

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 June 2011 (09.06.2011)

(10) International Publication Number
WO 2011/068722 A1

(51) International Patent Classification:

A61K 9/70 (2006.01) A61L 15/20 (2006.01)
A61K 31/568 (2006.01) A61L 15/58 (2006.01)
A61K 47/32 (2006.01)

(21) International Application Number:

PCT/US2010/057797

(22) International Filing Date:

23 November 2010 (23.11.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/265,411 1 December 2009 (01.12.2009) US

(71) Applicant (for all designated States except US): **NOVEN PHARMACEUTICALS, INC.** [US/US]; 11960 South-west 144th Street, Miami, FL 33186 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **MANTELLE, Juan, A.** [US/US]; 10821 S.W. 92nd Avenue, Miami, FL 33176 (US).

(74) Agents: **BRINCKERHOFF, Courtenay, C.** et al; Foley & Lardner LLP, 3000 K Street NW, Washington, DC 20007 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available):

AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

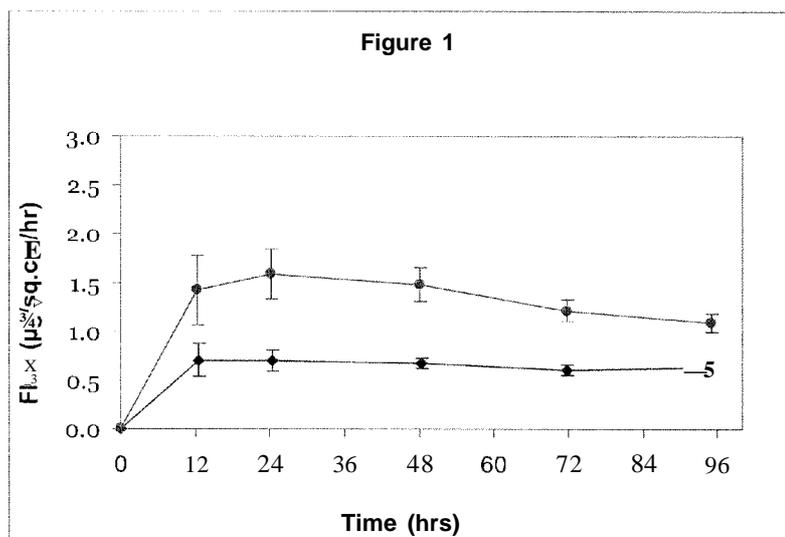
(84) Designated States (unless otherwise indicated, for every kind of regional protection available):

ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: TRANSDERMAL TESTOSTERONE DEVICE AND DELIVERY



(57) Abstract: Described are transdermal drug delivery systems for the transdermal administration of testosterone, comprising a polymer matrix and testosterone. Methods of making and using such systems also are described.

WO 2011/068722 A1

TRANSDERMAL TESTOSTERONE DEVICE AND DELIVERY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. 61/265,411, filed December 1, 2009, the entire contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] Described herein are compositions and methods for the transdermal delivery of testosterone.

BACKGROUND

[0003] This invention relates generally to transdermal drug delivery systems, and more particularly, to transdermal drug delivery systems for the delivery of testosterone. 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 testosterone, and there remains a particular need for smaller transdermal drug delivery systems that exhibit desired pharmacokinetic properties.

[0004] 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.

[0005] 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

[0006] 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 testosterone, wherein the system includes less than 0.3 mg/cm² testosterone and achieves a testosterone flux that is at least about 0.7 μg/cm²/hour, such as at least about 0.89 μg/cm²/hour, 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 0-15% penetration enhancer, about 0.1-10% by weight testosterone, and, optionally, about 0.001-0.1 % by weight antioxidant, 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 59% by weight silicone adhesive, about 12% by weight soluble PVP, about 6.0% by weight oleyl alcohol, about 2-3% by weight testosterone, and, optionally about 0.01% by weight butylhydroxytoluene, all based on the total dry weight of the polymer matrix. 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.

[0007] In some embodiments, the penetration enhancer comprises oleyl alcohol or dipropylene glycol, or both.

[0008] In some embodiments, the polymer matrix comprises an amount of testosterone effective to deliver a therapeutically effective amount of testosterone 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 testosterone effective to deliver an amount of testosterone of at least 300 $\mu\text{g}/\text{day}$, over a period of at least 3 days.

[0009] 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 12.0, about 12.5, about 13.0 and about 15 mg/cm^2 .

