PHARMACEUTICAL COMPOSITIONS OF 5-ALPHA-REDUCTASE INHIBITORS AND METHODS OF USE THEREOF

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Abstract

Non-occlusive compositions for transdermal delivery of 5-alpha-reductase inhibitors, and more particularly finasteride or dutasteride or pharmaceutically acceptable salts or derivatives thereof, and methods of making same. The composition may, for example, be a gel suitable for transdermal or transmucosal applications. The compositions of the present invention typically include a mixture of water and alcohol, and a solvent system having a mono alkyl ether of diethylene glycol and a glycol present in specified ratios and in specific amounts, wherein the pH of the gel is usually between about pH 4.5 and about pH 8. The compositions may include further components, for example, the hydroalcoholic vehicle may further include additional penetration enhancer(s), buffering agent(s), antioxidant(s), stabilizer(s) and/or gelling agent(s). Also, a method for the sustained delivery of 5-alpha-reductase inhibitors to treat a variety of conditions and disorders.

Equilibrium Solubility (16H) of DUTASTERIDE in various pure solvents

- Ethanol
- Isopropanol
- CAPMUL MCM NF
- Transcutol
- Propylene glycol
- PEG 400
- Ethanol (Lit)
- PEG 400 (Lit)
Equilibrium Solubility (16H) of DUTASTERIDE in various pure solvents

- Ethanol
- Isopropanol
- CAPMUL MCM NF
- Transcutol
- Propylene glycol
- Ethanol (Lit)
- PEG 400
- PEG 400 (Lit)

FIG. 1
Equilibrium Solubility (16H) of DUTASTERIDE in various solvents systems

FIG. 2
Effect of pH on Equilibrium Solubility (16H) of DUTASTERIDE in various solvents systems

FIG. 3
PHARMACEUTICAL COMPOSITIONS OF 5-ALPHA-REDUCTASE INHIBITORS AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS


TECHNICAL FIELD

[0002] The present invention relates to novel transdermal or transmucosal pharmaceutical formulations, including compositions and dosage forms, of dutasteride and its pharmaceutically acceptable salts thereof, and a hydroalcoholic solvent system, wherein the solvent system includes monoaeryl glycol ethers and glycols in specific ratios.

[0003] Described herein are formulations that are useful and efficacious for transdermal delivery, as well as methods of use and methods of manufacturing for such formulations.

BACKGROUND OF THE INVENTION

[0004] Transdermal delivery, i.e. the ability to deliver pharmaceuticals agents into and through skin surfaces, provides many advantages over oral or parenteral delivery techniques. In particular, transdermal delivery provides a safe, convenient and non invasive alternative to traditional administration systems that can provide a straightforward dosage regimen, relatively slow release of the drug into a patient’s system, and control over blood concentrations of the drug. In contrast to oral administration, transdermal delivery typically does not produce the plasmatic peaks and valleys created by oral delivery and G.I. tract absorption. Second, transdermal delivery causes no gastrointestinal irritation, does not present restrictions around the time that the drug should be administered or whether or not the patient may eat afterwards. In particular, once-a-day transdermal delivery offers ease of use and is convenient, without the requirement to remember to take a drug at a specific time. Third, transdermal delivery improves patient compliance for patients who cannot swallow medication, for drugs with unpleasant taste and/or undergoing significant metabolism in the liver; the resulting increased bioavailability, which means that smaller doses may be used for the same drug, is responsible for minimized side effects. In contrast to parenteral administration, transdermal delivery typically does not cause pain and/or anxiety associated with needles, and does not present the risk of introducing infection to treated individuals, the risk of contamination or infection of health care workers caused by accidental needle-sticks and the risk of disposal of used needles.

[0005] The advantage of transdermal delivery is particularly enhanced in case of hydrophilic drugs, because of the molecular nature of the G.I. tract. As a lipid membrane, the G.I. tract possesses hydrophobic properties, thus the more hydrophilic a drug is, and the more likely it is to be absorbed poorly through the G.I. tract. A well known example of this problem is sodium alendronate, a bisphosphonate, which needs to be administered in very large doses because only a very small fraction of the drug (about 0.6%) is absorbed when administered orally (please refer to FOSamax® Tablets and Oral Solutions Prescribing Information, issued by Merck & Co., Inc., the entire content is incorporated herein for information).

