2013 are acknowledged and have been fully considered. Claims 1-9, 11, 13-17, 19, 21-30 are now pending. Claims 10, 12, 18, and 20 are canceled; claims 1, 13, 14, 16, 27, and 30 are amended; claims 1-9, 11, 13, 16, and 17 are withdrawn; no claims are new.

Claims 14, 15, and 21-30 will be examined on the merits herein.

Information Disclosure Statement

The Information Disclosure Statement (IDS) filed 11/14/2013 has been considered by the examiner.

Objections/Rejections Withdrawn

The rejection of claim 27 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph is withdrawn in view of the amendment to the claim.

The rejection of claims 14, 15, and 30 over nonstatutory double patenting over claims 11 and 12 of U.S. Patent No. 8,231,906 is withdrawn in view of the Terminal Disclaimer filed 11/14/2013 and approved 11/29/2013.

Claim Rejections - 35 USC § 102 (modified)

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14, 21, and 27-29 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Kanios et al. (US 2006/0078601).

Regarding claim 14, Kanios et al. discloses a transdermal drug delivery system in which the drug is delivered from the pressure-sensitive adhesive composition and through dermis when the pressure-sensitive adhesive composition is in contact with human skin (see abstract). Kanios et al. discloses an active agent carrier layer comprising a pressure-sensitive adhesive composition and a drug incorporated therein and that the agent-carrier composition may comprise one layer (see [0014]) (i.e. a monolithic transdermal drug delivery system). Kanios et al. discloses the transdermal system includes a backing or release liner (see [0003]). Kanios et al. discloses the adhesive coated backing or release liner may be processed or manufactured separately from the polymeric and/or adhesive drug carrier layer (see [0003]). Kanios et al. discloses the use of estradiol at a coat weight of about 5mg/cm^2 (see [0117]), meeting the limitation recited by the instant claim of wherein the amount of estradiol in the polymer matrix and the coat weight thereof are such that the system includes greater than 0.156 mg/cm^2 estradiol. In Figure 4, the flux of the disclosed system is 0.4mg/cm^2/hr (9.6um/cm^2/day or 0.096 mg/cm^2/day), meeting the limitation recited by the instant claim of a flux that is greater than 0.01 mg/cm^2/day. Further, Kanios et al. discloses examples with estradiol as the only drug (see [0117]). Kanios et al. discloses the attachment to the skin or mucosa of the user (see [0015]).

Regarding claim 21, Kanios et al. discloses that the carrier composition is a blend an acrylic-based polymer and at least one polymer selected from a group that includes silicone-based polymers and polyvinylpyrrolidone (see claim 5). Although Kanios et al. does not explicitly recite that the PVP is soluble; the solubility of the material is an inherent property.

Regarding claim 27, Kanios et al. discloses that the polymeric coating has a coat weight from about 2.5mg/cm^2 to about 15mg/cm^2 (see [0090]).

Regarding claim 28, Kanios et al. discloses amounts of estradiol delivered over a period of 84 hours (3.5 days) (see Figure 4).

Regarding claim 29, Kanios et al. discloses in Figure 4, the flux of the disclosed system is 0.4mg/hr (9.6um/day or 0.096 mg/day), meeting the limitation recited by the instant claim of a flux that is about 0.1 mg/day.

Claim Rejections - 35 USC § 103 (modified)

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 of this title, 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.

Claims 14 and 21-29 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Kanios et al. (US 2006/0078601) in view of Kanios (US 6638528, referred to as Kanios II).

The teachings of Kanios et al. have been set forth above. Additionally, Kanios et al. teaches an example with a dry weight of 20% acrylic adhesive, 56% silicone adhesive, 6% oleyl alcohol (a penetration enhancer), 8% dipropylene glycol (a penetration enhancer), and 2% estradiol (see [0117]) and suggests the use of polyvinylpyrrolidone (see claim 5).

Kanios et al. does not teach that the polymer matrix comprises about 2-25% by weight soluble PVP.

Kanios II teaches compositions and methods for the transdermal delivery of active agents (see abstract). Kanios II 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 II teaches an example with 48.6% polysiloxane 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).

Regarding claim 22, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to utilize the concentration of PVP taught by Kanios II in a monolithic transdermal drug delivery system. One would be motivated to do so because Kanios et al. teaches the use of PVP (see claim 5) in the polymer blend and Kanios II teaches a similar composition utilizing PVP which was successfully used for the transdermal delivery of estradiol.

Regarding claims 23-25, Kanios et al. teaches an example with a dry weight of 20% acrylic adhesive, 56% silicone adhesive, 6% oleyl alcohol (a penetration enhancer), 8% dipropylene glycol (a penetration enhancer), and 2% estradiol (see [0117]).

Regarding claim 26, Kanios et al. teaches an example with a dry weight of 20% acrylic adhesive and 56% silicone adhesive (see [0117]). MPEP 2144.05 states that "[i]n the case where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a prima facie case of obviousness exists" quoting *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976).

Claims 14, 15, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kanios et al. (US 2006/0078601) in view of Nuwayser (US 4624665).

The teachings of Kanios et al. have been set forth above.

Kanios et al. does not teach a surface area that is about 60% of a size selected from the group consisting of 2.5, 3.75, 5.0, 7.5, and 10cm^2.

Nuwayser teaches a transdermal drug delivery system (see abstract). 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.

A person of ordinary skill in the art at the time that the invention was made would utilize the size of the patch taught by Nuwayser in the system taught by Kanios et al. One would be motivated to do so as the transdermal patches with the surface area taught by Nuwayser were successfully used for the transdermal delivery of estradiol.

Response to Arguments

Applicant's arguments filed 11/14/2013 have been fully considered but they are not persuasive.

Applicant argues that Kanios I is directed to multilayer transdermal systems formed with two polymeric layers, (i) a polymeric drug-loaded carrier layer and (ii) a polymeric non-drug containing coating layer (in addition to a backing layer and/or release liner), while the instant claims recite monolithic transdermal drug delivery systems consisting of a backing layer and a single polymer matrix layer (and, in some claims, optionally, a release liner). However, Kanios et al. discloses an active agent carrier layer comprising a pressure-sensitive adhesive composition and a drug incorporated therein and that the agent-carrier composition may comprise one layer (see [0014]) (i.e. a monolithic transdermal drug delivery system). “The use of patents

as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989).

Applicant argues that the coat weight of Kanios relates to the drug-loaded carrier composition as a whole. However, Kanios teaches that the drug containing layer is present at a coat weight of 5mg/cm^2 and the non-drug containing layer can be present from 2.5mg/cm^2 to about 15mg/cm^2, thus the total polymer matrix coat weight is greater than the instantly claimed coat weight.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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

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

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, Daniel Sullivan can be reached on 571-272-0779. 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

/Kevin S. Orwig/
Primary Examiner, Art Unit 1611

PTO/SB/08 (09-06)
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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/553972
Date Submitted: November 12, 2013				**Filing Date**	7/20/2012
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	1611
				Examiner Name	Melissa L. Javier
Sheet	1	of	1	Attorney Docket Number	041457-0992

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	2006/0078602	04/13/2006	KANIOS ET AL.	
	A2	2012/0258942	10/11/2012	KANIOS 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]

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	NOVARTIS PHARMACUETICALS CORPORTION, "Vivelle-Dot® (estradiol transdermal system)," prescripton labeling, August 2004.	

Examiner Signature	/Melissa Javier/	Date Considered	02/21/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP . if possible. and . 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 . This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

4811-9164-9558.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J./

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13553972	MANTELLE, JUAN
	Examiner	Art Unit
	MELISSA JAVIER	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 history)	8/25/2013	MJ
Inventor search in EAST	8/25/2013	MJ
Google Scholar search (keywords used: transdermal monolithic estradiol)	8/25/2013	MJ
Updated EAST search	2/21/2014	MJ
Updated Google Scholar search	2/21/2014	MJ

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/M.J./ Examiner.Art Unit 1611	

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 05/19/2014
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EXAMINER	
JAVIER, MELISSA L	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
05/19/2014	PAPER

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.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/553,972	MANTELLE, JUAN	
	Examiner	Art Unit	
	Melissa Javier	1611	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Melissa Javier*.

(2) *Kevin Orwig*.

(3) *CourtenayBrinkerhoff*.

(4) *Jay Kolman*.

Date of Interview: *14 May 2014*.

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: *14 and 30*.

Identification of prior art discussed: *Kanios et al. (US 2006/0078601)*.

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 background of the invention, specifically the coat weight of estradiol, and the rejections of record.

No agreement was reached .

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

/Kevin S. Orwig/ Primary Examiner, Art Unit 1611	/M. J./ 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Appl. No.: 13/553,972

Filing Date: 7/20/2012

Examiner: Melissa L. Javier

Art Unit: 1611

Confirmation Number: 3635

RESPONSE UNDER 37 CFR 1.116

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

Commissioner:

This is a response to the final Office Action mailed March 5, 2014.

A **Listing of Claims** begins on page 2 of this document.

Remarks/Arguments begin on page 7 of this document.

Amendments to the Claims:

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

Listing of Claims:

1. (Withdrawn) A monolithic transdermal drug delivery system for estradiol, consisting of (i) a backing layer, (ii) a single polymer matrix layer defining an active surface area and, optionally, (iii) a release liner, wherein the single polymer matrix layer_ comprises a polymer matrix comprising estradiol as the only drug, wherein the polymer matrix layer 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. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The transdermal drug delivery system of claim 3, wherein the penetration enhancer comprises oleyl alchol.

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

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

7. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) 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. (Canceled)

11. (Withdrawn) 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. (Canceled)

13. (Withdrawn) A monolithic transdermal drug delivery system for estradiol consisting of (i) a backing layer, (ii) a single polymer matrix layer and, optionally, (iii) a release liner, wherein the single polymer matrix layer comprises estradiol as the only drug, 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. (Previously Presented) 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 polymer matrix layer defining an active surface area and comprising a polymer matrix comprising estradiol as the only drug, wherein the polymer

matrix 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. (Original) 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. (Withdrawn) A method of making a monolithic transdermal drug delivery system for administering estradiol consisting of (i) a backing layer, (ii) a single polymer matrix layer and, optionally, (iii) a release liner, comprising forming a 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 polymer matrix to a support layer to form a single polymer matrix layer such that the polymer matrix layer includes greater than 0.156 mg/cm^2 estradiol.

17. (Withdrawn) 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. (Canceled)

19. (Withdrawn) 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. (Canceled)

21. (Previously Presented) The method of claim 14, wherein the polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble polyvinylpyrrolidone (PVP).

22. (Previously Presented) The method of claim 14, 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.

23. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alchol.

24. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises dipropylene glycol.

25. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

26. (Previously Presented) The method of claim 22, 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.

27. (Previously Presented) The method of claim 22, wherein the polymer matrix has a coat weight of greater than about 10 mg/cm^2.

28. (Previously Presented) The method of claim 14, 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.

29. (Previously Presented) The method of claim 14, 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.

30. (Previously Presented) A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system for estradiol consisting of (i) a backing layer and (ii) a single polymer matrix layer comprising estradiol as the only drug, 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.

REMARKS

Claims 1-9, 11, 13-17, 19 and 21-30 remain pending and are not amended. Claims 14, 15 and 21-30 are drawn to elected subject matter. These claims are presented for reconsideration.

Patent Office Interview

Applicant thanks Examiner Javier and Supervisory Examiner Orwig for the courtesies extended during the Patent Office Interview on May 14, 2014. Applicant's Statement of the Substance of the Interviews is provided here, in accordance with MPEP 713.04. As reflected in the Examiner's Interview Summary, Applicant discussed the cited prior art, and explained that Kanios I (US 2006/0078601) is directed to multilayer systems in contrast to the recited monolithic systems and does not teach a system with the recited amount of estradiol per unit area. Applicant also explained that, prior to the present invention, the amount of drug per unit area (the "coat weight" of drug) was thought to impact the duration of drug delivery (e.g., how many days the system could be used) but not the drug flux (the rate of drug delivery). Applicant explained that the invention permits the development of smaller sized system that achieve the drug flux (and therapeutic efficacy) of a larger sized prior art system, and noted that the smaller sized systems offer commercial and clinical advantages.

Restriction Requirement

Applicant again asks for reconsideration of the Restriction Requirement, at least with respect to Group I and elected Group II, because examining the subject matter of these groups of claims would not impose a serious burden on the Examiner. Although Group I is directed to monolithic transdermal drug delivery systems *per se* while Group II is directed to methods using them, this difference does not give rise to a significant examination burden. In this regard, Applicant notes that the mere possibility of using different search terms or identifying different references does not amount to a "significant examination burden," where the overwhelming majority of relevant prior art will be coextensive. Applicant also notes that both product claims and method claims were granted in the parent patent, further showing that no significant

examination burden is required to examine both types of claims in a single application. Applicant therefore respectfully urges reconsideration and withdrawal of the Restriction Requirement at least with respect to Group I and Group II.

§ 102 Rejection

Claims 14, 21 and 27-29 are rejected as allegedly anticipated by Kanios I (US 2006/0078601). Applicant respectfully traverses this rejection.

As reflected in independent claim 14, the method claims under examination are directed to methods 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 polymer matrix layer defining an active surface area and comprising a polymer matrix comprising estradiol as the only drug, wherein the polymer matrix 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. Kanios I does not teach or suggest such systems.

As discussed during the May 13, 2014, Patent Office Interview, Kanios I is directed to ***multilayer*** transdermal systems formed with two polymeric layers, (i) a polymeric drug-loaded carrier layer and (ii) a polymeric non-drug containing coating layer (in addition to a backing layer and/or release liner), while the instant claims recite ***monolithic*** transdermal drug delivery systems ***consisting of*** a backing layer and a ***single polymer matrix layer*** (and, in some claims, optionally, a release liner). Kanios I does not teach or suggest a monolithic transdermal drug delivery system comprising a single polymer matrix layer as recited in the instant claims.

During the Interview, a question was raised as to whether the recited "backing layer" might read on a structure comprising both a backing material and a polymeric non-drug containing coating layer as taught in Kanios I. Applicant explained that such an interpretation of the term "backing layer" would be inconsistent with how that term is used in the art, inconsistent with how that term is used in the specification, and inconsistent with claims.

As reflected in Kanios I, the art typically uses the term "backing layer" to refer to a film, sheet, fabric or foil material that is substantially impermeable to the drug(s) being formulated and protects the transdermal composition from the environment. *See, e.g.*, Kanios I, [0099]; [0100]; *see also* Nuwayser (referring to an "impervious backing"). There is no art of record that uses the term "backing layer" to refer to a structure comprising both a backing material and a polymeric non-drug containing coating layer as taught in Kanios I. Rather, consistent with how the term is used in the art, when a transdermal system includes other layers, they are described separately. *See, e.g.*, Kanios I (backing layer **20,** non-drug containing polymeric layer **18**, carrier composition layer **12**, release layer **15**); Kanios II (backing layer **13,** matrix composition layer **11;** release liner **12**); Nuwayer (impervious backing sheet **12,** macroporous face membrane **14,** adhesive layer **22**). Indeed, Kanios I uses the term "backing composite," not "backing layer" to refer to a structure comprised of both its "non-drug containing polymeric and/or adhesive coating" and its "drug-impermeable layer." *See* Kanios I, [0014]. Further, as noted above, Kanios I describes the drug-impermeable layer as a "backing" or "backing layer" consistent with standard usage in the art. *See* Kanios I, [0100].

The instant specification also uses the term "backing layer" consistent with its ordinary meaning in the art. For example, paragraph [0035] of the published application describes the backing layer as "a drug impermeable backing layer or film," that may be "adjacent one face of the polymer matrix layer." The same paragraph explains that "[w]hen 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." That paragraph also provides examples of materials suitable for use as backing layers, including "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." Thus, the specification does not indicate that "backing layer" should be given a meaning different from its ordinary and customary meaning in the art.

Reading the recited "backing layer" as a structure comprising both a backing material and a polymeric non-drug containing coating layer also would be inconsistent with the express language of the claims and the claimed subject matter as a whole. Several aspects of the instant claims exclude a multilayer system such as disclosed in Kanios I. For example:

- the claims recite ***monolithic*** transdermal drug delivery systems
- the claims recite systems ***consisting of*** (i) a backing layer, (ii) a single polymer matrix layer defining an active surface area and, optionally, (iii) a release liner
- the claims recite ***a single polymer matrix layer***

If Applicant intended the claims to encompass methods using multilayer systems such as those described in Kanios I, Applicant would not have included all of this "single layer"-type language in the claims.

For at least these reasons, concerns that the instant "backing layer" might read on a structure comprising both a backing material and a polymeric non-drug containing coating layer as taught in Kanios I are unfounded, and do not support the § 102 rejection.

During the Interview, Applicant also again explained that Kanios I does not teach or suggest a transdermal delivery system that includes greater than 0.156 mg/cm^2 estradiol as recited in the instant claims. While the Examiners appear to understand that the examples of Kanios I contain less than the recited amount of estradiol per unit area, a question was raised as to whether the disclosure of paragraph [0088] of Kanios I might suggest a transdermal delivery system that includes greater than 0.156 mg/cm^2 estradiol. As Applicant explained during the Interview, Kanios I includes no teaching or suggestion that would have led the skilled artisan to prepare a system with an amount of estradiol of greater than 0.156 mg/ cm^2 estradiol, for at least the following reasons.