[0010] In accordance with some embodiments, there is provided a transdermal drug delivery system comprising a polymer matrix comprising testosterone, wherein the system has an active surface area that is about 50% of 28.0 cm^2 , including about 14 cm^2 , and is effective to deliver an amount of testosterone per day of at least 300 $\mu\text{g}/\text{day}$.

[0011] In accordance with some embodiments, there is provided a method for administering testosterone, 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 testosterone, wherein the system includes less than 0.3 mg/cm^2 testosterone and achieves an testosterone flux that is at least about 0.7 $\mu\text{g}/\text{cm}^2/\text{hour}$, such as at least about 0.89 $\mu\text{g}/\text{cm}^2/\text{hour}$, based on the active surface area. In some embodiments, the

system has an active surface area that is about 50% of 28.0 cm², including about 14 cm², and is effective to deliver an amount of testosterone per day of at least 300 μg/day.

[0012] In accordance with some embodiments, there is provided a method of making a transdermal drug delivery system for administering testosterone, comprising forming a polymer matrix comprising testosterone 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 less than 0.3 mg/cm² testosterone. In some embodiments, the system has an active surface area that is about 50% of 28.0 cm², including about 14 cm². In some embodiments, the polymer matrix comprises about 20% by weight acrylic adhesive, about 59% by weight silicone adhesive, about 12% by weight soluble PVP, about 6.0% by weight oleyl alcohol, about 2-3% by weight testosterone and, optionally about 0.01% by weight butylhydroxytoluene, all based on the total dry weight of the polymer matrix. In some embodiments, the polymer matrix is applied to the support layer at a coat weight of greater than about 10 mg/cm². In some embodiments, the polymer matrix coat weight is selected from the group consisting of 12.0, about 12.5, about 13.0 and about 15 mg/cm².

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Figure 1 illustrates the testosterone flux (μg/cm²/hr) over time (0-96 hours) from a transdermal delivery system according to the invention (·), as compared to Intrinsa® (◆).

[0014] Figure 2 illustrates the cumulative amount of drug delivered per unit area (μg/cm²) over time (0-96 hours) from a transdermal delivery system according to the invention (·), as compared to Intrinsa® (◆).

DETAILED DESCRIPTION

[0015] 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 Intrinsa® transdermal testosterone product (manufactured by Watson Pharmaceuticals Inc.) is 28 cm² and contains 8.4 mg of testosterone. Thus, the Intrinsa® product includes 0.3 mg/cm² testosterone. The Intrinsa® product is said to deliver 300 µg testosterone per day.

[0016] In accordance with some embodiments, the present invention provides transdermal drug delivery systems for the transdermal delivery of testosterone that have a smaller active surface area than Intrinsa® but achieve daily dosages that are about equal to or greater than the Intrinsa® products. For example, the present invention includes transdermal drug delivery systems that achieve daily dosages that are about equal to an Intrinsa® product, in a smaller sized system. The ability to provide a smaller system without sacrificing daily dosage represents a significant advance.

[0017] Applicant surprisingly discovered that adjusting the coat weight of the drug-containing adhesive layer could be used to adjust the flux per unit area, and thus permitted the development of smaller transdermal drug delivery systems that achieve comparable daily dosages. This result is 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.

[0018] Moreover, Applicant surprisingly discovered that the drug-containing adhesive layers described herein achieve a flux per unit area that is greater than that of the Intrinsa® product, but with a similar amount drug per unit area. This permitted the development of smaller transdermal drug delivery systems that achieve comparable daily dosages. This result is surprising because Applicant is able to achieve comparable drug delivery with less drug.

[0019] In accordance with some aspects, there are provided transdermal drug delivery systems and methods for the transdermal delivery of testosterone. In specific

embodiments, the systems exhibit increased flux than other known testosterone devices (such as Intrinsa®, manufactured by Watson Pharmaceuticals Inc.) and, therefore, exhibit increased drug delivery per unit area. For example, in some embodiments, the systems exhibit a flux greater than the about $0.45 \mu\text{g}/\text{cm}^2/\text{hour}$ exhibited by the Intrinsa® product, such as a flux that is at least about $0.70 \mu\text{g}/\text{cm}^2/\text{hour}$, including a flux that is at least $0.70 \mu\text{g}/\text{cm}^2/\text{hour}$, including a flux that is at least about $0.89 \mu\text{g}/\text{cm}^2/\text{hour}$, at least $0.89 \mu\text{g}/\text{cm}^2/\text{hour}$, at least about $1.0 \mu\text{g}/\text{cm}^2/\text{hour}$, at least $1.0 \mu\text{g}/\text{cm}^2/\text{hour}$, at least about $1.5 \mu\text{g}/\text{cm}^2/\text{hour}$, and at least $1.5 \mu\text{g}/\text{cm}^2/\text{hour}$. In some embodiments, the systems described herein achieve a flux that at least is about $0.70 \mu\text{g}/\text{cm}^2/\text{hour}$, including at least $0.70 \mu\text{g}/\text{cm}^2/\text{hour}$, at least about $0.89 \mu\text{g}/\text{cm}^2/\text{hour}$, at least $0.89 \mu\text{g}/\text{cm}^2/\text{hour}$, at least about $1.0 \mu\text{g}/\text{cm}^2/\text{hour}$, at least $1.0 \mu\text{g}/\text{cm}^2/\text{hour}$, at least about $1.5 \mu\text{g}/\text{cm}^2/\text{hour}$, or at least $1.5 \mu\text{g}/\text{cm}^2/\text{hour}$, over a period of time of a least 3 days, including a period of time of 3 days, or a period of time of 4 days or longer.