[0006] However, despite its clear advantages, transdermal delivery also poses inherent challenges, in part because of the nature of skin. Skin is essentially a thick membrane that protects the body by acting as a barrier. Consequently, passive delivery through intact skin necessarily entails the transport of molecules through a number of structurally different tissues, including the stratum corneum, the viable epidermis, the papillary dermis and the capillary walls in order for the drug to gain entry into the blood or lymph system. Each tissue features a different resistance to penetration, but the stratum corneum is the strongest barrier to the absorption of transdermal and topical drugs. The tightly packed cells of the stratum corneum are filled with keratin. The keratinization and density of the cells may be responsible for skin’s impermeability to certain drugs. Transdermal delivery systems must therefore be able to overcome the various resistances presented by each type of tissue.

[0007] In recent years, advances in transdermal delivery include the formulation of skin penetration enhancing agents, also known as permeation enhancers. Permeation enhancers are often lipophilic chemicals that readily move into the stratum corneum and enhance the movement of drugs through the skin. Energy-assisted skin penetration techniques also have emerged to improve transdermal delivery, including heat, ultrasound, iontophoresis, and electroporation. But even with these methodologies, only a limited number of drugs can be administered transdermally without problems such as sensitization or irritation occurring.

[0008] Transdermal delivery is different from topical delivery. Drugs administered transdermally are absorbed through skin or mucous membranes and provide effects beyond the application site. In contrast, purpose of a topical drug, e.g., antibiotic ointment, anti-acne cream, hair-growing lotion, anti-itching spray, is to administer medication at the site of intended action. Topical medications typically should be designed not to permit significant drug passage into the patient’s blood and/or tissues. Topical formulations are often used to treat infections or inflammations. They also are used as cleansing agents, astringents, absorbents, keratolytics, and emollients. The vehicle of a topical treatment, i.e. the non-active component(s) that carries the active ingredient(s), may interact with the active ingredient(s), changing the drug’s effectiveness. The vehicle may also cause skin irritation or allergic reactions in some patients. Thus, the vehicle must be selected with extreme care. Topical formulations may be prepared as pastes, gels, creams, ointments, lotions, solutions, or aerosols. Occlusion with household plastic wrap, bandages, plasters, or plastic tape, is often used in conjunction with topical treatments to improve the drug’s absorption and its effectiveness. Typically non-occlusive dosage forms are applied to the skin or mucosa and are left uncovered and open in the atmosphere. Because the non-occlusive dosage form is left uncovered, unwanted transfer of the pharmaceutical formulation to the clothing of the user or even to other individuals in close proximity to the user is unavoidable. Other drawbacks of the non-occlusive dosage form include evaporation of the formulation, removal of the formulation from the skin
or mucosa, for example, by bathing or by other activities, and the non absorption of the formulation through the skin, which is discussed below.

**[0009]** The inefficiencies of drug permeation across or through the skin or mucosa barriers are known. It is also known that the permeation of a drug in a non-occlusive transdermal or transmucosal dosage form can be as little as 1% and usually is no more than 15%. Thus, a vast majority of the active drug remains unabsorbed on the skin or mucosa surface. Because the vast majority of the drug remains on the skin and does not penetrate the skin or mucosa surfaces, the bioavailability of the particular drug is not optimal, and also a high risk of contamination of other individuals in close proximity to the user is presented by the unwanted transfer of the pharmaceutical formulation in the non-occlusive dosage form.


**[0011]** Moreover, the patient information brochure for ANDROGEL® (1% testosterone gel from Unimed Pharmaceuticals Inc.) emphasizes the potential for transfer of test-osterone to other people and/or clothing and the brochure includes safety measures to be taken by the individual using the non-occlusive dosage form.

**[0012]** One way to overcome or minimize this contamination issue is to physically protect the transdermal dosage form by covering skin with the applied pharmaceutical formulation means of a patch device, a fixed reservoir, an application chamber, a tape, a bandage, a sticking plaster, or the like, which remain on the skin at the site of application of the formulation for a prolonged length of time. This is usually accomplished with occlusive dosage forms.