Paragraph [0088] of Kanios I discloses a broad range of the amount of drug that can be formulated in the transdermal delivery systems of Kanios I, reported as "% by weight ... based on the total dry weight of the agent-carrier composition." As explained during the Interview, this passage does not discuss, mention, or suggest the amount of estradiol ***per unit area*** of the system, which is the parameter recited in the instant claims. To the contrary, other than the specific example of a drug-containing carrier composition being applied at 5 mg/cm^2, Kanios I does not provide any direct or indirect teachings on the amount of drug per unit area. Instead, Kanios I focuses on adjusting the coat weight of the ***non-drug containing polymer layer*** to control drug delivery. *See, e.g.*, Kanios I [0015]; [0090].

The absence from Kanios I of any teaching or suggestion that the amount of drug per unit area has any criticality with regard to drug flux is consistent with the statements in the instant specification regarding the contribution of the invention over the state of the art. As discussed during the Interview, paragraph [0015] of the published application explains that "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." The specification explains further, "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." That is, "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."

As discussed during the Interview, while this passage refers to "the coat weight of the drug-containing adhesive layer," it is apparent from the specification as a whole that the inventors understood these surprising and unexpected results to relate to the amount of estradiol per unit area, and used the coat weight of the drug-containing adhesive layer as a proxy for that parameter. *See, e.g.*, paragraphs [0005] and [0010] of the published application, discussing the invention in terms of the amount of estradiol per unit area. Indeed, for a given polymer matrix

formulation, the coat weight of the polymer matrix as a whole will determine the amount of drug per unit area. That "the coat weight of the drug-containing adhesive layer" was used as a proxy for the amount of estradiol per unit area is directly reflected in paragraphs [0016] and [0074] of the published application, which state that "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® product." Thus, it is apparent from the specification as a whole that the invention relates to the amount of estradiol per unit area, and that it was surprising and unexpected that increasing the amount of estradiol per unit area resulted in an increased flux per unit area.

As discussed in the specification, the surprising and unexpected discovery relating to the impact of the amount of estradiol per unit area has permitted the development of transdermal drug delivery systems that achieve comparable drug delivery from a significantly smaller system. As discussed in the specification and recited in specific claims, a system according to the invention can be only 60% the size of a prior art composition that includes only 0.156 mg/cm^2 estradiol and yet achieve comparable, therapeutically effective drug flux, such as a drug flux of greater than 0.01 mg/cm^2/day. This surprising and unexpected benefit has commercial and clinical significance from the perspectives of at least patient preference and patient compliance.

There is no teaching or suggestion in Kanios I or any other reference of record that teaches or suggests a method as claimed using a monolithic transdermal drug delivery system as claim, consisting of (i) a backing layer and (ii) 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 includes greater than 0.156 mg/cm^2 estradiol, let alone any reasonable expectation that such a system could achieve an estradiol flux that is greater than 0.01 mg/cm2/day, based on the active surface area, as recited in the claims. For at least these reasons, the § 102 rejection based on Kanios I should be withdrawn.

§ 103 Rejections

Claims 14 and 21-29 are rejected as allegedly obvious in view of Kanios I and Kanios II (US 6,638,528). Claims 14, 15, and 30 are rejected as allegedly obvious in view of Kanios I and Nuwayser (US 4,624,665). Applicant traverses these rejections in as much as they may be applied to the instant claims.

The obviousness rejections rely on Kanios I for allegedly teaching the subject matter of the independent claims, which it does not, as shown above. Combining Kanios I with Kanios II and/or Nuwayser does not overcome this deficiency, as no combination of the cited references teaches or suggests a monolithic transdermal drug delivery systems for estradiol consisting of (i) a backing layer and (ii) a single polymer matrix layer comprising greater than 0.156 mg/cm^2 estradiol that achieves an estradiol flux that is greater than 0.01 mg/cm^2/day. Applicant therefore respectfully urges reconsideration and withdrawal of the prior art rejections based on Kanios I and Kanios II and/or Nuwayser.

Conclusion

The application is believed to be in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

Respectfully submitted,

Date May 23, 2014 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

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 a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Electronic Acknowledgement Receipt

EFS ID:	19112855
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	23-MAY-2014
Filing Date:	20-JUL-2012
Time Stamp:	11:39:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response After Final Action	response.pdf	191248 21275b58ecdcf066181e4317985e4b210fdcd569	no	14

Warnings:	
Information:	

Total Files Size (in bytes):	191248

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 13/553,972	Filing Date 07/20/2012	☐ 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 **05/28/2014**

	(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))	* 26	Minus	** 16	= 10	X $80 =	800
Independent (37 CFR 1.16(h))	* 5	Minus	***5	= 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	**800**

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.

LIE
/GOIGA DUCKETT/

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 07/23/2014

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
JAVIER, MELISSA L	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
07/23/2014	PAPER

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.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 13/553,972	**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 --

THE REPLY FILED 23 May 2014 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.

   Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): (a) ☐ will not be entered, or (b) ☐ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
13. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
14. ☐ Other: _____.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:
    Claim(s) allowed: .
    Claim(s) objected to: .
    Claim(s) rejected: 14,15 and 21-30.
    Claim(s) withdrawn from consideration: 1-9,11,13,16 and 17.

/DANIEL SULLIVAN/
Supervisory Patent Examiner, Art Unit 1611

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's arguments filed 5/23/2014 have been considered but are not found to be persuasive.

Applicant argues that Kanios I is directed to multilayer transdermal systems formed with two polymeric layers, (i) a polymeric drug-loaded carrier layer and (ii) a polymeric non-drug containing coating layer (in addition to a backing layer and/or release liner), while the instant claims recite monolithic transdermal drug delivery systems consisting of a backing layer and a single polymer matrix layer (and, in some claims, optionally, a release liner). Applicant argues that there is no teaching or suggestion in Kanios I or any other reference of record that teaches or suggests a method as claimed using a monolithic transdermal drug delivery system as claim, consisting of (i) a backing layer and (ii) 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 includes greater than 0.156 mg/cm2 estradiol, let alone any reasonable expectation that such a system could achieve an estradiol flux that is greater than 0.01 mg/cm2/day, based on the active surface area, as recited in the claims.

However, Kanios et al. discloses an active agent carrier layer comprising a pressure-sensitive adhesive composition and a drug incorporated therein and that the agent-carrier composition may comprise one layer (see [0014]) (i.e. a monolithic transdermal drug delivery system). Kanios et al. discloses the transdermal system includes a backing or release liner (see [0003]). Kanios et al. discloses the adhesive coated backing or release liner may be processed or manufactured separately from the polymeric and/or adhesive drug carrier layer (see [0003]). Specifically, if the pressure-sensitive adhesive composition and a drug incorporated therein and that the agent-carrier composition may comprise one layer, it meets the limittaion recited by the instnat claim of a monolithic system. While Kanios et al. may have additional embodiements which require more than one layer, "[t]he use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989).

Applicant argues that the backing layer as instantly claimed does not include a non-drug contaiing polymer layer. However, as noted above, Kanios et al. discloses an active agent carrier layer comprising a pressure-sensitive adhesive composition and a drug incorporated therein and that the agent-carrier composition may comprise one layer (see [0014]) (i.e. a monolithic transdermal drug delivery system).

Applicant argues that Kanios I does not teach or suggest a transdermal delivery system that includes greater than 0.156mg/cm2. However, Kanios teaches that the drug containing layer is present at a coat weight of 5mg/cm2 and the non-drug containing layer can be present from 2.5mg/cm2 to about 15mg/cm2, thus the total polymer matrix coat weight is greater than the instantly claimed coat weight.

Applicant argues that as discussed in the specification, the surprising and unexpected discovery relating to the impact of the amount of estradiol per unit area has permitted the development of transdermal drug delivery systems that achieve comparable drug delivery from a significantly smaller system. However, unexpected results are not sufficient to overcome a rejection made under anticipation.

Applicant argues the obviousness rejections rely on Kanios I for allegedly teaching the subject matter of the independent claims, which it is Applicant's position it does not. However, this is not found persuasive for the reasons set forth above regarding Kanios I.

.

OK TO ENTER: /M.J./

Atty. Dkt. No. 041457-0992

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553,972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

RESPONSE UNDER 37 CFR 1.116

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

Commissioner:

This is a response to the final Office Action mailed March 5, 2014.

A **Listing of Claims** begins on page 2 of this document.

Remarks/Arguments begin on page 7 of this document.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553972
Appl. Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

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

Commissioner:

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application. This RCE and the enclosed items listed below are being filed prior to the earliest of: (1) payment of the issue fee (unless a petition under 37 C.F.R. § 1.313 is granted); (2) abandonment of the application; or (3) the filing of a notice of appeal to the U.S. Court of Appeals for the Federal Circuit under 35 U.S.C. §141, or the commencement of a civil action under 35 U.S.C. §145 or §146 (unless the appeal or civil action is terminated).

1. Submission **required** under 37 C.F.R. §1.114: (check items that apply)

   a. Previously submitted:

[ ] Please enter and consider the amendment and/or reply previously filed on __.

[ ] Please consider the Affidavit(s)/Declaration(s) previously filed on __ but not considered.

[ ] Please consider the arguments in the Appeal Brief or Reply previously filed on __.

[ ] Other Documents .

b. Enclosed are:

[**X**] Amendment/Reply.

[**X**] Affidavit(s)/Declaration(s).

[**X**] Information Disclosure Statement.

[**X**] Form PTO/SB/08 with copies of 2 listed reference(s).

[ ] PTO/SB/424 - Request for Prioritized Examination.

[ ] Other Documents

Miscellaneous:

[ ] Suspension of action of the above-identified application is requested under 37 C.F.R. § 1.103(c) for a period of __ months.

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

	Claims as Amended		Previously Paid For		Extra Claims Present		Rate		Fee Totals
RCE Fee 1.17(e):							$1,200.0 0	=	$1,200.00
Total Claims:	26	-	26	=	0	x	$80.00	=	$0.00
Independents	5	-	5	=	0	x	$420.00	=	$0.00
First presentation of any Multiple Dependent Claims:						+	$780.00	=	$0.00
RCE and CLAIMS FEE TOTAL:								=	$1,200.00

[**X**] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

[ ]	Extension for response filed within the first month:	$200.00	0	$0.00
[ ]	Extension for response filed within the second month:	$600.00		$0.00
[X]	Extension for response filed within the third month:	$1,400.00		$1,400.00
[ ]	Extension for response filed within the fourth month:	$2,200.00		$0.00
[ ]	Extension for response filed within the fifth month:	$3,000.00		$0.00
			EXTENSION FEE SUBTOTAL:	$1,400.00
			EXTENSION FEE ALREADY PAID: -	$0.00
			EXTENSION FEE TOTAL	$1,400.00
			RCE, CLAIMS AND EXTENSION FEE TOTAL:	$2,600.00
			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
			Publication Fee	$0.00
[ ]	Suspension of action requested under 37 C.F.R. § 1.103(c)			$0.00
			TOTAL FEE:	$2,600.00

The above-identified fees of $2,600.00 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 5, 2014

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Appl. No.: 13/553,972

Filing Date: 7/20/2012

Examiner: Melissa L. Javier

Art Unit: 1611

Confirmation Number: 3635

RESPONSE UNDER 37 CFR § 1.114

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

Commissioner:

This response addresses rejections set forth in the final Office Action mailed March 5, 2014, and the Advisory Action mailed July 23, 2014, and is filed with a Request for Continued Examination. Applicant hereby petitions for an extension of time to make this response timely.

A **Listing of Claims** begins on page 2 of this document.

Remarks/Arguments begin on page 7 of this document.

Listing of Claims:

1. (Withdrawn) A monolithic transdermal drug delivery system for estradiol, consisting of (i) a backing layer, (ii) a single polymer matrix layer defining an active surface area and, optionally, (iii) a release liner, wherein the single polymer matrix layer comprises a polymer matrix comprising estradiol as the only drug, wherein the polymer matrix layer 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. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The transdermal drug delivery system of claim 3, wherein the penetration enhancer comprises oleyl alchol.

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

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

7. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) 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. (Canceled)

11. (Withdrawn) 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. (Canceled)

13. (Withdrawn) A monolithic transdermal drug delivery system for estradiol consisting of (i) a backing layer, (ii) a single polymer matrix layer and, optionally, (iii) a release liner, wherein the single polymer matrix layer comprises estradiol as the only drug, 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. (Previously Presented) 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 polymer matrix layer defining an active surface area and comprising a polymer matrix comprising estradiol as the only drug, wherein the polymer matrix 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. (Original) 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. (Withdrawn) A method of making a monolithic transdermal drug delivery system for administering estradiol consisting of (i) a backing layer, (ii) a single polymer matrix layer and, optionally, (iii) a release liner, comprising forming a 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 polymer matrix to a support layer to form a single polymer matrix layer such that the polymer matrix layer includes greater than 0.156 mg/cm^2 estradiol.

17. (Withdrawn) 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. (Canceled)

19. (Withdrawn) 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. (Canceled)

21. (Previously Presented) The method of claim 14, wherein the polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble polyvinylpyrrolidone (PVP).

22. (Previously Presented) The method of claim 14, 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.

23. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alchol.

24. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises dipropylene glycol.

25. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

26. (Previously Presented) The method of claim 22, 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.

27. (Previously Presented) The method of claim 22, wherein the polymer matrix has a coat weight of greater than about 10 mg/cm^2.

28. (Previously Presented) The method of claim 14, 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.

29. (Previously Presented) The method of claim 14, 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.

30. (Previously Presented) A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system for estradiol consisting of (i) a backing layer and (ii) a single polymer matrix layer comprising estradiol as the only drug, 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.

REMARKS

Claims 1-9, 11, 13-17, 19 and 21-30 remain pending and are not amended. Claims 14, 15 and 21-30 are drawn to elected subject matter. These claims are presented for reconsideration.

Restriction Requirement

Applicant again asks for reconsideration of the Restriction Requirement, at least with respect to Group I and elected Group II, because examining the subject matter of these groups of claims would not impose a serious burden on the Examiner. Although Group I is directed to monolithic transdermal drug delivery systems *per se* while Group II is directed to methods using them, this difference does not give rise to a significant examination burden. In this regard, Applicant notes that the mere possibility of using different search terms or identifying different references does not amount to a "significant examination burden," where the overwhelming majority of relevant prior art will be coextensive. Applicant also notes that both product claims and method claims were granted in the parent patent, further showing that no significant examination burden is required to examine both types of claims in a single application. Applicant therefore respectfully urges reconsideration and withdrawal of the Restriction Requirement at least with respect to Group I and Group II.

§ 102 Rejection

As reflected in the Advisory Action, the § 102 rejection based on Kanios I is maintained based on what Applicant believes are misunderstandings of the claimed subject matter and/or misunderstandings of the cited reference. To address these issues, Applicant submits herewith a Rule 132 Declaration of Viet Nguyen. As set forth in paragraph 1 of his declaration, Mr. Nguyen is employed by the assignee as a Principle Scientist in the Research & Development Department. He has worked for the assignee in the field of transdermal drug delivery systems since 1993, and is a named inventor on numerous patents and patent applications in the field of transdermal drug delivery systems.

Although claims 14, 21 and 27-29 are rejected as allegedly anticipated by Kanios I (US 2006/0078601), Mr. Nguyen attests that Kanios I does not describe "monolithic" transdermal drug delivery systems, as recited in the instant claims.

Mr. Nguyen explains in ¶ 5 of his declaration that the person of ordinary skill in the art would understand that the instant claims are directed to "monolithic" systems that do "not include any other additional layers except a backing layer and/or a release liner," and do "not contain any other layers -- be they adhesive or non-adhesive layers, or layers that affect drug delivery, such as an additional rate-controlling polymer layer, rate-controlling membrane, or drug reservoir layer."

Mr. Nguyen explains in ¶ 6 of his declaration that Kanios I describes "multi-layered transdermal drug delivery systems that include at least two polymeric layers (in addition to a protective backing and/or release liner)." For example, Mr. Nguyen points out that Kanios I at paragraphs [0013] – [0015], [0043], [0058], [0089] – [0093], [0101] – [0111], [0117] – [0118], and Figures 1-2 describes multilayer systems. Nguyen Declaration, ¶6. As Mr. Nguyen attests, "Kanios I as a whole is focused on the use of the second polymeric non-drug containing **layer to control drug delivery and pharmacokinetic profiles."** Nguyen Declaration, ¶6. Thus, Kanios I does not describe "monolithic" transdermal drug delivery systems, as recited in the instant claims.

Mr. Nguyen addresses the comment in the Advisory Action noting that paragraph [0014] of Kanios I states that its "agent-carrier composition" may comprise "one layer," and explains that "that does not mean that the systems of Kanios I as a whole are 'monolithic.'" Nguyen Declaration, ¶7. To the contrary, Mr. Nguyen notes that "the very same paragraph of Kanios I that discusses the second non-drug containing polymer layer that makes the systems of Kanios I multilayer systems, not monolithic systems." Nguyen Declaration, ¶7 (citing Kanios I, paragraph [0014], first, third and sixth sentences). Thus, as Mr. Nguyen explains, "even when the carrier composition of Kanios I is comprised of only a single layer, the systems of Kanios I will include

another polymeric layer (the non-drug containing polymeric layer), plus the protective backing and release liner (which is removed prior to use)." Nguyen Declaration, ¶7.