[0020] In some embodiments, the systems have a lower amount of drug per unit area than other known testosterone devices, but still achieve effective drug delivery. For example, in some embodiments, the systems have a coat weight such that the amount of testosterone per unit area is less than the $0.3 \text{ mg}/\text{cm}^2$ testosterone of the Intrinsa® product, such as an amount of drug per unit area of about $0.28 \text{ mg}/\text{cm}^2$.

[0021] Thus, in accordance with some aspects, the invention permits the use of smaller devices to achieve comparable drug delivery.

DEFINITIONS

[0022] 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.

[0023] 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.

[0024] 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.

[0025] 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.

[0026] 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 testosterone, or may be taking testosterone for health maintenance purposes.

[0027] 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.

[0028] As used herein, "active surface area" means the surface area of the drug-containing layer of the transdermal drug delivery system.

[0029] 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.

[0030] As used herein, "testosterone" includes androgenic steroids such as testosterone, testosterone acetate, testosterone enanthate, testosterone propionate, 17-beta-cypionate, testosterone nicotinate, testosterone phenylacetate, and non-esters that have groups on the 17 position, such as testosterone 17-chloral hemiacetal.

[0031] 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/cm²/sec, D is the diffusion coefficient of the drug through the skin or mucosa in cm²/sec and dCm/dx is the concentration gradient of the drug across the skin or mucosa.

[0032] 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.

[0033] As used herein, "transdermal drug delivery system" refers to a system (e.g., a device) comprising a composition that releases testosterone upon application to the skin (or any other surface noted above). A transdermal drug delivery system may comprise a drug-containing layer, and, optionally, a backing layer and/or 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.

[0034] 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 testosterone dissolved or dispersed therein. The polymer matrix also may comprise tackifiers, plasticizers, crosslinking agents, enhancers, co-solvents, fillers, antioxidants, solubilizers, crystallization inhibitors, 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.

[0035] 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.

[0036] 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.

[0037] 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 $-70\text{ }^\circ\text{C}$. and $0\text{ }^\circ\text{C}$.

[0038] 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.

[0039] 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.

[0040] 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 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. For example, 3M's Scotch Pak™ 1012 or 9732 backing material (a polyester film with an ethylene vinyl acetate copolymer heat seal layer) is useful in the transdermal drug delivery systems described herein.

[0041] 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 (both silicone-based) and 3M's 1020, 1022, 9744, 9748 and 9749 Scotchpak™ (fluoropolymer coated polyester films).

[0042] The transdermal drug delivery system may be packaged or provided in a package, such as a pouchstock material used in the prior art for transdermal drug delivery systems in general or for transdermal testosterone drug delivery systems in particular. For example, DuPont's Surlyn® can be used in a pouchstock material.

[0043] A used herein, a "monolithic" transdermal drug delivery system may include a backing layer and/or release liner, and may be provided in a package.

[0044] 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

[0045] 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.

[0046] 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 testosterone used.

[0047] 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.

[0048] 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, methyl methacrylate, 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.

[0049] Non-functional acrylic-based polymers can include any acrylic based polymer having no or substantially no free functional groups.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] 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

[0054] The term "silicone-based" polymer is used interchangeably with the terms silicon polymers, 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.

[0055] 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, volatile 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).

[0056] 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, such as -4502, and -4600 series.

[0057] 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.

[0058] 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

[0059] 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 testosterone, in adhesive-type transdermal drug delivery system. Soluble PVP also may modulate the transdermal permeation rate of the drug.

[0060] 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).

[0061] The amount and type of soluble PVP used may depend on the quantity and type of testosterone 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.

[0062] 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.

[0063] 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 polymer 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.