Mr. Nguyen also attests that Kanios I does not describe systems with greater than 0.156 mg/cm^2 estradiol, as recited in some of the rejected claims. In this regard, Mr. Nguyen addresses the citation in the final Office Action of paragraph [0117] of Kanios I for allegedly describing a system with greater than 0.156 mg/cm^2 estradiol, and explains that "that section of Kanios I does not describe a system with greater than 0.156 mg/cm^2 estradiol." Nguyen Declaration, ¶9. As Mr. Nguyen notes, "Paragraph [0117] of Kanios I relates to its working examples, and describes the 'drug-loaded carrier compositions' used to prepare the systems used in the examples." Nguyen Declaration, ¶9. As Mr. Nguyen explains, the details provided in this paragraph indicate that "the amount of estradiol per unit area was 0.1 mg/cm^2 (2% of 5 mg/cm^2 = 0.1 mg/cm^2)," which is "not 'greater than 0.156 mg/cm^2 estradiol,' as specified in some claims of the Application." Nguyen Declaration, ¶9.

Mr. Nguyen also addresses the statement in the Advisory Action that Kanios I "teaches that the drug containing layer is present at a coat weight of 5 mg/cm^2 and the non-drug containing layer can be present from 2.5 mg/cm^2 to about 15 mg/cm^2, thus the total polymer matrix coat weight is greater than the instantly claimed coat weight," noting that the Examiner "appears to be citing paragraph [0090] of Kanios I for the coat weight of the non-drug containing layer." Nguyen Declaration, ¶10. As Mr. Nguyen explains, "[i]t is true that the systems of Kanios I include at least one additional layer that will contribute to the total weight of the systems, but the presence of an additional non-drug containing polymer layer will not affect the amount of estradiol ***per unit area***." Nguyen Declaration, ¶10. Rather, "[e]ach of Examples 1-6 of Kanios I relate to systems made from the same drug-loaded carrier composition containing 2% estradiol and applied at 5 mg/cm^2," such that "each system had 0.1 mg /cm^2 estradiol." Nguyen Declaration, ¶10. As Mr. Nguyen emphasizes, "[t]he fact that the systems also included a non-drug containing layer applied at 5.0 (Examples 1-3) or 2.5, 5.0 or 10.0 (Examples 4-6) mg/cm^2 does not impact the amount of estradiol per unit area." Nguyen Declaration, ¶10. Thus, as Mr.

Nguyen attests, "a person of ordinary skill in the field of transdermal drug delivery at the time of the 2008 priority date of the application would not have understood Kanios I to describe a transdermal drug delivery system having a polymer matrix layer that includes greater than 0.156 mg/cm^2 estradiol, as specified in the claims of the Application."

As explained previously, the absence from Kanios I of any teaching or suggestion that the amount of drug per unit area has any criticality with regard to drug flux is consistent with the statements in the instant specification regarding the contribution of the invention over the state of the art. It is apparent from the specification as a whole that the invention relates to the amount of estradiol per unit area, and that it was surprising and unexpected that increasing the amount of estradiol per unit area resulted in an increased flux per unit area. As discussed in the specification, the surprising and unexpected discovery relating to the impact of the amount of estradiol per unit area has permitted the development of transdermal drug delivery systems that achieve comparable drug delivery from a significantly smaller system. As discussed in the specification and recited in specific claims, a system according to the invention can be only 60% the size of a prior art composition that includes only 0.156 mg/cm^2 estradiol and yet achieve comparable, therapeutically effective drug flux, such as a drug flux of greater than 0.01 $mg/cm^2/day$. This surprising and unexpected benefit has commercial and clinical significance from the perspectives of at least patient preference and patient compliance.

There is no teaching or suggestion in Kanios I or any other reference of record that teaches or suggests a method as claimed using a monolithic transdermal drug delivery system as claim, consisting of (i) a backing layer and (ii) 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 includes greater than 0.156 mg/cm^2 estradiol, let alone any reasonable expectation that such a system could achieve an estradiol flux that is greater than 0.01 mg/cm2/day, based on the active surface area, as recited in the claims. For at least these reasons, the § 102 rejection based on Kanios I should be withdrawn.

§ 103 Rejections

Claims 14 and 21-29 are rejected as allegedly obvious in view of Kanios I and Kanios II (US 6,638,528). Claims 14, 15, and 30 are rejected as allegedly obvious in view of Kanios I and Nuwayser (US 4,624,665). Applicant traverses these rejections in as much as they may be applied to the instant claims.

The obviousness rejections rely on Kanios I for allegedly teaching the subject matter of the independent claims, which it does not, as shown above. Combining Kanios I with Kanios II and/or Nuwayser does not overcome this deficiency, as no combination of the cited references teaches or suggests a monolithic transdermal drug delivery systems for estradiol consisting of (i) a backing layer and (ii) a single polymer matrix layer comprising greater than 0.156 mg/cm^2 estradiol that achieves an estradiol flux that is greater than 0.01 $mg/cm^2/day$. Applicant therefore respectfully urges reconsideration and withdrawal of the prior art rejections based on Kanios I and Kanios II and/or Nuwayser.

Conclusion

The application is believed to be in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

Respectfully submitted,

Date September 5, 2014

By _____

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Courtenay C. Brinckerhoff
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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 a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553,972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

DECLARATION UNDER 37 CFR 1.132

I, Viet Nguyen, hereby declare and say that:

1. I am currently employed as a Principle Scientist in the Research & Development Department of Noven Pharmaceuticals, Inc., the assignee of U.S. patent application 13/553,972 (the "Application"). I earned a B.S. in Chemical Engineering from the University of Florida in 1993. Since 1993, I have worked at Noven in the field of transdermal drug delivery systems including Noven's DOT-matrix patches, and was the primary formulator on the team that created the Vivelle-dot® patch -- launched in 1999 as the world's smallest transdermal estrogen patch which had over a 60% market share of the estrogen patch users in 2013, and for which there is still no generic equivalent due to the patch's superior adhesion properties. I am a named inventor on numerous patents and patent applications in the field of transdermal drug delivery systems.

2. I provide the following statements which I understand may be used to support the Application. Any opinions expressed here are based on my knowledge and experience in the field of transdermal drug delivery.

3. I understand that the Application was filed in July of 2012 with a priority claim to July of 2008. I have reviewed the Application and understand that it describes and claims

monolithic transdermal drug delivery systems for estradiol, consisting of (i) a backing layer, (ii) a single polymer matrix layer defining an active surface area and, optionally, (iii) a release liner, wherein the single polymer matrix layer comprises a polymer matrix comprising estradiol as the only drug, wherein the polymer matrix layer 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 (claim 1); monolithic transdermal drug delivery system for estradiol consisting of (i) a backing layer, (ii) a single polymer matrix layer and, optionally, (iii) a release liner, wherein the single polymer matrix layer comprises estradiol as the only drug, 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 (claim 13); methods 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 polymer matrix layer defining an active surface area and comprising a polymer matrix comprising estradiol as the only drug, wherein the polymer matrix 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 (claim 14); methods of making a monolithic transdermal drug delivery system for administering estradiol consisting of (i) a backing layer, (ii) a single polymer matrix layer and, optionally, (iii) a release liner, comprising forming a 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 polymer matrix to a support layer to form a single polymer matrix layer such that the polymer matrix layer includes greater than 0.156 mg/cm^2 estradiol (claim 16); and methods for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system for estradiol consisting of (i) a backing layer and (ii) a single polymer matrix layer comprising estradiol as the only drug, 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 (claim 30).

4. I have reviewed the Office Action mailed March 5, 2014, the Advisory Action mailed July 23, 2014, and US 2006/0078601 ("Kanios I") cited by the Patent Office Examiner. I understand that the Patent Office Examiner believes that Kanios I describes transdermal drug delivery systems that are the same as those claimed in the Application. However, the Examiner's position appears to rest on at least two factual misunderstandings of the disclosure of Kanios I. For example, the Patent Office Examiner appears to believe that Kanios I describes a monolithic system and that Kanios I describes a system with the amount of estradiol per unit area specified in certain claims of the application. Neither is true.

Kanios I Does Not Describe Monolithic Transdermal Drug Delivery Systems

5. As recognized in the Advisory Action, the claims of the Application relate to transdermal drug delivery systems (TDDSs) that are "monolithic." Although a polymer matrix comprising a pressure-sensitive adhesive can serve as one or more layers of a multi-layer TDDS as noted for certain embodiments described in the Application, when the embodiment is "monolithic" as defined in paragraphs [0034] and [0037] in conjunction with that embodiment's precise descriptions in paragraphs [0071-0072], the TDDS does not include any other additional layers except a backing layer and/or a release liner. This definition and description comports with the understanding in the field of transdermal drug delivery of what constitutes a "drug-in-adhesive" TDDS, meaning a transdermal patch having a single polymeric layer that contains the drug and that also functions as the adhesive layer to attach the TDDS to the skin after removal of the release liner which protects the drug-in-adhesive layer prior to use. Accordingly, one of ordinary skill in the transdermal art would clearly and fully understand that a "monolithic transdermal drug delivery system for estradiol consisting of (i) a backing layer, (ii) a single polymer matrix layer and, optionally, (iii) a release liner" as described and claimed in the Application does not contain any other layers -- be they adhesive or non-adhesive layers, or layers that affect drug delivery, such as an additional rate-controlling polymer layer, rate-controlling membrane, or drug reservoir layer.

6. In contrast, Kanios I describes multi-layered transdermal drug delivery systems that include at least two polymeric layers (in addition to a protective backing and/or release liner): (i) a polymeric drug-loaded carrier layer and (ii) a polymeric non-drug containing coating layer. *See, e.g.*, Kanios I at paragraphs [0013] – [0015], [0043], [0058], [0089] – [0093], [0101] – [0111], [0117] – [0118], and Figures 1-2. With reference to Figure 1, the systems of Kanios I include (i) protective backing **20**, (ii) non-drug containing polymeric layer **18**, (iii) drug-containing carrier layer **12**, and (iv) release liner **15.** Figure 2 illustrates a manufacturing process, showing an intermediate release liner **22** being removed from a composite comprised of (i) protective backing **20** and (ii) non-drug containing polymeric layer **18**, which are then applied to a composite comprised of (iii) drug-containing carrier layer **12** and **(iv)** release liner **15**. As reflected in paragraphs [0013] – [0015], [0089] – [0093], and in the examples, Kanios I as a whole is focused on the use of the second polymeric non-drug containing **layer to control drug delivery and pharmacokinetic profiles.** As noted above, the definition and description of a "monolithic transdermal drug delivery system for estradiol consisting of" in the Application makes clear that such embodiment does not contain a "rate-controlling membrane" (paragraph [0034]) or any other layers that affect drug delivery, ***such as an additional rate-controlling polymer layer***, rate-controlling membrane, or drug reservoir layer (paragraph [0072]) but which are the embodiments described in Kanios I.

7. In the Advisory Action, the Patent Office Examiner notes that paragraph [0014] of Kanios I states that its "agent-carrier composition" may comprise "one layer," but that does not mean that the systems of Kanios I as a whole are "monolithic." To the contrary, the very same paragraph of Kanios I that discusses the second non-drug containing polymer layer that makes the systems of Kanios I multilayer systems, not monolithic systems. *See, e.g.*, Kanios I, paragraph [0014], first, third and sixth sentences. Thus, even when the carrier composition of Kanios I is comprised of only a single layer, the systems of Kanios I will include another polymeric layer (the non-drug containing polymeric layer), plus the protective backing and release liner (which is removed prior to use).

8. For at least these reasons, a person of ordinary skill in the field of transdermal drug delivery at the time of the 2008 priority date of the application would not have

understood Kanios I to describe a "monolithic" transdermal drug delivery system as specified in the claims of the Application.

Kanios I Does Not Describe Systems With Greater Than 0.156 mg/cm^2 Estradiol

9. Certain claims of the Application specify that the systems include greater than 0.156 mg/cm^2 estradiol. In both the Office Action and the Advisory Action, the Patent Office Examiner appears to believe that Kanios I describes compositions with greater than 0.156 mg/cm^2 estradiol, but that is not correct.

10. The Office Action cites paragraph [0117] of Kanios I for describing a system with greater than 0.156 mg/cm^2 estradiol, but that section of Kanios I does not describe a system with greater than 0.156 mg/cm^2 estradiol. Paragraph [0117] of Kanios I relates to its working examples, and describes the "drug-loaded carrier compositions" used to prepare the systems used in the examples. As set forth in paragraph [0117], the compositions were made from "20% acrylate pressure-sensitive adhesive (GMS 788), 56% silicone pressure-sensitive adhesive (BIO-PSA-4502), 8% soluble povidone, 6% oleyl alcohol, 8% dipropylene glycol and 2% estradiol." The compositions were applied "at [a] coat weight of about 5 mg/cm^2," meaning that the amount of estradiol per unit area was 0.1 mg/cm^2 (2% of 5 mg/cm^2 = 0.1 mg/cm^2). That is not "greater than 0.156 mg/cm^2 estradiol," as specified in some claims of the Application.

11. In the Advisory Action, the Patent Office Examiner states that Kanios I "teaches that the drug containing layer is present at a coat weight of 5 mg/cm^2 and the non-drug containing layer can be present from 2.5 mg/cm^2 to about 15 mg/cm^2, thus the total polymer matrix coat weight is greater than the instantly claimed coat weight." (The Patent Office Examiner appears to be citing paragraph [0090] of Kanios I for the coat weight of the non-drug containing layer. The examples of Kanios I report systems with non-drug containing polymers layers applied at coat weights of 2.5, 5.0 or 10.0 mg/cm^2.) It is true that the systems of Kanios I include at least one additional layer that will contribute to the total weight of the systems, but the presence of an additional non-drug containing polymer layer will not affect the amount of estradiol ***per unit area***. Each of Examples

1-6 of Kanios I relate to systems made from the same drug-loaded carrier composition containing 2% estradiol and applied at 5 mg/cm^2. That is, each system had 0.1 mg /cm^2 estradiol. The fact that the systems also included a non-drug containing layer applied at 5.0 (Examples 1-3) or 2.5, 5.0 or 10.0 (Examples 4-6) mg/cm^2 does not impact the amount of estradiol per unit area.

12. For at least these reasons, a person of ordinary skill in the field of transdermal drug delivery at the time of the 2008 priority date of the application would not have understood Kanios I to describe a transdermal drug delivery system having a polymer matrix layer that includes greater than 0.156 mg/cm^2 estradiol, as specified in the claims of the Application.

13. 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.

9/5/14
Date

Viet Nguyen

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

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 of a first Office action after the filing of a RCE.

RELEVANCE OF LISTED DOCUMENTS

The listed documents were cited during prosecution of the corresponding Japanese application.

English-language translations are provided for the listed documents.

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 Sep 5, 2014

By _____

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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**	13/553972
Date Submitted: September 5, 2014				**Filing Date**	7/20/2012
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	1611
				Examiner Name	Melissa L. Javier
Sheet	1	of	1	Attorney Docket Number	041457-0992

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]
	A1	NAGAI ET AL., "New Drug Delivery Systems," Kurashiki Printing Co. Ltd., Academic Document 2009-00984-005, published January 31, 2000.	√
	A2	SEKINE ET AL., "New Cosmetic Handbook," Nikko Chemical Co. Ltd., et al., Academic Documents 2008-02180-001, published October 30, 2006.	√

Examiner Signature		Date Considered	

Electronic Patent Application Fee Transmittal

Application Number:	13553972
Filing Date:	20-Jul-2012
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-0992

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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:				
Extension - 3 months with $0 paid	1253	1	1400	1400

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**2600**

Electronic Acknowledgement Receipt

EFS ID:	20056923
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	05-SEP-2014
Filing Date:	20-JUL-2012
Time Stamp:	13:59:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$2600
RAM confirmation Number	221
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		rceresponseids.pdf	623023 ee25411c28953ab5252242504b71ff379b0cf814	yes	26

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Request for Continued Examination (RCE)	1	5
Amendment Submitted/Entered with Filing of CPA/RCE	6	17
Affidavit-traversing rejectns or objectns rule 132	18	23
Transmittal Letter	24	25
Information Disclosure Statement (IDS) Form (SB08)	26	26

Warnings:

Information:

2		refs.pdf	455499 8aff34afb8acd464f1f4dcf7dbb11e4f552fd201	yes	19

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Non Patent Literature	1	11
Non Patent Literature	12	19

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	32325 70ba2ad38a43db060d15ca8350644ab200b9be23	no	2

Warnings:

Information:

Total Files Size (in bytes):	1110847

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
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/553,972	Filing Date 07/20/2012	☐ 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 **09/05/2014**

	(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))	* 26	Minus	** 26	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 5	Minus	***5	= 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.

LIE
/YOLANDA CHADWICK/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Appl. No.: 13/553,972

Filing Date: 7/20/2012

Examiner: Melissa L. Javier

Art Unit: 1611

Confirmation Number: 3635

AMENDMENT ACCOMPANYING TRACK I REQUEST

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

Commissioner:

This amendment supports the Request for Track I expedited examination submitted herewith.

Amendments to the claims are set forth in the **Listing of Claims** which begins on page 2 of this document.

Remarks/Arguments begin on page 6 of this document.

Listing of Claims:

1. (Withdrawn) A monolithic transdermal drug delivery system for estradiol, consisting of (i) a backing layer, (ii) a single polymer matrix layer defining an active surface area and, optionally, (iii) a release liner, wherein the single polymer matrix layer_ comprises a polymer matrix comprising estradiol as the only drug, wherein the polymer matrix layer 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. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The transdermal drug delivery system of claim 3, wherein the penetration enhancer comprises oleyl alchol.

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

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

7. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) 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. (Canceled)

11. (Withdrawn—Currently Amended) The transdermal drug delivery system of claim [[3]] 1, wherein the polymer matrix has a coat weight of greater than about 10 mg/cm^2.

12. (Canceled)

13. (Canceled)

14. (Previously Presented) 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 polymer matrix layer defining an active surface area and comprising a polymer matrix comprising estradiol as the only drug, wherein the polymer matrix 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. (Original) 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. (Withdrawn) A method of making a monolithic transdermal drug delivery system for administering estradiol consisting of (i) a backing layer, (ii) a single polymer matrix layer

and, optionally, (iii) a release liner, comprising forming a 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 polymer matrix to a support layer to form a single polymer matrix layer such that the polymer matrix layer includes greater than 0.156 mg/cm^2 estradiol.

17. (Withdrawn) 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. (Canceled)

19. (Withdrawn) 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. (Canceled)

21. (Previously Presented) The method of claim 14, wherein the polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble polyvinylpyrrolidone (PVP).

22. (Previously Presented) The method of claim 14, 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.

23. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alchol.

24. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises dipropylene glycol.

25. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

26. (Previously Presented) The method of claim 22, 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.

27. (Currently Amended) The method of claim [[22]] 14, wherein the polymer matrix has a coat weight of greater than about 10 mg/cm^2.

28. (Previously Presented) The method of claim 14, 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.

29. (Previously Presented) The method of claim 14, 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.

30. (Previously Presented) A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system for estradiol consisting of (i) a backing layer and (ii) a single polymer matrix layer comprising estradiol as the only drug, 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.

REMARKS

This Amendment supports the Request for Track I expedited examination submitted herewith.

Claim 13 is canceled without prejudice or disclaimer, to comply with the requirement for Track I expedited examination that the application contain no more than 4 independent claims. Claims 11 and 27 are amended to revise their dependencies. These amendments are made without prejudice or disclaimer and do not introduce any new matter.

Upon entry of these amendments, claims 1-9, 11, 14-17, 19 and 21-30 will remain pending. Of these, claims 14, 15 and 21-30 are under active examination.

Applicant again asks for reconsideration of the Restriction Requirement, at least with respect to Group I and elected Group II, because examining the subject matter of these groups of claims would not impose a serious burden on the Examiner. Although Group I is directed to monolithic transdermal drug delivery systems *per se* while Group II is directed to methods using them, this difference does not give rise to a significant examination burden. Applicant also notes that both product claims and method claims were granted in the parent patent, further showing that no significant examination burden is required to examine both types of claims in a single application. Applicant therefore respectfully urges reconsideration and withdrawal of the Restriction Requirement at least with respect to Group I and Group II, and examination of at least claims 1-9, 11, 14, 15, and 21-30.

Applicant believes that the application is in condition for allowance for at least the reasons set forth in the previous response. Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

Respectfully submitted,

Date: February 9, 2015

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

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 a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Commissioner:

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

Applicant respectfully requests that the 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 document is being submitted in compliance with 37 CFR §1.97(b), before the mailing of a first Office action after the filing of a RCE.

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: February 9, 2015

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

Substitute for form 1449/PTO				***Complete if Known***	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/553972
				Filing Date	7/20/2012
Date Submitted: February 9, 2015				**First Named Inventor**	Juan Mantelle
				Art Unit	1611
(use as many sheets as necessary)				Examiner Name	Melissa L. Javier
Sheet	1	of	1	Attorney Docket Number	041457-0992

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]
	A1	BENSON, "Transdermal Drug Delivery: Penetration Enhancement Techniques," Current Drug Delivery, Vol. 2, pp. 22-33, 2005.	

Examiner Signature		Date Considered	

Electronic Acknowledgement Receipt

EFS ID:	21443860
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	09-FEB-2015
Filing Date:	20-JUL-2012
Time Stamp:	18:06:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	TrackOne Request	track1.pdf	419635 88b1a3b929e1a107a79d2330818d22225d794a84	no	1
Warnings:					
Information:					

2	Amendment Submitted/Entered with Filing of CPA/RCE	response.pdf	122526 c55a12cc392a335568a557262cd6ee5c208e155e	no	7
Warnings:					
Information:					
3	Transmittal Letter	ids.pdf	98689 de12a346c658cbb56edb91b57bcae7b72e6ed159	no	2
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Form (SB08)	sb08.pdf	93191 38ebf5cbbe8c734eab0ed2bc479b7d058a73f78c	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
5	Non Patent Literature	ref.pdf	9581343 a729c3f8140d2a96454404e144804c9589fc1c6a	no	11
Warnings:					
Information:					
		Total Files Size (in bytes):	10315384		

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.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Juan Mantelle	Nonprovisional Application Number (if known):	13/553972
Title of Invention:	Transdermal Estrogen Device and Delivery		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Courtenay C. Brinckerhoff/	Date 02-09-2015
Name (Print/Typed) Courtenay C. Brinckerhoff	Practitioner Registration Number 37,288

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

☑ *Total of 1 forms are submitted.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 03/12/2015

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
03/12/2015	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

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Doc Code: TRACK1.DENY

Decision Dismissing Request for Prioritized Examination (Track I)	Application No.: 13/553,972

1. THE REQUEST FILED February 9, 2015 IS **DISMISSED** BECAUSE:

A. ☐ The application is not a utility application under 35 U.S.C. 111(a) filed by EFS-Web or a plant application under 35 U.S.C. 111(a) filed by paper:
   i. ☐ The application is a utility application that was not filed by EFS-Web.
   ii. ☐ The application is neither a utility application nor a plant application, but rather is a _____, which is excluded from the Track I program.

B. ☐ The request was not filed with the application or on the same date the application was filed.

C. ☐ One or more of the following fees were not filed with the application or on the same date the application was filed:
   i. ☐ Basic filing fee, as set forth in 37 CFR 1.16(a), or for a plant application, 37 CFR 1.16(c).
   ii. ☐ Search fee, as set forth in 37 CFR 1.16(k), or for a plant application, 37 CFR 1.16(m).
   iii. ☐ Examination fee, as set forth in 37 CFR 1.16(o), or for a plant application, 37 CFR 1.16(q).
   iv. ☐ Publication fee, as set forth in 37 CFR 1.18(d).
   v. ☐ Track I processing fee, as set forth in 37 CFR 1.17(i).
   vi. ☐ Track I prioritized examination fee, as set forth in 37 CFR 1.17(c).

D. ☐ The executed inventor's oath or declaration, **or** an application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) was not filed with the application or on the same date the application was filed.

E. ☒ The application contains or has been amended to contain:
   i. ☒ More than four independent claims.
   ii. ☐ More than thirty total claims.
   iii. ☐ One or more multiple dependent claims.

F. ☐ The Track I program has exceeded its limit of 10,000 requests for the current fiscal year.

G. ☐ Other: _____.

2. CONCLUSION

☒ **ALL of the above defect(s) consist only of one or more of items E (i-iii). Applicant is hereby accorded a non-extendable ONE MONTH time period from the mailing date of this Decision to (1) correct the subject defect(s) and (2) file a petition under 37 CFR 1.181 requesting reconsideration of prioritized examination. If no such petition is timely filed, the application will not undergo prioritized examination.**

-OR-

☐ **The application will not undergo prioritized examination, because the request was not accompanied by all of the required items.**

Telephone inquiries with regard to this decision should be directed to JoAnne Burke at 571-272-4584.

/JoAnne Burke/
[*Signature*]

Paralegal Specialist, Office of Petitions
(Title)

Office of Petitions: Routing Sheet

Application No. 13/553,972

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

- [ ] **GRANTED**
- [X] **DISMISSED**
- [ ] **DENIED**

Office of Petitions: Decision Count Sheet

Mailing Month

Application No. 13553972

For US serial numbers: enter number only, no slashes or commas. Ex: 10123456

For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official: BURKE, JOANNE

Count (1) - Palm Credit 13/553,972

Decision: DISMISSED

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type: 643 - Track One request

Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

If more than 3 decisions, attach 2nd count sheet & mark this box ☐

Printed on:

Office of Petitions Internal Document - Ver. 5.0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553,972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

PETITION UNDER 37 CFR 1.181
REQUESTING RECONSIDERATION OF DECISION ON TRACK I REQUEST

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

Commissioner:

Applicant hereby requests reconsideration of the Decision issued March 12, 2015, dismissing the Request for Prioritized Examination (Track I) filed February 9, 2015 in the captioned application.

The Decision dismisses the Track I Request because the application allegedly contains more than 4 independent claims. However, the Amendment Accompanying Track I Request filed concurrently with the Track 1 Request amended the claims to cancel independent claim 13, such that the application would not contain more than 4 independent claims, as explained in the Remarks at page 6 pf the Amendment. Thus, the application satisfied this requirement when the Track I Request was filed.

To further clarify the record, Applicant submits herewith a Fee Worksheet (PTO/SB/06), which details the history of the claims presented in the application, and shows that the application contains no more than 4 independent claims.

In view of the foregoing, Applicant respectfully requests reconsideration of the Decision dismissing the Track I Request, and respectfully urges that the Request for Prioritized Examination (Track I) be approved without further delay.

This petition is timely filed within one month of the March 12, 2015 Decision. Applicant believes that no fee is due; however, the Commissioner is hereby authorized to charge any additional fees which may be required under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741.

Respectfully submitted,

Date March 17, 2015

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

Doc Code: WFEE
Document Description: Fee Worksheet (PTO-875)

PTO/SB/06 (03-13)
Approved for use through 01/31/2014. 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: 13/553,972

■ LARGE ENTITY ☐ SMALL ENTITY ☐ MICRO ENTITY

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))	16 minus 20 =	* 0	x =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	* 0	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))			N/A	
			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

■ LARGE ENTITY ☐ SMALL ENTITY ☐ MICRO ENTITY

APPLICATION AS AMENDED – PART II

AMENDMENT FILED 5/13/2013

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDI-TIONAL FEE ($)
Total (37 CFR 1.16(i))	* 26	Minus	** 20	= 6	x 80. =	480.00
Independent (37 CFR 1.16(h))	* 5	Minus	*** 3	= 2	x 420. =	840.00
Application Size Fee (37 CFR 1.16(s))						
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A	
					TOTAL ADD'L FEE	1320.00

FEES PAID 05/13/2013

AMENDMENT FILED 02/09/2015

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDI-TIONAL FEE ($)
Total (37 CFR 1.16(i))	* 26	Minus	** 26	= 0	x =	0.00
Independent (37 CFR 1.16(h))	* 3	Minus	*** 5	= 0	x =	0.00
Application Size Fee (37 CFR 1.16(s))						
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A	
					TOTAL ADD'L FEE	0.00

* 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.

Electronic Acknowledgement Receipt

EFS ID:	21791313
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	17-MAR-2015
Filing Date:	20-JUL-2012
Time Stamp:	12:59:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	TrackOne Request	Reqrecontrack1.pdf	99152 1f00e3d13e42f5e1feda6f43f24bf7336225d e1c	no	2

Warnings:	
Information:	

2	Fee Worksheet (SB06)	feesheet.pdf	1436193 a6954f593b2aaf11dc3ac4950c8ed1ce4e09d501	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	1535345

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.

Electronic Patent Application Fee Transmittal

Application Number:	13553972
Filing Date:	20-Jul-2012
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-0992

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**4000**

Electronic Acknowledgement Receipt

EFS ID:	21865668
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	24-MAR-2015
Filing Date:	20-JUL-2012
Time Stamp:	16:49:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$4000
RAM confirmation Number	3463
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Fee Worksheet (SB06)	fee-info.pdf	30688 5a0e05e7febf5e9ea4323c08e68dd7b37079667a	no	2

Warnings:

Information:

Total Files Size (in bytes):	30688

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.

Electronic Patent Application Fee Transmittal

Application Number:	13553972
Filing Date:	20-Jul-2012
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-0992

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:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**140**

Electronic Acknowledgement Receipt

EFS ID:	21865792
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	24-MAR-2015
Filing Date:	20-JUL-2012
Time Stamp:	16:54:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$140
RAM confirmation Number	3551
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Fee Worksheet (SB06)	fee-info.pdf	30462 4072c3676d9c113dead2cb837f2f883db6f740d9	no	2

Warnings:

Information:

Total Files Size (in bytes):	30462

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 03/25/2015

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
03/25/2015	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

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Doc Code:
TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/553,972

The petition, filed March 17, 2015, requesting reconsideration of the decision, mailed March 12, 2015, which initially dismissed the Request for Prioritized Examination, Track 1, is **GRANTED**.

1. THE REQUEST FILED February 9, 2015 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;

C. filing a **request for continued examination**;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to JoAnne Burke at 571-272-4584.

/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

Office of Petitions: Decision Count Sheet

Mailing Month

Application No. 13553972

For US serial numbers: enter number only, no slashes or commas. Ex: 10123456
For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official: BURKE, JOANNE

Count (1) - Palm Credit 13/553,972

Decision: GRANT

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: 643 - Track One request

Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

If more than 3 decisions, attach 2nd count sheet & mark this box ☐

Printed on:

Office of Petitions Internal Document - Ver. 5.0

Office of Petitions: Routing Sheet

Application No. 13/553,972

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

- [X] **GRANTED**
- [ ] **DISMISSED**
- [ ] **DENIED**

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 05/05/2015

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
05/05/2015	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. 13/553,972	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 *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 *3/17/2015*.

☐ 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) *1-9,11,14-17,19 and 21-30* is/are pending in the application.

5a) Of the above claim(s) *1-9,11,16,17 and 19* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *14, 15, and 21-30* 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.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/5/2014 has been entered.

Status of Claims

The amendments and arguments filed on 2/9/2015 are acknowledged and have been fully considered. Claims 1-9, 11, 14-17, 19, 21-30 are now pending. Claims 10, 12, 13, 18, and 20 are canceled; claims 11 and 27 are amended; claims 1-9, 11, 16, 17, and 19 are withdrawn; no claims are new.

Claims 14, 15, and 21-30 will be examined on the merits herein.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed 2/9/2015 and 9/5/2014 have been considered by the examiner.

Claim Rejections - 35 USC § 103

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 of this title, 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 14, 15, 21-26, and 28-30 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 teaches application of the composition to the skin.

Kanios does not teach greater than 0.156mg/cm^2 of estradiol in the matrix or explicitly teach an estradiol flux that is greater than 0.01mg/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 claims 14, 21-26, and 29, 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 claims 15, a person of ordinary skill in the art at the time that the invention was made would utilize the size of the patch taught by Nuwayser in the system taught by Kanios et al. One would be motivated to do so as the transdermal patches with the surface area taught by Nuwayser were successfully used for the transdermal delivery of estradiol.

Regarding claim 28, 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 30, 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. Further, a person of ordinary skill in the art at the time that the invention was made would utilize the size of the patch taught by Nuwayser in the system taught by Kanios et al. One would be motivated to do so as the transdermal patches with the surface area taught by Nuwayser were successfully used for the transdermal delivery of estradiol.

Claims 14, 15, and 21-30 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Kanios (US 6638528) and Nuwayser (US 4624665), and further in view of Miller et al. (US 2009/0041831).

The teachings of Kanios and Nuwayser have been set forth above.

Kanios and Nuwayser do not teach that the polymer matrix has a coat weight of greater than about 10 mg/cm^2.

Miller et al. teaches silicone pressure sensitive adhesive formulations and their use in making devices for improved transdermal delivery (see [0002]). Miller et al. teaches that the devices are monolithic for improved transdermal administration (see [0019]). Miller et al. teaches in examples that the composition is cast with a coat weight from 90-110g/m^2 (9-11mg/cm^2) (see [0109]-[0115]).

Regarding claim 27, it would have been obvious to a person of ordinary skill in the art at the time that the invention was made to utilize a coat weight of 90-110g/m^2 (9-11mg/cm^2) as taught by Miller et al. in the patch of Kanios and Nuwayser. One would be motivated to do so with a reasonable expectation of success as Miller et al. teaches that monolithic transdermal patches for the delivery of an active agent can be successfully formed using a polymer coat weight of 90-110g/m^2 (9-11mg/cm^2). MPEP 2144.05 states that "[i]n the case where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists" quoting *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976).

Response to Arguments

Applicant's arguments filed 2/9/2015 have been fully considered but they are not persuasive in view of the modified grounds of rejection set forth above.

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 claims at issue 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); and *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 a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form 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

http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 14, 15, 27, 29, and 30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 11 and 12 of U.S. Patent No. 8231906. Although the claims at issue are not identical, they are not patentably distinct from each other because claims 11 and 12 of U.S. Patent No. 8231906 are drawn to a method for administering estradiol, con to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system 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/cm^2 and 15 mg/cm^2, includes greater than 0.156 mg/cm^2 estradiol, and achieves an estradiol flux that is greater than 0.01 mg/cm2/day, based on the active surface area and 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.

Conclusion

No claims are allowed.

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.

/BETHANY BARHAM/
Supervisory Patent Examiner, Art Unit 1611

Melissa Javier
Examiner
Art Unit 1611

Notice of References Cited	Application/Control No. 13/553,972	Applicant(s)/Patent Under Reexamination MANTELLE, JUAN	
	Examiner Melissa Javier	Art Unit 1611	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2009/0041831	02-2009	Miller et al.	424/448
	B	US-			
	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	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.