[0064] The concentration by weight of the testosterone 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 testosterone is testosterone, 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 dry weight of the polymer matrix. Irrespective of whether there is high-loading or low-loading of the testosterone into the transdermal drug delivery system, the pressure-sensitive adhesive composition can be formulated to maintain acceptable shear, tack, and peel adhesive properties.

Stabilizers

[0065] In some embodiments, the polymer matrix comprises a stabilizer that stabilizes the testosterone. For example, testosterone can be formulated with an antioxidant such as butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), ascorbyl palmitate, alpha-tocopherol and its esters, citric acid and propyl gallate, and mixtures thereof. In some embodiments, a stabilizer may be used in an amount of about .001 to about 0.1% by weight, including about 0.01% by weight, such as 0.01% by weight, based on the dry weight of the polymer matrix.

Other Components

[0066] 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.

[0067] 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 dimethydecylphosphoxide, methyloctylsulfoxide, dimethylaurylamide, dodecylpyrrolidone, isosorbitol, dimethylacetone, 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.

[0068] 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.

[0069] 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.

[0070] The amount of testosterone 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 testosterone 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., testosterone) 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.

[0071] In some embodiments, a therapeutically effective amount of testosterone delivered by the composition is from about 100 to about 500 $\mu\text{g}/\text{day}$, including 100-500 $\mu\text{g}/\text{day}$ and 100-450 $\mu\text{g}/\text{day}$, and further including at least about 300 $\mu\text{g}/\text{day}$, including 300 $\mu\text{g}/\text{day}$. Thus, in some embodiments, the transdermal drug delivery system comprises an amount of testosterone effective to achieve a delivery of from about 100 to about 500 $\mu\text{g}/\text{day}$, including 100-500 $\mu\text{g}/\text{day}$ or 100-450 $\mu\text{g}/\text{day}$, or at least about 300 $\mu\text{g}/\text{day}$, including 300 $\mu\text{g}/\text{day}$. 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.

[0072] In some embodiments, the transdermal drug delivery system comprises a smaller amount of testosterone than an Intrinsa® product, but achieves comparable drug delivery. For example, in some embodiments a transdermal drug delivery system according to the invention may contain about 4 mg, including 3.94 mg, testosterone in a 14 cm^2 device, and achieve drug delivery comparable to an Intrinsa® product that contains about 8 mg, including 8.4 mg, testosterone in a 28 cm^2 device.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] In some embodiments, the system comprises a polymer matrix comprising an amount of an antioxidant, such as butylhydroxytoluene (BHT), of about .001 to about 0.1% by weight, including about 0.01 % by weight, based on the dry weight of the polymer matrix, such as 0.01% by weight butylhydroxytoluene (BHT).

[0079] 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 0-1 5% penetration enhancer, and about 0.1-10% by weight testosterone, and, optionally, about .001 to about 0.1% by weight butylhydroxytoluene (BHT), all based on the dry weight of the polymer matrix. In specific embodiments, the polymer matrix comprises about 20% by weight acrylic adhesive, about 59% by weight silicone adhesive, about 12% by weight soluble PVP, about 6% by weight oleyl alcohol, about 2-3% by weight testosterone and, optionally, about 0.01% by weight butylhydroxytoluene (BHT).

[0080] 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.

[0081] 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.

[0082] 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.

[0083] As discussed above, in some embodiments, the systems have a greater flux than other known testosterone devices for use by females (such as Intrinsa®, manufactured by Watson Pharmaceuticals 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 about $0.45 \mu\text{g}/\text{cm}^2/\text{hour}$ exhibited by the Intrinsa® product, such as a flux that is about double, such as a flux of about $0.89 \mu\text{g}/\text{cm}^2/\text{hour}$. In some embodiments, the systems described herein achieve a flux that is at least about $0.7 \mu\text{g}/\text{cm}^2/\text{hour}$, including at least $0.7 \mu\text{g}/\text{cm}^2/\text{hour}$, including at least about $0.89 \mu\text{g}/\text{cm}^2/\text{hour}$ and at least $0.89 \mu\text{g}/\text{cm}^2/\text{hour}$, or at least about $1.0 \mu\text{g}/\text{cm}^2/\text{hour}$, including at least $1.0 \mu\text{g}/\text{cm}^2/\text{hour}$, over a period of time 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.

[0084] In some embodiments, the systems have a different coat weight than other known testosterone devices. In some embodiments, the polymer matrix has a coat weight of greater than about $10 \text{ mg}/\text{cm}^2$. In some embodiments, the polymer matrix has a coat weight selected from the group consisting of about 12.0, about 12.5, about 13.0 and about $15 \text{ mg}/\text{cm}^2$.

[0085] In some embodiments, the systems have an amount of testosterone per unit area of the active surface area that is less than the $0.3 \text{ mg}/\text{cm}^2$ testosterone of the Intrinsa® product, such as an amount of testosterone of about $0.28 \text{ mg}/\text{cm}^2$.

[0086] The system may be of any shape or size suitable for transdermal application. In some embodiments, the systems are smaller than the Intrinsa® product, but achieve comparable daily dosages. For example, the systems may have an active surface area of 50% of the active surface area of an Intrinsa product, such as about 50% of 28 cm², and deliver a daily dosage of testosterone comparable to that of the Intrinsa® product, such as an amount of testosterone of at least about 300 µg/day. In one embodiment, the system has an active surface area of about 14 cm² and delivers a daily dosage of testosterone comparable to that of the 28 cm² Intrinsa® product, e.g., about 300 µg/day.

[0087] 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.

[0088] 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.

[0089] 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 testosterone can be added at any stage. In one embodiment, all polymer matrix components, including testosterone, are blended together. In another embodiment, the polymer matrix components other than testosterone are blended together, and then the testosterone 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:

Appropriate amounts of soluble PVP, solvent(s), enhancer(s), and organic solvent(s) (for example toluene, or ethyl acetate an/or isopropyl alcohol) are combined and thoroughly mixed together in a vessel.

Testosterone and any antioxidant being used (such as BHT) are added to the mixture and agitation is carried out until the drug is uniformly mixed in.

Appropriate 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.

[0090] Other manufacturing methods are known in the art that are suitable for making the systems described herein.

[0091] In some embodiments, there is provided a method of effecting transdermal drug delivery of testosterone, such as testosterone, by applying a system as described herein to the skin or mucosa of a subject in need thereof. In some embodiments, the system comprises testosterone, 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 testosterone in the subject during the application period. As noted above, a typical testosterone dosage ranges from at least about 100 to about 500 $\mu\text{g}/\text{day}$, including 100-500 $\mu\text{g}/\text{day}$ and 100-450 $\mu\text{g}/\text{day}$, including at least about 300 $\mu\text{g}/\text{day}$, including 300 $\mu\text{g}/\text{day}$.

[0092] In some embodiments, the systems described herein are designed for use by female patients, including female patients undergoing testosterone therapy for congestive heart failure. In other embodiments, the systems described herein are designed for use by female patients undergoing hormone replacement therapy or therapy to improve their libido. In some embodiments, the systems described herein may be designed are adapted for use by male patients.

[0093] 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

[0094] A polymer matrix with the following composition is prepared:

Ingredient	% w/w in Finished Dry Product
Silicone polymer (BIO PSA 4502)	59.74
Acrylic polymer (Gelva 788)	20.00
PVP (Povidone 30)	12.00
Oleyl Alcohol	6.00
Butylated Hydroxytoluene	0.01
Testosterone USP, CIII	2.25
Total	100.00

[0095] The polymer matrix is applied with a coat weight of 12.5 mg/cm² to a Scotch Pak™ 1022 release liner, and Scotch Pak™ 9732 (polyethylene) backing material is applied. Individual systems with an active surface area of 14 cm² are prepared. The systems are packaged in Surlyn® 0.0007 pouchstock material.

[0096] Human cadaver skin permeation studies are performed to quantitatively determine the effective permeation through the stratum corneum. The stratum corneum is obtained from split thickness, cryo-preserved cadaver skin by the heat separation technique. Samples of 5/16" diameter are cut from the laminate, in quadruplicate, and mounted onto 1/2" cut pieces of the stratum corneum. These samples are placed on modified Franz diffusion cells. The receptor is filled with 7.5 mL of 0.9% NaCl and 0.01% NaN₃ in deionized water. The cells are maintained at a constant 32°C and magnetically stirred at approximately 300 rpm. At specified time points, samples of the receptor phase are taken with complete replacement of the receptor phase. These samples are quantified by high-performance liquid chromatography (HPLC) utilizing Waters HPLC instrumentation. C-8 (15 cm x 4.6 mm) 5 μm particle size columns (HYPERASIL made by MetaChem Technologies, Inc., Torrance, Calif.) are used at 50 °C. (column temperature).

[0097J] Figure 1 illustrates the testosterone flux ($\mu\text{g}/\text{cm}^2/\text{hr}$) over time (0-96 hours) from a transdermal delivery system according to the invention (·, top line), as compared to Intrinsa® (♦, bottom line).