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/553972
Date Submitted: February 9, 2015				**Filing Date**	7/20/2012
				First Named Inventor	Juan Mantelle
				Art Unit	1611
(use as many sheets as necessary)				Examiner Name	Melissa L. Javier
Sheet	1	of	1	Attorney Docket Number	041457-0992

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]
	A1	BENSON, "Transdermal Drug Delivery: Penetration Enhancement Techniques," Current Drug Delivery, Vol. 2, pp. 22-33, 2005.	

Examiner Signature	/Melissa Javier/	Date Considered	04/29/2015

4815-5826-2561.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J./

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/553972
Date Submitted: September 5, 2014				**Filing Date**	7/20/2012
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	1611
				Examiner Name	Melissa L. Javier
Sheet	1	of	1	Attorney Docket Number	041457-0992

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]
	A1	NAGAI ET AL., "New Drug Delivery Systems," Kurashiki Printing Co. Ltd., Academic Document 2009-00984-005, published January 31, 2000.	√
	A2	SEKINE ET AL., "New Cosmetic Handbook," Nikko Chemical Co. Ltd., et al., Academic Documents 2008-02180-001, published October 30, 2006.	√

Examiner Signature	/Melissa Javier/	Date Considered	04/29/2015

4841-0657-4110.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J./

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2	"6638528".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 16:45
L2	4	"4624665".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 17:16
L3	3	"20090041831".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:21
L4	13486	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L5	4676	L4 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L6	749	L5 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L7	31	L6 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L8	234	L6 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L9	46	L6 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L10	82	L4 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L11	240	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L12	33	L11 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L13	135	L11 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L14	176	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L15	36	L14 NOT L11	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L16	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2015/04/29 18:33

L17	581	L4 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2015/04/29 18:33
L18	105	L6 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2015/04/29 18:33
L19	13486	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L20	4676	L19 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L21	749	L20 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L22	31	L21 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L23	234	L21 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L24	46	L21 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L25	82	L19 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L26	240	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L27	33	L26 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L28	135	L26 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L29	176	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L30	36	L29 NOT L26	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/04/29 18:33
L31	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2015/04/29 18:33
L32	581	L19 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2015/04/29 18:33
L33	105	L21 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2015/04/29 18:33

EAST Search History (Interference)

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4/29/2015 6:38:15 PM
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13553972	MANTELLE, JUAN
	Examiner	Art Unit
	MELISSA JAVIER	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 history)	8/25/2013	MJ
Inventor search in EAST	8/25/2013	MJ
Google Scholar search (keywords used: transdermal monolithic estradiol)	8/25/2013	MJ
Updated EAST search	2/21/2014	MJ
Updated Google Scholar search	2/21/2014	MJ
Updated EAST search	4/29/2015	MJ
Updated Google Scholar search	4/29/2015	MJ

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/M.J./ Examiner.Art Unit 1611	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553,972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

AMENDMENT AND REQUEST FOR RECONSIDERATION UNDER 35 USC § 1.111

MAIL STOP: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This is a reply to the Office Action mailed May 5, 2015 in the captioned application, which is being examined under the Track I expedited examination program. The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application or credit any overpayment to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Amendments to the claims are set forth in the **Listing of Claims** which begins on page 2..

Remarks/Arguments begin on page 5.

Listing of Claims:

Claims 1-13 (Cancelled)

14. (Currently Amended) 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 [[a]] 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 achieves an estradiol flux that is greater than 0.01 mg/cm^2/day, based on the active surface area.

15. (Original) 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. (Withdrawn—Currently Amended) 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 [[a]] 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.

17. (Withdrawn) 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. (Canceled)

19. (Canceled)

20. (Canceled)

21. (Currently Amended) The method of claim 14, wherein the adhesive polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble polyvinylpyrrolidone (PVP).

22. (Currently Amended) The method of claim 14, 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.

23. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alchol.

24. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises dipropylene glycol.

25. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

26. (Previously Presented) The method of claim 22, 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.

27. (Canceled)

28. (Currently Amended) The method of claim 14, 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.

29. (Currently Amended) The method of claim 14, 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.

30. (Currently Amended) A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system for estradiol consisting of (i) a backing layer and (ii) a single adhesive polymer matrix layer comprising estradiol as the only drug and having a coat weight of greater than about 10 mg/cm^2, 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.

REMARKS

Applicant respectfully requests reconsidering in view of the foregoing amendments and the following remarks

Status Of The Claims

Claims 1-9 and 11 are canceled without prejudice or disclaimer as being drawn to non-elected subject matter.

Independent claim 14 is amended to recite specific embodiments, e.g., where the polymer matrix is an adhesive polymer matrix and has a coat weight of greater than about 10 mg/cm^2. Parallel amendments are made to withdrawn independent claim 16 and independent claim 30. Conforming amendments are made to dependent claims. These embodiments are described throughout the specification as filed, and in previous claim 27. In view of these amendments, claims 19 and 27 are canceled without prejudice or disclaimer. These amendments are made without prejudice or disclaimer, and Applicant reserves the right to pursue claims directed to any canceled subject matter..

Upon entry of these amendments, claims 14-17, 21-26, and 28-30 will remain pending. Of these, claims 14, 15 and 21-26, and 28-30 are under active examination. Withdrawn claims 16 and 17 are retained as subject to rejoining.

Patent Office Interview

Applicant thanks Examiners Javier and Barham for the courtesies extended during the Patent Office Interview on June 10, 2015. Applicant's statement of the substance of the interview is provided here. Applicant's representative discussed the claimed subject matter, and explained that the cited references do not teach or suggest a monolithic transdermal drug delivery system as recited in the claims. The Examiners suggested amending the claims to recite specific embodiments regarding the coat weight of the polymer matrix. Such amendments are reflected in the foregoing claim amendments which incorporate the subject matter of claim 27 into claim 14,

and make parallel amendments to the other claims. Thus, Applicant believes that the pending claims will be found to be in condition for allowance. Nevertheless, to provide a complete record, Applicant addresses below the §103 rejection raised in the Office Action.

Rejections Under 35 USC § 103

Claims 14, 15, 21-26 and 28-30 were rejected for alleged obviousness over the combination of Kanios (U.S. 6,638,528) and Nuwayser (U.S. 4,624,665), and for alleged obviousness over the combination of Kanios, Nuwayser and Miller (US 2009/0041831). Applicant respectfully traverses these rejections in as much as they may be applied to the instant claims.

As discussed during the Patent Office Interview, none of the cited references teach or suggest that the amount of drug per unit area of a monolithic polymer matrix-type transdermal drug delivery system as claimed is a result-effective variable for drug flux (e.g., drug delivery rate). Indeed, as discussed in the specification, Applicants were surprised by the discovery that increasing the amount of estradiol per unit area resulted an increased rate of drug delivery per unit area in the context of the claimed transdermal drug delivery systems. As explained in the specification, prior to the invention increasing coat weight was thought to provide delivery over a longer period of time, but it was not known that increasing the amount of drug per unit area could increase the drug delivery rate.

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 improve 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).

The unexpected nature of the invention may be further appreciated when it is understood that polymer matrix-type drug transdermal drug delivery systems already are formulated with much more drug than is delivered over their intended periods of use. For example, the prior art Vivelle-Dot® products deliver only about 22% of their drug content over their intended period of use:

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.

Since the systems already include a large excess of drug than is delivered over the intended delivery period, it was unexpected that increasing the amount of drug per unit area would impact drug delivery rate.

The Vivelle-Dot® products also show that the state of the art used the ***size*** of a system to control drug flux, using larger systems to provide higher daily doses. (This also is reflected in paragraph [0070] of Miller.)

In contrast, the instant specification teaches that drug flux can be increased by increasing the amount of drug per unit area. This is illustrated in Figure 1 of the specification as filed, which compares drug flux from two embodiments of a polymer matrix as recited in the instant claims with drug flux from a Vivelle-Dot® polymer matrix. Although all three of the polymer matrices comprise 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, drug flux from the two polymer matrices within the scope of the claims is greater than drug flux from the Vivelle-Dot® polymer matrix. This impact of the amount of estradiol per unit area could not have predicted or expected from the cited references.

As recognized in the Office Action, Kanios discloses matrix-type transdermal drug delivery systems, but does not teach or suggest a system comprising an adhesive polymer matrix that 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 (as recited in claim 14) or a system that 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 (as recited in claim 30).

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 provide any guidance with regard to the subject matter of the instant claims, which recite monolithic transdermal drug delivery systems 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 achieves an estradiol flux that is greater than 0.01 mg/cm^2/day, based on the active surface area.

As explained during the Patent Office Interview, Nuwayser is directed to a very different type of transdermal drug delivery system than those recited in the instant claims. Where the instant claims recite monolithic transdermal drug delivery systems consisting of (i) a backing layer and (ii) a single adhesive polymer matrix layer, 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 "monolithic" 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 a single 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.

The cited statement in Nuwayser regarding flux rates is based on Feldman (1969) and Schafer (1979) (copies attached), which relate to topically applied ***liquid*** compositions, not adhesive polymer-matrix type compositions as claimed. As discussed during the Patent Office Interview, a person of ordinary skill in the art would not have extrapolated the statement in Nuwayser relating to topically applied liquid compositions to an adhesive polymer-matrix type composition as claimed, because of the different drug delivery principles and mechanisms of action of these systems. For example, Feldmann explains at page 89 that its protocol "comes "as close as possible ... to depositing pure chemical on the skin surface." Indeed, the protocol involved promoting rapid evaporation of the solvent in less than 15 seconds. Similarly, Schaefer states at age 234 that the base (vehicle) should be saturated with the drug ... or should reach a saturated status on the skin by evaporation." In such protocols, therefore, increasing the concentration of drug in the vehicle increases the amount of drug that is ***applied directly to the skin***. That drug flux would increase in that content does not suggest that drug flux would increase by increasing the amount of drug per unit area in an adhesive polymer-matrix type composition that typically already includes a large excess of drug beyond that which is delivered (as shown by the Vivelle-Dot® formulations discussed above).

Even taking the statement in Nuwayser at face value would not suggest the claimed invention, because the concentration of drug in a liquid vehicle 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"). This is because 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 and the coat weight of the polymer matrix. As explained during the Patent Office Interview, applying a polymer matrix having a given concentration of drug over a smaller or larger area (or

using it to form a smaller or larger system) would result in a smaller or larger amount of drug per unit area.

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.

Nuwayser also fails to teach or suggest a monolithic transdermal drug delivery systems having an adhesive polymer matrix layer comprising estradiol as the only drug, 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. In this regard, Applicant emphasizes that Nuwayser's disclosure of a system with a size of 2.4cm^2 is largely irrelevant, because Nuwayser does not teach or suggest a monolithic adhesive polymer matrix-type system having that size, let alone such a system that achieves a drug flux of about 0.0375 mg/day estradiol from such a system.

Although Miller is cited for disclosing a transdermal system having a polymer matrix coat weight of greater than 10 mg/cm^2, Miller is largely irrelevant to the subject matter of the pending claims because its systems comprise fentanyl (not estradiol) suspended in solvated silicone adhesives.

For at least the foregoing reasons, the cited combinations of references fails to teach or suggest the subject matter recited in the pending claims. Applicant therefore respectfully urges reconsideration and withdrawal of the pending obviousness rejections.

Obviousness-Type Double Patenting

Claims 14, 15, 27, 29 and 30 were rejected under the doctrine of obviousness-type double patenting over claims of the parent patent, U.S. Patent No. 8,231,906. Without acquiescing to the merits of this rejection, and solely to expedite allowance, Applicant submits herewith a Terminal Disclaimer to obviate this rejection.

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 invited to contact the undersigned by telephone in order to advance prosecution.

Respectfully submitted,

Date: June 12, 2015

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

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 document is 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 DOCUMENTS

Document A1 is an Office Action which was issued in the co-pending parent application.

Documents A2 and A3 are discussed in the Response being filed concurrently herewith.

FEE

Fees in the amount of $180.00 to cover the fee associated with an information disclosure statement under 37 CFR §1.97(c) 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 submission 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.

Respectfully submitted,

Date June 12, 2015

By

FOLEY & LARDNER LLP
Customer Number: 22428
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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**	13/553972
Date Submitted: June 12, 2015				**Filing Date**	7/20/2012
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	1611
				Examiner Name	Melissa L. Javier
Sheet	1	of	1	Attorney Docket Number	041457-0992

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]
	A1	Office Action issued on 05/20/2015 in application number 14/024,985 (US 2014/0200530)	
	A2	FELDMANN ET AL., "Percutaneous Penetration of Steroids in Man," The Journal of Investigative Dermatology, Vol. 52, No. 1, pp. 89-94, 1969.	
	A3	SCHAEFER ET AL., "Contraception via Topical Application? A Review," Contraception, Vol. 20, No. 3, pp. 225- 236, September 1979.	

Examiner Signature		Date Considered	

Electronic Patent Application Fee Transmittal

Application Number:	13553972
Filing Date:	20-Jul-2012
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-0992

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:	22619012
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	12-JUN-2015
Filing Date:	20-JUL-2012
Time Stamp:	15:39:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	2268
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		responseids.pdf	266310 fe6bf615ffb855c93b42ca5016ee51d09ae697e6	yes	16
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	12	
	Transmittal Letter		13	15	
	Information Disclosure Statement (IDS) Form (SB08)		16	16	
Warnings:					
Information:					
2	Non Patent Literature	a1.pdf	390044 bf2b116971c61dd71c3b548c5bb30842e5d2e084	no	11
Warnings:					
Information:					
3	Non Patent Literature	a2.pdf	3342439 1dc803079fd023b1d537e2ba8fa33b4636157ee8	no	7
Warnings:					
Information:					
4	Non Patent Literature	a3.pdf	2412636 0f8430d243b584045305dda91f5452134acd4c8f	no	12
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30653 00ea4a07e4a17fa9930c74a6398a87d22bb444de	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	6442082		

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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.

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	13553972
Filing Date	20-Jul-2012
First Named Inventor	Juan Mantelle
Attorney Docket Number	041457-0992
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) 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)

8231906

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.

Applicant 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:	13553972
Filing Date:	20-Jul-2012
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-0992

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.: 13553972

Filing Date: 20-Jul-2012

Applicant/Patent under Reexamination: Mantelle et al.

Electronic Terminal Disclaimer filed on June 12, 2015

☒ 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:	22617885
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	12-JUN-2015
Filing Date:	20-JUL-2012
Time Stamp:	16:38:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$160
RAM confirmation Number	3423
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	33419 633528f24442485638dfa967f6fe86e517bbfaee	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30526 e4cd23db1bebd06c7502523d26e3eba5bd45198b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	63945		

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 13/553,972	Filing Date 07/20/2012	☐ 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 **06/12/2015**

	(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))	* 13	Minus	** 26	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***5	= 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.

LIE
/BRENDA J. DENNY/

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 06/15/2015

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
06/15/2015	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

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/553,972	MANTELLE, JUAN	
	Examiner	Art Unit	
	Melissa Javier	1611	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Melissa Javier*.

(2) *Bethany Barham*.

(3) *Courtenay Brinckerhoff*.

(4) *Jay Kolman*.

Date of Interview: *10 June 2015*.

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: *14 and 30*.

Identification of prior art discussed: *Kanios (US 6638528, Nuwayser (US 4624665), and Miller et al. (US2009/0041831)*.

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...)

Applicants briefly described the invention. Applicants discussed the prior art of record. Discussed possible claim amendments such as an adhesive polymer matrix or the addition of a coat weight.

No agreement was reached, and the Examiner's indicated that any amendment would require further search and consideration .

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

/BETHANY BARHAM/
Supervisory Patent 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.

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

22428 7590 10/02/2015

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

EXAMINER
JAVIER, MELISSA L

ART UNIT	PAPER NUMBER
1611	

DATE MAILED: 10/02/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

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	01/04/2016

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: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

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 10/02/2015
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.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

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	01/04/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
JAVIER, 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. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 10/02/2015

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

EXAMINER	
JAVIER, MELISSA L	

ART UNIT	PAPER NUMBER
1611	

DATE MAILED: 10/02/2015

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. 13/553,972	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--

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 *6/12/2015*.
   ☐ 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 *14-17, 21-26, and 28-30*. 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 Javier/
Examiner, Art Unit 1611

DETAILED ACTION

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

Election/Restrictions

Claims 14-17, 21-26, and 28-30 are allowable. The restriction requirement between groups, as set forth in the Office action mailed on 4/12/2013 , has been reconsidered in view of the allowability of claims to the elected invention pursuant to MPEP § 821.04(a). **The restriction requirement is hereby withdrawn as to any claim that requires all the limitations of an allowable claim.** Specifically, the restriction requirement of 4/12/2013 is withdrawn. Claims 16 and 17, directed to a method of making a monolithic transdermal drug delivery system for administering estradiol is no longer withdrawn from consideration because the claim(s) requires all the limitations of an allowable claim.

In view of the above noted withdrawal of the restriction requirement, applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The following is an examiner's statement of reasons for allowance: The prior art does not teach nor reasonably suggest a method for administering estradiol with the claimed monolithic transdermal drug delivery system. Further, the prior art does not teach nor reasonably suggest a method for making 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.