[0098] Figure 2 illustrates the cumulative amount of drug delivered per unit area ($\mu\text{g}/\text{cm}^2$) over time (0-96 hours) from a transdermal delivery system according to the invention (·, top line), as compared to Intrinsa® (♦, bottom line).

[0099] The results show that the system according to the invention achieves a greater flux than the Intrinsa® product and is able to achieve therapeutic daily dosages (such as at least $300 \mu\text{g}/\text{day}$ over three to four days) despite its 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 testosterone, wherein the system includes less than 0.3 mg/cm² testosterone and achieves a testosterone flux that is at least 0.7 g/cm²/hour, based on the active surface area.
2. The transdermal drug delivery system of claim 1, wherein the system achieves a testosterone flux that is at least 0.89 g/cm²/hour, based on the active surface area.
3. 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.
4. 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 testosterone, all based on the total dry weight of the polymer matrix.
5. The transdermal drug delivery system of claim 4, wherein the penetration enhancer comprises oleyl alcohol.
6. The transdermal drug delivery system of claim 4, wherein the composition further comprises an antioxidant selected from the group consisting of butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), ascorbyl palmitate, alpha-tocopherol and its esters, citric acid and propyl gallate, and mixtures thereof.
7. The transdermal drug delivery system of claim 6, wherein the antioxidant comprises BHT.

8. The transdermal drug delivery system of claim 4, 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.

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

10. The transdermal drug delivery system of claim 1, wherein the polymer matrix comprises an amount of testosterone effective to deliver an amount of testosterone of at least about 100 to about 500 $\mu\text{g}/\text{day}$.

11. The transdermal drug delivery system of claim 1, wherein the polymer matrix comprises an amount of testosterone effective to deliver an amount of testosterone of at least about 100 to about 450 $\mu\text{g}/\text{day}$.

12. The transdermal drug delivery system of claim 1, wherein the polymer matrix comprises an amount of testosterone effective to deliver an amount of testosterone of at least about 100 to about 450 $\mu\text{g}/\text{day}$.

13. The transdermal drug delivery system of claim 4, wherein the polymer matrix comprises about 20% by weight acrylic adhesive, about 59% by weight silicone adhesive, about 12% by weight soluble PVP, about 6% by weight oleyl alcohol, and about 2-3% by weight testosterone, all based on the total dry weight of the polymer matrix.

14. The transdermal drug delivery system of claim 13, wherein the polymer matrix further comprises about 0.01% by weight BHT, based on the total dry weight of the polymer matrix.

15. The transdermal drug delivery system of claim 4, wherein the polymer matrix has a coat weight of greater than about 10 mg/cm².

16. The transdermal drug delivery system of claim 4, wherein the polymer matrix has a coat weight of about 12.5 mg/cm².

17. A transdermal drug delivery system comprising a polymer matrix comprising testosterone, wherein the system has an active surface area of 14.0 cm² and is effective to deliver an amount of testosterone per day of at least 300 µg.

18. A method for administering testosterone, 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 testosterone, wherein the system includes less than 0.3 mg/cm² testosterone and achieves an testosterone flux that is at least 0.7 µg/cm²/hour, based on the active surface area.

19. The method of claim 14, wherein the system achieves a testosterone flux that is at least 0.89 µg/cm²/hour, based on the active surface area.

20. The method of claim 18, wherein the system has an active surface area that is about 14.0 cm² and is effective to deliver an amount of testosterone per day of at least about 300 µg.

21. A method of making a transdermal drug delivery system for administering testosterone, comprising forming a polymer matrix comprising testosterone 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 less than 0.3 mg/cm² testosterone.

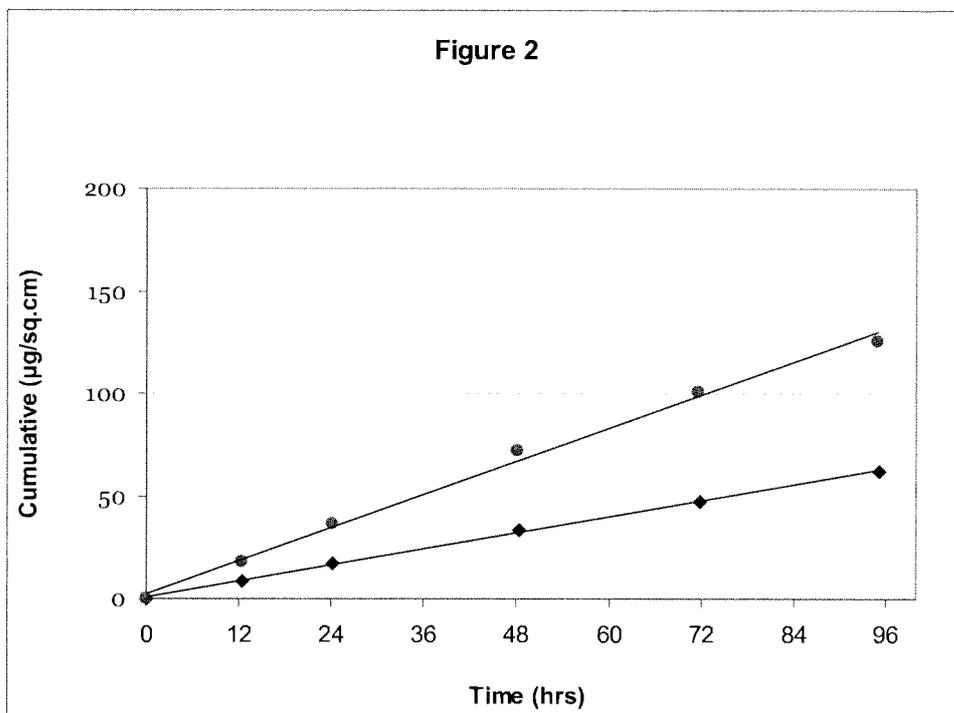
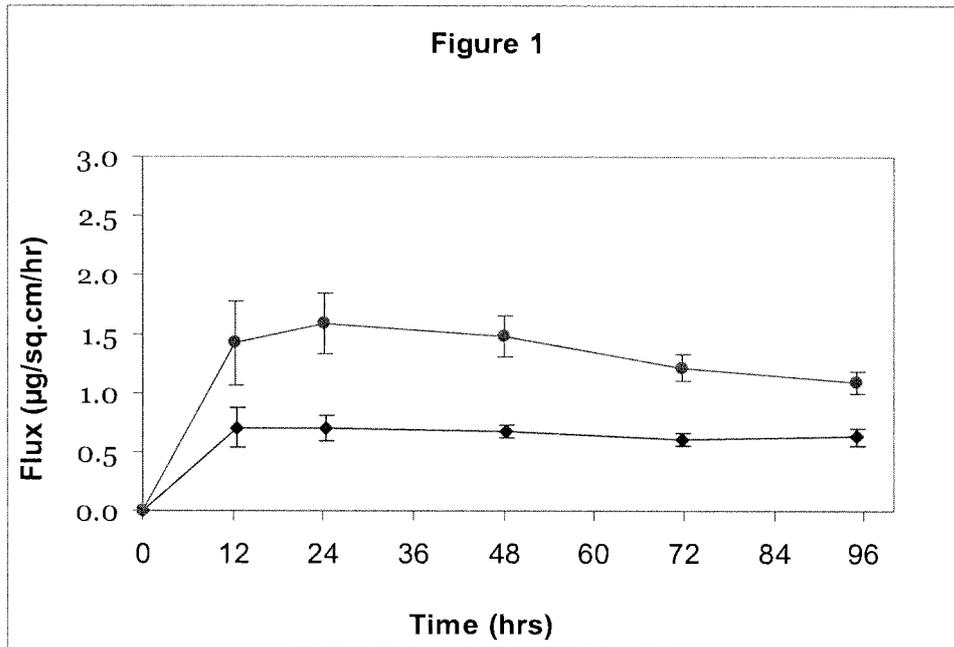
22. The method of claim 21, wherein the system has an active surface area that is about 14.0 cm².

23. The method of claim 21, wherein the polymer matrix comprises about 20% by weight acrylic adhesive, about 59% by weight silicone adhesive, about 12% by weight soluble PVP, about 6% by weight oleyl alcohol, and about 2-3% by weight testosterone, all based on the total dry weight of the polymer matrix.

24. The method of claim 23, wherein the polymer matrix further comprises about 0.01% by weight BHT, based on the total dry weight of the polymer matrix.

25. The method of claim 21, wherein the polymer matrix is applied to the support layer at a coat weight of greater than about 10 mg/cm².