Conclusion

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 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

/BETHANY BARHAM/

Supervisory Patent Examiner, Art Unit 1611

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13553972	MANTELLE, JUAN
	Examiner	**Art Unit**
	MELISSA JAVIER	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	A	2013-01-01
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CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

/MELISSA JAVIER/ Examiner.Art Unit 1611 (Assistant Examiner)	9/28/2015 (Date)	**Total Claims Allowed:** 13	
/BETHANY BARHAM/ Supervisory Patent Examiner.Art Unit 1611 (Primary Examiner)	09/28/2015 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13553972	MANTELLE, JUAN
	Examiner	**Art Unit**
	MELISSA JAVIER	1611

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION													
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED								
		A	6	1	K	31 / 565 (2006.01.01)									
CROSS REFERENCE(S)		A	6	1	K	9 / 70 (2006.0)									
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)														

/MELISSA JAVIER/ Examiner.Art Unit 1611	9/28/2015	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	13	
/BETHANY BARHAM/ Supervisory Patent Examiner.Art Unit 1611	09/28/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13553972	MANTELLE, JUAN
	Examiner	**Art Unit**
	MELISSA JAVIER	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
	1	13	17												
	2		18												
	3		19												
	4		20												
	5	3	21												
	6	4	22												
	7	5	23												
	8	6	24												
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	10	8	26												
	11		27												
	12	9	28												
	13	10	29												
1	14	11	30												
2	15														
12	16														

/MELISSA JAVIER/ Examiner.Art Unit 1611 (Assistant Examiner)	9/28/2015 (Date)	**Total Claims Allowed:** 13	
/BETHANY BARHAM/ Supervisory Patent Examiner.Art Unit 1611 (Primary Examiner)	09/28/2015 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	13954	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L2	4834	L1 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L3	784	L2 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L4	31	L3 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L5	240	L3 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L6	46	L3 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L7	82	L1 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L8	242	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L9	35	L8 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L10	137	L8 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L11	178	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L12	37	L11 NOT L8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L13	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2015/09/28 15:43
L14	613	L1 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2015/09/28 15:43
L15	108	L3 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2015/09/28 15:43
L16	13954	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L17	4834	L16 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO;	OR	OFF	2015/09/28 15:43

			JPO; DERWENT			
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L19	31	L18 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L20	240	L18 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L21	46	L18 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L22	82	L16 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L23	242	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
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L25	137	L23 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L26	178	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
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L33	3	"20090041831".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
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L35	4834	L34 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L36	784	L35 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L37	31	L36 and estradiol.ab.	US-PGPUB; USPAT;	OR	OFF	2015/09/28

			USOCR; FPRS; EPO; JPO; DERWENT			15:43
L38	240	L36 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L39	46	L36 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L40	82	L34 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L41	242	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L42	35	L41 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L43	137	L41 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L44	178	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L45	37	L44 NOT L41	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L46	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2015/09/28 15:43
L47	613	L34 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2015/09/28 15:43
L48	108	L36 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2015/09/28 15:43
L49	13954	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L50	4834	L49 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L51	784	L50 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
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L53	240	L51 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L54	46	L51 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L55	82	L49 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L56	242	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43

L57	35	L56 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L58	137	L56 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L59	178	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L60	37	L59 NOT L56	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/28 15:43
L61	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2015/09/28 15:43
L62	613	L49 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2015/09/28 15:43
L63	108	L51 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2015/09/28 15:43

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L64	683041	(monolith$2 estradiol transdermal adhesive coat weight flux).clm.	USPAT; UPAD	OR	OFF	2015/09/28 15:52
L65	1	(monolith$2 estradiol transdermal adhesive coat weight flux).clm.	USPAT; UPAD	AND	OFF	2015/09/28 15:53

9/28/2015 3:54:18 PM
C:\Users\mjavier\Documents\EAST\Workspaces\13553972.wsp

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BIB DATA SHEET

CONFIRMATION NO. 3635

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/553,972	07/20/2012 RULE	424	1611	041457-0992

APPLICANTS

INVENTORS

Juan Mantelle, Miami, FL;

**** CONTINUING DATA ***************************

This application is a CON of 12/216,811 07/10/2008 PAT 8231906

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

07/31/2012

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 JAVIER/ Examiner's Signature	☐ Initials	FL	1	16	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	FEES: Authority has been given in Paper	
2540	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

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/553972
Date Submitted: June 12, 2015				**Filing Date**	7/20/2012
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	1611
				Examiner Name	Melissa L. Javier
Sheet	1	of	1	Attorney Docket Number	041457-0992

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]
	A1	Office Action issued on 05/20/2015 in application number 14/024,985 (US 2014/0200530)	
	A2	FELDMANN ET AL., "Percutaneous Penetration of Steroids in Man," The Journal of Investigative Dermatology, Vol. 52, No. 1, pp. 89-94, 1969.	
	A3	SCHAEFER ET AL., "Contraception via Topical Application? A Review," Contraception, Vol. 20, No. 3, pp. 225- 236, September 1979.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J./

Examiner Signature	/Melissa Javier/	Date Considered	09/28/2015

4848-1035-3444.1

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13553972	MANTELLE, JUAN
	Examiner	Art Unit
	MELISSA JAVIER	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 history)	8/25/2013	MJ
Inventor search in EAST	8/25/2013	MJ
Google Scholar search (keywords used: transdermal monolithic estradiol)	8/25/2013	MJ
Updated EAST search	2/21/2014	MJ
Updated Google Scholar search	2/21/2014	MJ
Updated EAST search	4/29/2015	MJ
Updated Google Scholar search	4/29/2015	MJ
Updated EAST search	9/28/2015	MJ
Updated Google Scholar search	9/28/2015	MJ

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
	(monolith$2 estradiol transdermal adhesive coat weight flux).clm.	9/28/2015	MJ

/M.J./ Examiner.Art Unit 1611	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Appl. No.: 13/553,972

Filing Date: 7/20/2012

Examiner: Melissa L. Javier

Art Unit: 1611

Confirmation Number: 3635

AMENDMENT UNDER 35 USC § 1.312

MAIL STOP: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

A Notice of Allowance was mailed in the captioned application on October 2, 2015. Applicant respectfully requests that the application be amended as follows under 37 CFR § 1.312.

If there are any questions regarding the amendments, Applicant respectfully urges the Examiner to telephone Applicant's representative at the telephone number set forth below.

Amendments to the claims are set forth in the **Listing of Claims** which begins on page 1.

Remarks/Arguments begin on page 5.

Listing of Claims:

Claims 1-13 (Cancelled)

14. (Currently Amended) 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~~ from about 0.195 to about 0.260 mg/cm^2 estradiol and achieves an estradiol flux ~~that is greater than 0.01~~ of from about 0.0125 to about 0.0167 mg/cm^2/day, based on the active surface area.

15. (Original) 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. (Currently Amended) 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~~ from about 0.195 to about 0.260 mg/cm^2 estradiol.

17. (Original) 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- 20 (Canceled)

21. (Previously Presented) The method of claim 14, wherein the adhesive polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble polyvinylpyrrolidone (PVP).

22. (Previously Presented) The method of claim 14, 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.

23. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alchol.

24. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises dipropylene glycol.

25. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

26. (Previously Presented) The method of claim 22, 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.

27. (Canceled)

28. (Previously Presented) The method of claim 14, 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.

29. (Previously Presented) The method of claim 14, 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.

30. (Previously Presented) A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system for estradiol consisting of (i) a backing layer and (ii) a single adhesive polymer matrix layer comprising estradiol as the only drug and having a coat weight of greater than about 10 mg/cm^2, 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.

REMARKS

Claims 14-17, 21-26, and 28-30 have been allowed. The foregoing amendments improve the clarity of the allowed claims by reciting ranges for the amount of estradiol per unit area (from about 0.195 to about 0.260 mg/cm^2) and ranges for the estradiol flux achieved per unit area per day (from about 0.0125 to about 0.0167 mg/cm^2/day). These amendments are made without prejudice or disclaimer and are believed to be appropriate under 37 CFR § 1.312 for at least the following reasons.

The amendments are supported throughout the specification as filed, for example, in paragraph [0016] of the specification as filed. This paragraph discloses embodiments having "about 1.25, 1.33, 1.5, [or] 1.67" times the amount of estradiol per unit area as the Vivelle-Dot® product, which is taught in this paragraph to have 0.156 mg/cm^2 estradiol, and so discloses embodiments having from about 0.195 to about 0.260 mg/cm^2 estradiol (1.25 x 0.156 = 0.195; 1.67 x 0.156 = 0.260). In parallel, this paragraph discloses embodiments that achieve an estradiol flux that is "about 1.25, 1.33, 1.5, [or] 1.67 … times the flux of the Vivelle-Dot® products," which is taught in this paragraph to be 0.01 mg/cm^2/day, and so discloses embodiments that achieve an estradiol flux of from about 0.0125 to about 0.0167 mg/cm^2/day (1.25 x 0.01 = 0.0125; 1.67 x 0.01 = 0.0167). Thus, no new matter is added.

The amended claims are fully supported by the specification as filed, including the examples. For example, the composition of Example 1 having a 12.5 mg/cm^2 adhesive polymer matrix (about 1.25 times that of the Vivelle-Dot® product) had about 0.20 mg/cm^2 estradiol, while the composition having a 15 mg/cm^2 adhesive polymer matrix (about 1.5 times that of the Vivelle-Dot® product) had about 0.24 mg/cm^2 estradiol, both of which are within the range of from about 0.195 to about 0.260 mg/cm^2. As seen in Figure 1, both compositions (▲,●) achieved an estradiol flux greater than that of the Vivelle-Dot® product (♦), and within the range of from about 0.0125 to about 0.0167 mg/cm^2/day recited in the amended claims.

No new search or examination is required by the amendments, because the amended claims recite more specific embodiments than the allowed claims, and are patentable over the art of record for at least the same reasons as the allowed claims.

Applicant therefore respectfully urges entry of the amendments under 37 CFR § 1.312.

If the Examiner has any questions or concerns regarding the amendments, she is urged to contact the undersigned by telephone.

It is believed that no fees are due in connection with this amendment. In the event this is not correct, the undersigned authorizes the Commissioner to charge Deposit Account No. 19-0741.

Respectfully submitted,

Date: December 18, 2015

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

Electronic Acknowledgement Receipt

EFS ID:	24414976
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	18-DEC-2015
Filing Date:	20-JUL-2012
Time Stamp:	16:40:36
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment after Notice of Allowance (Rule 312)	312amend.pdf	121242 896a2fdfc4892d0af8672e0f4cc28131dc563234	no	6
Warnings:					
Information:					

Total Files Size (in bytes):	121242

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.

DO NOT ENTER: /M.L.J/

Atty. Dkt. No. 041457-0992

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Appl. No.: 13/553,972

Filing Date: 7/20/2012

Examiner: Melissa L. Javier

Art Unit: 1611

Confirmation Number: 3635

AMENDMENT UNDER 35 USC § 1.312

MAIL STOP: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

A Notice of Allowance was mailed in the captioned application on October 2, 2015. Applicant respectfully requests that the application be amended as follows under 37 CFR § 1.312.

If there are any questions regarding the amendments, Applicant respectfully urges the Examiner to telephone Applicant's representative at the telephone number set forth below.

Amendments to the claims are set forth in the **Listing of Claims** which begins on page 1.

Remarks/Arguments begin on page 5.

Listing of Claims:

Claims 1-13 (Cancelled)

14. (Currently Amended) 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~~ from about 0.195 to about 0.260 mg/cm^2 estradiol and achieves an estradiol flux ~~that is greater than 0.01~~ of from about 0.0125 to about 0.0167 mg/cm^2/day, based on the active surface area.

15. (Original) 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. (Currently Amended) 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~~ from about 0.195 to about 0.260 mg/cm^2 estradiol.

17. (Original) 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- 20 (Canceled)

21. (Previously Presented) The method of claim 14, wherein the adhesive polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble polyvinylpyrrolidone (PVP).

22. (Previously Presented) The method of claim 14, 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.

23. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alchol.

24. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises dipropylene glycol.

25. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

26. (Previously Presented) The method of claim 22, 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.

27. (Canceled)

28. (Previously Presented) The method of claim 14, 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.

29. (Previously Presented) The method of claim 14, 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.

30. (Previously Presented) A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system for estradiol consisting of (i) a backing layer and (ii) a single adhesive polymer matrix layer comprising estradiol as the only drug and having a coat weight of greater than about 10 mg/cm^2, 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.

REMARKS

Claims 14-17, 21-26, and 28-30 have been allowed. The foregoing amendments improve the clarity of the allowed claims by reciting ranges for the amount of estradiol per unit area (from about 0.195 to about 0.260 mg/cm^2) and ranges for the estradiol flux achieved per unit area per day (from about 0.0125 to about 0.0167 mg/cm^2/day). These amendments are made without prejudice or disclaimer and are believed to be appropriate under 37 CFR § 1.312 for at least the following reasons.

The amendments are supported throughout the specification as filed, for example, in paragraph [0016] of the specification as filed. This paragraph discloses embodiments having "about 1.25, 1.33, 1.5, [or] 1.67" times the amount of estradiol per unit area as the Vivelle-Dot® product, which is taught in this paragraph to have 0.156 mg/cm^2 estradiol, and so discloses embodiments having from about 0.195 to about 0.260 mg/cm^2 estradiol (1.25 x 0.156 = 0.195; 1.67 x 0.156 = 0.260). In parallel, this paragraph discloses embodiments that achieve an estradiol flux that is "about 1.25, 1.33, 1.5, [or] 1.67 … times the flux of the Vivelle-Dot® products," which is taught in this paragraph to be 0.01 mg/cm^2/day, and so discloses embodiments that achieve an estradiol flux of from about 0.0125 to about 0.0167 mg/cm^2/day (1.25 x 0.01 = 0.0125; 1.67 x 0.01 = 0.0167). Thus, no new matter is added.

The amended claims are fully supported by the specification as filed, including the examples. For example, the composition of Example 1 having a 12.5 mg/cm^2 adhesive polymer matrix (about 1.25 times that of the Vivelle-Dot® product) had about 0.20 mg/cm^2 estradiol, while the composition having a 15 mg/cm^2 adhesive polymer matrix (about 1.5 times that of the Vivelle-Dot® product) had about 0.24 mg/cm^2 estradiol, both of which are within the range of from about 0.195 to about 0.260 mg/cm^2. As seen in Figure 1, both compositions (▲,●) achieved an estradiol flux greater than that of the Vivelle-Dot® product (♦), and within the range of from about 0.0125 to about 0.0167 mg/cm^2/day recited in the amended claims.

No new search or examination is required by the amendments, because the amended claims recite more specific embodiments than the allowed claims, and are patentable over the art of record for at least the same reasons as the allowed claims.

Applicant therefore respectfully urges entry of the amendments under 37 CFR § 1.312.

If the Examiner has any questions or concerns regarding the amendments, she is urged to contact the undersigned by telephone.

It is believed that no fees are due in connection with this amendment. In the event this is not correct, the undersigned authorizes the Commissioner to charge Deposit Account No. 19-0741.

Respectfully submitted,

Date: December 18, 2015

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 12/30/2015

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
12/30/2015	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

Response to Rule 312 Communication	Application No.	Applicant(s)
	13/553,972	MANTELLE, JUAN
	Examiner	Art Unit
	Melissa Javier	1611

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

1. ☒ The amendment filed on *18 December 2015* under 37 CFR 1.312 has been considered, and has been:

a) ☐ entered.

b) ☐ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.

Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☒ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

The amendment filed on 12/18/2015 raises issues of new matter and also changes the scope of the claims. Specifically, Applicant has amended the claims to include ranges that are not supported by the instant specification. There is no support for the ranges or for the criticality of the endpoints selected.

/BETHANY BARHAM/ Supervisory Patent Examiner, Art Unit 1611	Melissa Javier 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.:	13/553972
Appl. Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

REQUEST FOR CONTINUED EXAMINATION (RCE)TRANSMITTAL

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

Commissioner:

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application. This RCE and the enclosed items listed below are being filed prior to the earliest of: (1) payment of the issue fee (unless a petition under 37 C.F.R. § 1.313 is granted); (2) abandonment of the application; or (3) the filing of a notice of appeal to the U.S. Court of Appeals for the Federal Circuit under 35 U.S.C. §141, or the commencement of a civil action under 35 U.S.C. §145 or §146 (unless the appeal or civil action is terminated).

1. Submission **required** under 37 C.F.R. §1.114: (check items that apply)

[**X**] Amendment/Reply.

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

	Claims as Amended		Previously Paid For		Extra Claims Present		Rate		Fee Totals
RCE Fee 1.17(e):							$1,700.00	=	$1,700.00
Total Claims:	13	-	26	=	0	x	$80.00	=	$0.00
Independents	3	-	5	=	0	x	$420.00	=	$0.00
First presentation of any Multiple Dependent Claims:						+	$780.00	=	$0.00
							TOTAL:	=	$1,700.00

The above-identified fees of $1,700.00 are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required for this application to Deposit Account No. 19-0741.

Respectfully submitted,

Date December 31, 2015

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Appl. No.:	13/553,972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation Number:	3635

AMENDMENT UNDER 35 USC § 1.114 AND 1.111

MAIL STOP: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper is filed with a Request for Continued Examination within three months of the Notice of Allowance mailed October 2, 2015. The Commissioner is hereby authorized to charge any fees which may be due for this application to Deposit Account No. 19-0741.

Amendments to the claims are set forth in the **Listing of Claims** which begins on page 2.

Remarks/Arguments begin on page 5.

Listing of Claims:

Claims 1-13 (Cancelled)

14. (Currently Amended) 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~~ from about 0.195 to about 0.260 mg/cm^2 estradiol and achieves an estradiol flux ~~that is greater than 0.01~~ of from about 0.0125 to about 0.0167 $mg/cm^2/day$, based on the active surface area.

15. (Original) 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. (Currently Amended) 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 [[a]] 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~~ from about 0.195 to about 0.260 mg/cm^2 estradiol.

17. (Original) 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- 20 (Canceled)

21. (Previously Presented) The method of claim 14, wherein the adhesive polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble polyvinylpyrrolidone (PVP).

22. (Previously Presented) The method of claim 14, 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.

23. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alchol.

24. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises dipropylene glycol.

25. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

26. (Previously Presented) The method of claim 22, 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.

27. (Canceled)

28. (Previously Presented) The method of claim 14, 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.

29. (Previously Presented) The method of claim 14, 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.

30. (Previously Presented) A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system for estradiol consisting of (i) a backing layer and (ii) a single adhesive polymer matrix layer comprising estradiol as the only drug and having a coat weight of greater than about 10 mg/cm^2, 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.

REMARKS

Claims 14-17, 21-26, and 28-30 were allowed in the Notice of Allowance mailed October 2, 2015. A Rule 312 Amendment presenting the foregoing amendments was submitted December 18, 2015 and denied entry in the Response to Rule 312 Communication mailed December 30, 2015. Thus, the foregoing amendments are presented vis-à-vis the allowed claims.

The foregoing amendments improve the clarity of the allowed claims by replacing unbounded "greater than" clauses with ranges, *e.g.*, by reciting ranges for the amount of estradiol per unit area (from about 0.195 to about 0.260 mg/cm^2) and ranges for the estradiol flux achieved per unit area per day (from about 0.0125 to about 0.0167 $mg/cm^2/day$). These amendments are made without prejudice or disclaimer.

The Response to Rule 312 Communication stated that the amendments raise issues of new matter; however, the amendments are supported throughout the specification as filed, for example, in paragraph [0016] of the specification as filed. This paragraph discloses embodiments having "about 1.25, 1.33, 1.5, [or] 1.67" times the amount of estradiol per unit area as the Vivelle-Dot® product, which is taught in this paragraph to have 0.156 mg/cm^2 estradiol, and so discloses embodiments having from about 0.195 to about 0.260 mg/cm^2 estradiol. That is, the low end of the recited range is disclosed by 1.25 x 0.156 mg/cm^2 = 0.195 mg/cm^2 estradiol and the upper end of the recited range is disclosed by 1.67 x 0.156 mg/cm^2 = 0.260 mg/cm^2 estradiol. In parallel, this paragraph discloses embodiments that achieve an estradiol flux that is "about 1.25, 1.33, 1.5, [or] 1.67 ... times the flux of the Vivelle-Dot® products," which is taught in this paragraph to be 0.01 $mg/cm^2/day$, and so discloses embodiments that achieve an estradiol flux of from about 0.0125 to about 0.0167 $mg/cm^2/day$. That is, the low end of the recited range is disclosed by 1.25 x 0.01 $mg/cm^2/day$ = 0.0125 $mg/cm^2/day$, and the upper end of the recited range is disclosed by 1.67 x 0.01 $mg/cm^2/day$ = 0.0167 $mg/cm^2/day$. Thus, no new matter is added by these amendments.

The Response to Rule 312 Communication stated that "[t]here is no support ... for the criticality of the endpoints selected." To the extent this comment pertains to written description support for the amendments, the specification indeed supports the recited endpoints, as shown above. To the extent this comment pertains to enablement or utility, Applicant notes that embodiments within the scope of the amended claims are fully supported by examples. For example, the composition of Example 1 having a 12.5 mg/cm^2 adhesive polymer matrix (about 1.25 times that of the Vivelle-Dot® product) had about 0.20 mg/cm^2 estradiol, while the composition having a 15 mg/cm^2 adhesive polymer matrix (about 1.5 times that of the Vivelle-Dot® product) had about 0.24 mg/cm^2 estradiol, both of which are within the range of from about 0.195 to about 0.260 mg/cm^2 estradiol. As seen in Figure 1, both compositions (▲,●) achieved an estradiol flux greater than that of the Vivelle-Dot® product (♦), and within the range of from about 0.0125 to about 0.0167 mg/cm^2/day recited in the amended claims.

The Response to Rule 312 Communication stated that the amendments "change[] the scope of the claims." Indeed, the amended claims recite more specific embodiments than the allowed claims, and so are patentable over the art of record for at least the same reasons as the allowed claims.

Applicant therefore respectfully urges entry of the amendments, and re-allowance of the application.

Applicant has submitted a request for a telephone interview via the USPTO's Automated Interview Request Form (08-15), and urges the Examiner to contact Applicant's representative at the telephone number set forth below in order to schedule a telephone interview prior to issuing a further Office Action if the Examiner has any questions or concerns regarding the amendments.

Respectfully submitted,

Date: December 31, 2015

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

Electronic Patent Application Fee Transmittal

Application Number:	13553972
Filing Date:	20-Jul-2012
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff
Attorney Docket Number:	041457-0992

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($)
Miscellaneous:				
RCE- 2nd and Subsequent Request	1820	1	1700	1700
		Total in USD ($)		**1700**

Electronic Acknowledgement Receipt

EFS ID:	24502900
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	31-DEC-2015
Filing Date:	20-JUL-2012
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Amendment Submitted/Entered with Filing of CPA/RCE	3	9

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2	Fee Worksheet (SB06)	fee-info.pdf	30430 f826510f0c81d17515f4a9c92e1a93928d0e9cf4	no	2

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Name(s):
Courtenay C Brinckerhoff

S-signature:
/Courtenay C Brinckerhoff/

Registration Number:
37288

U.S. Application Number:
13553972

Confirmation Number:
3635

E-mail Address:
cbrinckerhoff@foley.com

Phone Number:
2022954094

Proposed Time of Interview:
1-8-2016 10:00 AM ET

Prefered Interview Type:
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I am the applicant or applicant's representative for this application.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/553,972	Filing Date 07/20/2012	☐ 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 **12/31/2015**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	(Column 3) ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 13	Minus	** 26	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***5	= 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	PRESENT EXTRA	RATE ($)	(Column 3) ADDITIONAL FEE ($)
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".
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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/553,972
Date Submitted: April 21, 2016				**Filing Date**	07/20/2012
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				Art Unit	1611
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Sheet	1	of	1	Attorney Docket Number	041457-0992

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	7,456,159 B2	11/25/2008	HOUZE ET AL.	
	A2	5,656,286	08/12/1997	MIRANDA 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]
	A3	EP 0 887 075 A2	12/30/1998	BERTEK, INC.		

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]
	A4	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.	
	A5	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.	
	A6	PFISTER, "Transdermal and Dermal Therapeutic Systems: Current Status," Transdermal and Topical Drug Delivery Systems, Ghosh et al., eds., Chapter 2, pp. 33-112, 1997.	
	A7	Dow Corning, :"Dow Corning® BIO-PSA Standard Silicone Adhesives," Product Information, 07/28/2008.	
	A8	JANISCH ET AL., Email correspondence, March 10, 2016.	
	A9	MANNGOLD, 04/28/2004 letter to Angela Nwaneri re: Duro-Tak® 87-4287 and 87-2287.	
	A10	Noven Pharmaceuticals, Inc., Response filed in European application number 09790211.8 on 12/19/2014.	

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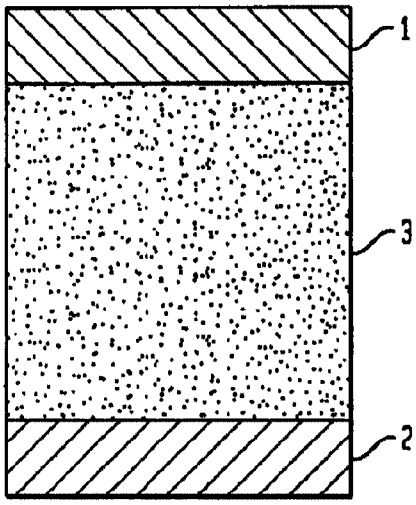
(54) Adhesive mixture for transdermal delivery of highly plasticizing drugs

(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
	-0-	~18	-	
GELVA 1753	-0-	~15%	1110	No Adhesive
	-0-	~10%	933	Transfer
	10% PG	8%	527	No Oozing
DUROTAK				Adhesive Transfer
87-2194	10% PG	8%	2217	(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	-0-	12%	—	No Adhesive Transfer
87-2852				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

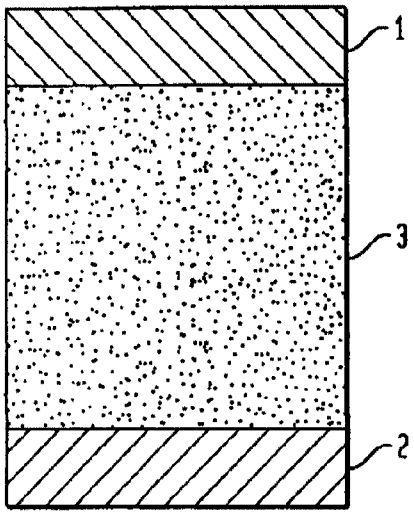
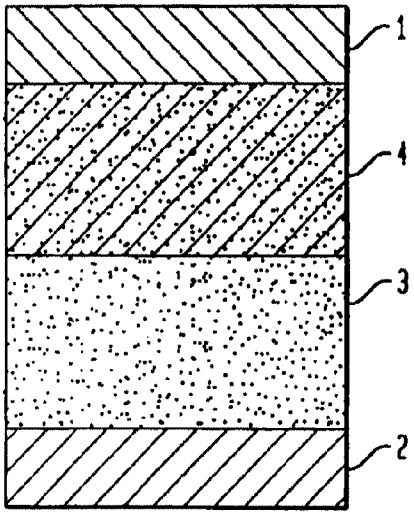


FIG. 2



Electronic Acknowledgement Receipt

EFS ID:	25599353
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	26-APR-2016
Filing Date:	20-JUL-2012
Time Stamp:	14:24:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		ids.pdf	171162 1e0d297ffcf50fd68e12bf314f28b8e07cdf2bf4	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:					
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):	11013680

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
Application No.:	13/553972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation No.:	3635

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. However, in accordance with MPEP §

609.04(a)(I), Applicant hereby states that for items for which the date of publication supplied does not include the month of publication, the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), before the mailing of a first Office action after the filing of a RCE.

RELEVANCE OF LISTED DOCUMENTS

The listed documents were cited in an opposition filed in the corresponding European patent. Documents A1 and A2 are also granted patents 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 Number 19-0741.

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 05/05/2016

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
05/05/2016	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. 13/553,972	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 *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 *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) *14-17,21-26 and 28-30* is/are pending in the application.

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

6)☒ Claim(s) *30* is/are allowed.

7)☒ Claim(s) *14-17, 21-26, and 28-29* 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.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12/31/2015 has been entered.

Status of Claims

The amendments and arguments filed on 12/31/2015 are acknowledged and have been fully considered. Claims 14-17, 21-26, and 28-30 are now pending. Claims 1-13, 18-20, and 27 are canceled; claims 14 and 16 are amended; no claims are withdrawn; no claims are new.

Claims 14-17, 21-26, and 28-30 will be examined on the merits herein.

Information Disclosure Statement

The Information Disclosure Statement (IDS) filed 4/26/2016 has been considered by the examiner.

Claim Rejections - 35 USC § 112 (new)

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 14-17, 21-26, and 28-29 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 14 recites “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/cm2/day, based on

the active surface area". The instant specification does not teach that the adhesive polymer matrix layer includes from about 0.195 to about 0.260 mg/cm2 estradiol. The instant specification teaches "[f]or 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/cm2 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". However, this is not a teaching of an amount of estradiol, it is a coat weight. The instant specification does not teach that the transdermal achieves an estradiol flux of from about 0.0125 to about 0.0167 mg/cm2/day. The instant specification teaches "[f]or example, in some embodiments, the systems exhibit a flux greater than the 0.01 mg/cm2/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". However, these are discrete points disclosed, not a range. The use of a range of estradiol flux includes values (i.e. those between the disclosed points) that are not disclosed in the originally filed specification. Further, there is no disclosure in the instant specification that the newly claimed amounts of estradiol achieve the newly claimed flux. This is a new matter rejection.

Claim 16 recites "includes from about 0.195 to about 0.260 mg/cm2 estradiol". The instant specification does not teach that the adhesive polymer matrix layer includes from about 0.195 to about 0.260 mg/cm2 estradiol. The instant specification teaches "[f]or 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/cm2 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". However, this is not a teaching of an amount of estradiol, it is a coat weight. This is a new matter rejection.

Response to Arguments

Applicant's arguments filed 12/31/2015 have been fully considered but they are not persuasive for the reasons set forth above.

Allowable Subject Matter

Claim 30 is allowed.

Conclusion

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

/Melissa Javier/
Examiner, Art Unit 1611

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	14723	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L2	5090	L1 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L3	841	L2 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L4	32	L3 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L5	253	L3 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L6	49	L3 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L7	87	L1 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L8	249	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L9	41	L8 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L10	144	L8 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L11	181	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L12	38	L11 NOT L8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L13	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L14	662	L1 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L15	121	L3 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L16	14723	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L17	5090	L16 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO;	OR	OFF	2016/04/22 16:48

			JPO; DERWENT			
L18	841	L17 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L19	32	L18 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L20	253	L18 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L21	49	L18 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L22	87	L16 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L23	249	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L24	41	L23 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L25	144	L23 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L26	181	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L27	38	L26 NOT L23	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L28	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L29	662	L16 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L30	121	L18 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L31	2	"6638528".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L32	4	"4624665".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L33	3	"20090041831".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L34	14723	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L35	5090	L34 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L36	841	L35 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L37	32	L36 and estradiol.ab.	US-PGPUB; USPAT;	OR	OFF	2016/04/22

			USOCR; FPRS; EPO; JPO; DERWENT			16:48
L38	253	L36 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L39	49	L36 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L40	87	L34 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L41	249	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L42	41	L41 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L43	144	L41 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L44	181	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L45	38	L44 NOT L41	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L46	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L47	662	L34 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L48	121	L36 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L49	14723	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L50	5090	L49 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L51	841	L50 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L52	32	L51 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L53	253	L51 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L54	49	L51 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L55	87	L49 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L56	249	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48

L57	41	L56 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L58	144	L56 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L59	181	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L60	38	L59 NOT L56	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L61	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L62	662	L49 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L63	121	L51 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L64	14723	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L65	5090	L64 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L66	841	L65 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L67	32	L66 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L68	253	L66 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L69	49	L66 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L70	87	L64 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L71	249	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L72	41	L71 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L73	144	L71 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L74	181	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L75	38	L74 NOT L71	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L76	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/04/22 16:48

L77	662	L64 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L78	121	L66 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L79	14723	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L80	5090	L79 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L81	841	L80 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L82	32	L81 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L83	253	L81 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L84	49	L81 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L85	87	L79 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L86	249	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L87	41	L86 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L88	144	L86 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L89	181	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L90	38	L89 NOT L86	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L91	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L92	662	L79 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L93	121	L81 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L94	2	"6638528".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L95	4	"4624665".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L96	3	"20090041831".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L97	14723	estradiol and transdermal	US-PGPUB; USPAT;	OR	OFF	2016/04/22

			USOCR; FPRS; EPO; JPO; DERWENT			16:48
L98	5090	L97 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L99	841	L98 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L100	32	L99 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L101	253	L99 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L102	49	L99 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L103	87	L97 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L104	249	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L105	41	L104 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L106	144	L104 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L107	181	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L108	38	L107 NOT L104	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L109	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L110	662	L97 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L111	121	L99 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L112	14723	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L113	5090	L112 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L114	841	L113 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L115	32	L114 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L116	253	L114 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48

L117	49	L114 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L118	87	L112 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L119	249	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L120	41	L119 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L121	144	L119 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L122	181	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L123	38	L122 NOT L119	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/04/22 16:48
L124	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L125	662	L112 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48
L126	121	L114 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/04/22 16:48

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PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/553,972
Date Submitted: April 21, 2016				**Filing Date**	07/20/2012
				First Named Inventor	Juan Mantelle
(use as many sheets as necessary)				Art Unit	1611
				Examiner Name	Melissa Javier
Sheet	1	of	1	Attorney Docket Number	041457-0992

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	7,456,159 B2	11/25/2008	HOUZE ET AL.	
	A2	5,656,286	08/12/1997	MIRANDA 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]
	A3	EP 0 887 075 A2	12/30/1998	BERTEK, INC.		

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]
	A4	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.	
	A5	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.	
	A6	PFISTER, "Transdermal and Dermal Therapeutic Systems: Current Status," Transdermal and Topical Drug Delivery Systems, Ghosh et al., eds., Chapter 2, pp. 33-112, 1997.	
	A7	Dow Corning, :"Dow Corning® BIO-PSA Standard Silicone Adhesives," Product Information, 07/28/2008.	
	A8	JANISCH ET AL., Email correspondence, March 10, 2016.	
	A9	MANNGOLD, 04/28/2004 letter to Angela Nwaneri re: Duro-Tak® 87-4287 and 87-2287.	
	A10	Noven Pharmaceuticals, Inc., Response filed in European application number 09790211.8 on 12/19/2014.	