26. The method of claim 21, wherein the polymer matrix coat weight is about 12.5 cm².



INTERNATIONAL SEARCH REPORT

International application No
PCT/US201Q/057797

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K9/70 A61K31/568 A61K47/32 A61L15/20 A61L15/58
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
 A61K A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
 EPO-Internal , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/078602 AI (KANIOS DAVID [US]) 13 April 2006 (2006-04-13) paragraphs [0015] - [0017] , [0103] ; example 7 -----	1-26
Y	W0 2009/142699 AI (PROCTER & GAMBLE [US] ; KARAM ROGER [US] ; ROSANO GIUSEPPE MASSIMO CLAUD) 26 November 2009 (2009-11-26) page 2, line 16 - page 3, line 7 page 15, line 13 - page 16, line 2 -----	1-26
Y	W0 2006/041907 A2 (NOVEN PHARMA [US] ; KANIOS DAVID [US] ; HARTWIG ROD [US]) 20 April 2006 (2006-04-20) paragraphs [0014] - [0015] ; examples ----- -/--	1-26

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 31 March 2011	Date of mailing of the international search report 13/04/2011
--	--

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Giese, Hans-Hermann
--	---

INTERNATIONAL SEARCH REPORT

International application No
PCT/US201Q/057797

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 024 976 A (MI RAN DA JESUS [US] ET AL) 15 February 2000 (2000-02-15) the whole document -----	1-26
Y	WO 02/102390 A1 (NOVEN PHARMA [US] ; HOUZE DAVID [US] ; NGUYEN VI ET [US]) 27 December 2002 (2002-12-27) paragraphs [0006] - [0016] ; exampl e 3 -----	1-26
Y	EP 1 329 225 A2 (NOVEN PHARMA [US]) 23 July 2003 (2003-07-23) paragraphs [0010] - [0012] , [0052] , [0066] ; exampl es -----	1-26
Y	us 5 460 820 A (EBERT CHARLES D [US] ET AL) 24 October 1995 (1995-10-24) exampl es 1-2 -----	1-26
A	"Drugs for female sexual dysfuncti on [1] ", OBSTETRICS AND GYNECOLOGY, LI PPINCOTT WILLIAMS & WILKINS, US, vol . 110, no. 4, 1 October 2007 (2007-10-01) , pages 918-919, XP008091620, ISSN : 0029-7844 the whole document -----	1-26
A	SEFTEL A: "Testosterone repl acement therapy for male hypogonadi sm: part III . Pharmacol ogi c and clinical profi les, moni toring, safety i ssues , and potenti al future agents" , INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH , STOCKTON, BASINGSTOKE, GB, vol . 19, no. 1, 1 January 2007 (2007-01-01) , pages 2-24, XP008082232, ISSN : 0955-9930, DOI : DOI : 10. 1038/SJ . IJIR. 3901366 the whole document -----	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US201Q/057797

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006078602	AI	13-04-2006	NON E

WO 2009 142699	AI	26-11-2009	AR 071824 AI 14-07-2010 PE 185 12009 AI 04-01-2010 US 2009285893 AI 19-11-2009

WO 200604 1907	A2	20-04-2006	NON E

US 6024976	A	15-02-2000	NON E

WO 02102390	AI	27-12-2002	AR 0345 18 AI 25-02-2004 BR Q2 105 16 A 05-10-2004 CA 245 1043 AI 27-12-2002 CL 4892Q08 AI 11-04-2008 CN 1543349 A 03-11-2004 EP 1406633 AI 14-04-2004 JP 2005500299 T 06-01-2005 MX PA030119 10 A 03-06-2004 NZ 530227 A 29-09-2006 RU 2358699 C2 20-06-2009 TW 12774 18 B 01-04-2007 US 2003 1526 13 AI 14-08-2003 US 2003232073 AI 18-12-2003 US 2003 1526 14 AI 14-08-2003 US 2003 1526 15 AI 14-08-2003 US 2008 167365 AI 10-07-2008 US 2008 167280 AI 10-07-2008

EP 1329225	A2	23-07-2003	NON E

US 5460820	A	24-10-1995	AT 304845 T 15-10-2005 AU 690578 B2 30-04-1998 AU 75 17894 A 28-02-1995 CA 2168879 AI 09-02-1995 CN 113 1907 A 25-09-1996 CN 1550233 A 01-12-2004 DE 122007000006 11 19-04-2007 DE 6943449 1 T2 22-06-2006 DK 07 12303 T3 16-01-2006 EP 07 12303 AI 22-05-1996 ES 2245777 T3 16-01-2006 JP 9500653 T 21-01-1997 JP 2002 12 1136 A 23-04-2002 JP 20052638 14 A 29-09-2005 JP 2009 185074 A 20-08-2009 LU 91309 A9 15-06-2007
US 5460820	A		NL 300259 11 02-04-2007 NO 960445 A 26-03-1996 TW 49288 1 B 01-07-2002 WO 9503764 AI 09-02-1995 ZA 9405782 A 10-03-1995