Examiner Signature	/MELISSA L JAVIER/	Date Considered	05/02/2016

4841-2305-3616.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.L.J/

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13553972	MANTELLE, JUAN
	Examiner	Art Unit
	MELISSA JAVIER	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 history)	8/25/2013	MJ
Inventor search in EAST	8/25/2013	MJ
Google Scholar search (keywords used: transdermal monolithic estradiol)	8/25/2013	MJ
Updated EAST search	2/21/2014	MJ
Updated Google Scholar search	2/21/2014	MJ
Updated EAST search	4/29/2015	MJ
Updated Google Scholar search	4/29/2015	MJ
Updated EAST search	9/28/2015	MJ
Updated Google Scholar search	9/28/2015	MJ
Updated EAST search	4/22/2016	MJ
Updated Google Scholar search	4/22/2016	MJ

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/M.J./ Examiner.Art Unit 1611	

INTERFERENCE SEARCH			
US Class/ CPC Symbol	**US Subclass / CPC Group**	**Date**	**Examiner**
	(monolith$2 estradiol transdermal adhesive coat weight flux).clm.	9/28/2015	MJ

/M.J./ Examiner.Art Unit 1611	

Doc Code: M865 or FAI.REQ.INTV

PTOL-413A (08-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Applicant Initiated Interview Request Form 41457-0092

Application No.: 13/553,972 First Named Applicant: Mantelle
Examiner: JAVIER Art Unit: 1611 Status of Application: pending

Tentative Participants:
(1) Courtenay Brinckerhoff (2) _____
(3) _____ (4) _____

Proposed Date of Interview: 7/5-7/8 **Proposed Time:** Any (AM/PM)

Type of Interview Requested:
(1) [X] Telephonic → acceptable (2) [X] Personal → preferred (3) [ ] Video Conference

Exhibit To Be Shown or Demonstrated: [ ] YES [X] NO
If yes, provide brief description: _____

Issues To Be Discussed

Issues (Rej., Obj., etc)	Claims/ Fig. #s	Prior Art	Discussed	Agreed	Not Agreed
(1) new matter	all (except cl. 30)		[ ]	[ ]	[ ]
(2)			[ ]	[ ]	[ ]
(3)			[ ]	[ ]	[ ]
(4)			[ ]	[ ]	[ ]

[ ] Continuation Sheet Attached [ ] Proposed Amendment or Arguments Attached
Brief Description of Arguments to be Presented: would like to discuss support for claim amendments
An interview was conducted on the above-identified application on _____

NOTE: This form should be completed and filed by applicant in advance of the interview (see MPEP § 713.01). If this form is signed by a registered practitioner not of record, the Office will accept this as an indication that he or she is authorized to conduct an interview on behalf of the principal (37 CFR 1.32(a)(3)) pursuant to 37 CFR 1.34. This is not a power of attorney to any above named practitioner. See the Instruction Sheet for this form, which is incorporated by reference. By signing this form, applicant or practitioner is certifying that he or she has read the Instruction Sheet. After the interview is conducted, applicant is advised to file a statement of the substance of this interview (37 CFR 1.133(b)) as soon as possible. This application will not be delayed from issue because of applicant's failure to submit a written record of this interview.

Courtenay C Brinckerhoff
Applicant/Applicant's Representative Signature

Examiner/SPE Signature

Courtenay C Brinckerhoff
Typed/Printed Name of Applicant or Representative

37,288 Phone: 202 295 4094
Registration Number, if applicable

Electronic Acknowledgement Receipt

EFS ID:	26127792
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	21-JUN-2016
Filing Date:	20-JUL-2012
Time Stamp:	14:40:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	intrequest.pdf	118450 10030ab5ac775110a4463bb588b389ee67e be75b	no	1
Warnings:					
Information:					

Total Files Size (in bytes):	118450

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 07/07/2016

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
07/07/2016	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

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/553,972	MANTELLE, JUAN	
	Examiner	Art Unit	
	Melissa Javier	1611	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Melissa Javier*. (3)_____.

(2) *Courtenay Brincherhoff*. (4)_____.

Date of Interview: *28 June 2016*.

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: *14*.

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 new matter rejection of record. The Examiner suggested to overcome the new matter rejection concerning the estradiol flux, Applicant consider amending the claim to include the entire range support by [0016] (i.e. 0.0125-0.05 mg/cm2/day) and possibly consider a dependent claim with the respective integer values. No agreement was reached on how to overcome the new matter rejection over the mg/cm2 estradiol. .

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 Javier/ 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Juan Mantelle

Title: Transdermal Estrogen Device and Delivery

Appl. No.: 13/553,972

Filing Date: 7/20/2012

Examiner: Melissa L. Javier

Art Unit: 1611

Confirmation Number: 3635

AMENDMENT UNDER 35 USC § 1.111

MAIL STOP: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper responds to the non-final Office Action mailed May 5, 2016. If any extensions of time are required for timely acceptance, Applicant hereby petitions for such extension of time. The Commissioner is hereby authorized to charge any fees which may be due for this application, including any extension of time fees or excess claim fees not submitted herewith, to Deposit Account No. 19-0741.

Amendments to the claims are set forth in the **Listing of Claims** which begins on page 2.

Remarks/Arguments begin on page 5.

Listing of Claims:

Claims 1-13 (Cancelled)

14. (Currently Amended) 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 ~~from about 0.195 to about 0.260~~ mg/cm^2 estradiol, and the system achieves an estradiol flux of from about 0.0125 to about 0.05 ~~0.0167~~ mg/cm^2/day, based on the active surface area.

15. (Canceled)

16. (Currently Amended) 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 ~~from about 0.195 to about 0.260~~ 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.

17. (Original) 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- 20 (Canceled)

21. (Previously Presented) The method of claim 14, wherein the adhesive polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble polyvinylpyrrolidone (PVP).

22. (Previously Presented) The method of claim 14, 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.

23. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alchol.

24. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises dipropylene glycol.

25. (Previously Presented) The method of claim 22, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.

26. (Previously Presented) The method of claim 22, 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.

27. (Canceled)

28. (Previously Presented) The method of claim 14, 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.

29. (Previously Presented) The method of claim 14, 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.

30. (Canceled)

31. (New) The method of claim 14, wherein the system achieves an estradiol flux of about 0.0125 mg/cm^2/day, based on the active surface area.

32. (New) The method of claim 14, wherein the system achieves an estradiol flux of about 0.0133 mg/cm^2/day, based on the active surface area.

33. (New) The method of claim 14, wherein the system achieves an estradiol flux of about 0.015 mg/cm^2/day, based on the active surface area.

34. (New) The method of claim 14, wherein the system achieves an estradiol flux of about 0.0167 mg/cm^2/day, based on the active surface area.

35. (New) The method of claim 14, wherein the system achieves an estradiol flux of about 0.0175 mg/cm^2/day, based on the active surface area.

36. (New) The method of claim 16, wherein the system achieves an estradiol flux of about 0.0125 mg/cm^2/day, based on the active surface area.

37. (New) The method of claim 16, wherein the system achieves an estradiol flux of about 0.0133 mg/cm^2/day, based on the active surface area.

38. (New) The method of claim 16, wherein the system achieves an estradiol flux of about 0.015 mg/cm^2/day, based on the active surface area.

39. (New) The method of claim 16, wherein the system achieves an estradiol flux of about 0.0167 mg/cm^2/day, based on the active surface area.

40. (New) The method of claim 16, wherein the system achieves an estradiol flux of about 0.0175 mg/cm^2/day, based on the active surface area.

REMARKS

Applicant respectfully request reconsideration in view of the foregoing amendments and the following remarks.

Applicant thanks Examiner Javier for the courtesies extended during the in-person interview on June 28, 2016. As reflected in the Examiner's Interview Summary, the new matter rejection set forth in the May 5, 2016 Office Action was discussed, as were further proposed amendments to address the Examiner's concerns.

Without acquiescing to the merits of the new matter rejection, and solely to advance prosecution towards allowance, Applicant has presented amendments above that conform to the Examiner's suggestions. In particular, claims 14 and 15 are amended as suggested by the Examiner and new claims 31-40 are added to recite specific embodiments, as also suggested by the Examiner, and as supported, for example in paragraph [0016] of the specification as filed.

Upon entry of these amendments claims 14, 16-17, 21-26, and 28-29 and 31-40 will be pending. Applicant believes that these claims are 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 to advance prosecution.

Respectfully submitted,

Date: August 2, 2016

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Juan Mantelle
Title:	Transdermal Estrogen Device and Delivery
Application No.:	13/553972
Filing Date:	7/20/2012
Examiner:	Melissa L. Javier
Art Unit:	1611
Confirmation No.:	3635

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(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 DOCUMENTS

Document A1 is a reference known to the Applicant.

Documents A2-A5 are Office Actions which were issued in co-pending applications previously made of record.

FEE

A credit card payment form in the amount of $180.00 is enclosed to cover the fee associated with an information disclosure statement.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this submission under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account Number 19-0741.

Respectfully submitted,

Date August 2, 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

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/553972
Date Submitted: August 2, 2016				**Filing Date**	7/20/2012
				First Named Inventor	Juan Mantelle
				Art Unit	1611
(use as many sheets as necessary)				Examiner Name	Melissa L. Javier
Sheet	1	of	1	Attorney Docket Number	041457-0992

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]
	A1	MANTELLE, "DOT Matrix® Technology," Modified-Release Drug Delivery Technology, Rathbone et al., eds., Chapter 30, pp. 405-415, May 28, 2008.	
	A2	Office Action issued on 05/05/2016 in application number 14/024,985 (US 2014-0200530)	
	A3	Notice of Allowance issued on 10/02/2015 in application number 14/024,985 (US 2014-0200530)	
	A4	Office Action issue on 04/29/2016 in application number 14/738,255 (US 2015-0272905)	
	A5	Office Action issue on 10/26/2015 in application number 14/738,255 (US 2015-0272905)	

Examiner Signature		Date Considered	

Electronic Patent Application Fee Transmittal

Application Number:	13553972
Filing Date:	20-Jul-2012
Title of Invention:	TRANSDERMAL ESTROGEN DEVICE AND DELIVERY
First Named Inventor/Applicant Name:	Juan Mantelle
Filer:	Courtenay C. Brinckerhoff/Christine Arthur
Attorney Docket Number:	041457-0992

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:	26520704
Application Number:	13553972
International Application Number:	
Confirmation Number:	3635
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:	041457-0992
Receipt Date:	02-AUG-2016
Filing Date:	20-JUL-2012
Time Stamp:	13:53:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	171
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		responseids.pdf	343157 8c60b75209ade81581fc2e28f24bbcecdab1a405	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	5
	Transmittal Letter	6	7
	Information Disclosure Statement (IDS) Form (SB08)	8	8

Warnings:

Information:

2	Non Patent Literature	mantelle2008.pdf	1016410 169b95ef8afd8567ec288b1828f12ea306d9d7bb	no	21

Warnings:

Information:

3		oarefs.pdf	1960045 7b6322a602e7e79592a12799cb06b394b3693cd7	yes	43

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Non Patent Literature	1	6
	Non Patent Literature	7	13
	Non Patent Literature	14	28
	Non Patent Literature	29	43

Warnings:

Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30694 8672826911edecc0d3a2f1a333fe6ada08143f18	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	3350306	

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 13/553,972	Filing Date 07/20/2012	☐ 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 **08/02/2016**

	(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))	* 21	Minus	** 26	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	***5	= 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.

LIE
KIM DOWNING

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

22428 7590 08/26/2016

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

EXAMINER
JAVIER, MELISSA L

ART UNIT	PAPER NUMBER
1611	

DATE MAILED: 08/26/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

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	11/28/2016

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: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

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 08/26/2016
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.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

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	11/28/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
JAVIER, 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. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/553,972	07/20/2012	Juan Mantelle	041457-0992	3635

22428 7590 08/26/2016

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

EXAMINER	
JAVIER, MELISSA L	

ART UNIT	PAPER NUMBER
1611	

DATE MAILED: 08/26/2016

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. 13/553,972	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--

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 *8/2/2016*.
   ☐ 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 *14,16,17,21-26,28,29 and 31-40*. 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 Javier/
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 8/2/2016 has been considered by the examiner.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: The amendments to claims 14 and 16 overcome the prior new matter rejections. Claims 14 and 16 as amended, as well as new claims 31-40, have support in [0016] of the instant specification for the claimed estradiol flux.

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 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

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13553972	MANTELLE, JUAN
	Examiner	Art Unit
	MELISSA JAVIER	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 history)	8/25/2013	MJ
Inventor search in EAST	8/25/2013	MJ
Google Scholar search (keywords used: transdermal monolithic estradiol)	8/25/2013	MJ
Updated EAST search	2/21/2014	MJ
Updated Google Scholar search	2/21/2014	MJ
Updated EAST search	4/29/2015	MJ
Updated Google Scholar search	4/29/2015	MJ
Updated EAST search	9/28/2015	MJ
Updated Google Scholar search	9/28/2015	MJ
Updated EAST search	4/22/2016	MJ
Updated Google Scholar search	4/22/2016	MJ
Updated EAST search	8/22/2016	MJ
Updated Google Scholar search	8/22/2016	MJ
(A61K31/565 A61K9/70).cpc. and estradiol	8/22/2016	MJ

INTERFERENCE SEARCH

/M.J./ Examiner.Art Unit 1611	

US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
	(monolith$2 estradiol transdermal adhesive coat weight flux).clm.	9/28/2015	MJ
	(monolith$2 estradiol transdermal system adhesive coat weight flux).clm.	8/22/2016	MJ
			MJ

/M.J./ Examiner.Art Unit 1611	

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. 3635

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/553,972	07/20/2012 RULE	424	1611	041457-0992

APPLICANTS

INVENTORS

Juan Mantelle, Miami, FL;

**** CONTINUING DATA ***************************

This application is a CON of 12/216,811 07/10/2008 PAT 8231906

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

07/31/2012

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 JAVIER/ Examiner's Signature	☐ Initials	FL	1	16	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		
2540	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	15082	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L2	5232	L1 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L3	872	L2 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L4	33	L3 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L5	258	L3 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L6	49	L3 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L7	87	L1 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L8	247	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L9	38	L8 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L10	141	L8 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L11	182	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L12	39	L11 NOT L8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L13	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L14	687	L1 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L15	127	L3 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L16	15082	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L17	5232	L16 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO;	OR	OFF	2016/08/22 09:57

			JPO; DERWENT			
L18	872	L17 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L19	33	L18 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L20	258	L18 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L21	49	L18 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L22	87	L16 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L23	247	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L24	38	L23 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L25	141	L23 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L26	182	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L27	39	L26 NOT L23	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L28	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L29	687	L16 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L30	127	L18 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L31	2	"6638528".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L32	4	"4624665".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L33	3	"20090041831".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L34	15082	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L35	5232	L34 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L36	872	L35 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L37	33	L36 and estradiol.ab.	US-PGPUB; USPAT;	OR	OFF	2016/08/22

			USOCR; FPRS; EPO; JPO; DERWENT			09:57
L38	258	L36 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L39	49	L36 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L40	87	L34 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L41	247	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L42	38	L41 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L43	141	L41 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L44	182	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L45	39	L44 NOT L41	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L46	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L47	687	L34 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L48	127	L36 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L49	15082	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L50	5232	L49 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L51	872	L50 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L52	33	L51 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L53	258	L51 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L54	49	L51 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L55	87	L49 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L56	247	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57

L57	38	L56 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L58	141	L56 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L59	182	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L60	39	L59 NOT L56	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L61	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L62	687	L49 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L63	127	L51 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L64	15082	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L65	5232	L64 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L66	872	L65 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L67	33	L66 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L68	258	L66 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L69	49	L66 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L70	87	L64 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L71	247	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L72	38	L71 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L73	141	L71 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L74	182	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L75	39	L74 NOT L71	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L76	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/08/22 09:57

L77	687	L64 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L78	127	L66 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L79	15082	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L80	5232	L79 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L81	872	L80 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L82	33	L81 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L83	258	L81 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L84	49	L81 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L85	87	L79 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L86	247	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L87	38	L86 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L88	141	L86 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L89	182	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L90	39	L89 NOT L86	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L91	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L92	687	L79 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L93	127	L81 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L94	2	"6638528".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L95	4	"4624665".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L96	3	"20090041831".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L97	15082	estradiol and transdermal	US-PGPUB; USPAT;	OR	OFF	2016/08/22

			USOCR; FPRS; EPO; JPO; DERWENT			09:57
L98	5232	L97 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L99	872	L98 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L100	33	L99 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L101	258	L99 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L102	49	L99 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L103	87	L97 and (estradiol NEAR flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L104	247	MANTELLE.in. and JUAN.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L105	38	L104 and estradiol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L106	141	L104 and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L107	182	Kanios.in. and David.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L108	39	L107 NOT L104	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L109	0	(11/245097).APP.	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L110	687	L97 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L111	127	L99 and ("dipropylene glycol" oleyl)	USPAT; USOCR	OR	OFF	2016/08/22 09:57
L112	15082	estradiol and transdermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L113	5232	L112 and ("surface area" flux)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L114	872	L113 and acrylic and silicone and (PVP polyvinyl pyrrolidone)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L115	33	L114 and estradiol.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57
L116	258	L114 and transdermal.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2016/08/22 09:57