**[0013]** Occlusive dosage forms present some advantages over non-occlusive dosage forms such as assisting the rate of penetration of drugs across the skin by maintaining the thermodynamic activity of the drug close to its maximum (the thermodynamic activity of a drug in a dermal formulation is proportional to the concentration of the drug and the selection of the vehicle, and according to the laws of thermodynamics, the maximum activity of a drug is related to that of the pure drug crystal). However occlusive dosage forms also exhibit several major drawbacks. For example, occlusive dosage forms present a high potential of local skin irritation caused by the prolonged contact on the skin of the drug, volatiles, vehicle excipients, and the adhesive used to attach the occlusive device, e.g., the patch, to the skin. In addition, the occlusive nature of certain occlusive dosage forms, such as the patch device, also restrict the natural ability of the skin to "breathe," and thereby increases the risk of irritation.

**[0014]** In addition to the aforementioned drawbacks of occlusive dosage forms, significant serious hazards have been documented regarding the high drug loading that is specific to patches. For example, several cases of abuses with remaining fentanyl in fentanyl patches have been reported. See, Marquardt K. A., Thrarrat R. S., “Inhalation abuse of fentanyl patch”, J Toxicol Clin. Toxicol. 1994; 32(1):75-8; Marquardt K. A., Thrarrat R. S., Musallam N. A., “Fentanyl remaining in a transdermal system following three days of continuous use”; Ann Pharmacother. 1995 October; 29(10):969-71; Flannagan L M, Butts JD, Anderson WH., “Fentanyl patches left on dead bodies — potential source of drug for abusers”, J Forensic Sci. 1996 March; 41(2):320-1. Severe incidental intoxication cases have also been documented. See Hardwick Jr., W, King, W, Palmisano, P., “Respiratory Depression in a Child Unintentionally Exposed to Transdermal Fentanyl Patch”, Southern Medical Journal, September 1997.

**[0015]** Patch products typically contain patient information, which clearly indicate the risks discussed above. For instance, OXYTROL™ (an oxynutrin patch commercialized by WATSON Pharmaceuticals, Inc. USA) contains patient information that indicates the following warning: “Since the patch will still contain some oxynutrin, throw it away so that it can not be accidentally worn or swallowed by another person, especially a child.” The high level of active drug residues is thus a critical drawback of patches. Such accidents could not occur with the use of gel formulations.

**[0016]** Although attempts have been made to overcome drawbacks associated with both occlusive and non-occlusive drug forms, such attempts have been futile. For example, as noted above, one drawback of non-occlusive dosage forms is evaporation of the formulation, which is left open in the atmosphere. The formulation of non-occlusive supersaturated systems could have achieved an ideal merge but transdermal formulations, which rely on supersaturation technologies, present a major drawback of formulation instability, both prior to and during application to the skin due to solvent evaporation. See Davis A F and Hadgraft J:—Supersaturated solutions as topical drug delivery systems, Pharmaceutical Skin Penetration Enhancement, Marcel Dekker Inc, New York (1993) 243-267 ISBN 0 8247 9017 0, which is incorporated herein by reference.

**[0017]** Notably, extraordinary physicochemical changes occur with the evaporation of the solvent system, which result in modifications of the concentration of the active agent, which may even lead to drug precipitation, thereby altering the diffusional driving force of the formulation. See Ma et al, Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 22 (1995). Consequently, the percutaneous absorption of the active agent may be quite different from that when the solvent was present.

**[0018]** In addition, controlling drug crystallization is of particular interest for non-occlusive transdermal systems. Campbell et al. resorted to a method of heating a crystalline hydrate to a temperature above the melting point in order to prevent the crystallization of the formulation. See, U.S. Pat. No. 4,832,953. Ma et al found that PVP added to the matrix acts as an effective crystallization inhibitor for norethindrone acetate transdermal delivery systems. See, Int. J. of Pharm. 142 (1996) pp. 115-119. DE-A-4210711 affirms that cholesteryl and SiO₂ are crystallization inhibitors for 17-beta-estradiol transdermal delivery system. WO 95/18603 describes soluble PVP as crystal inhibitor for patch devices and affirms that soluble PVP increases the solubility of a drug without negatively affecting the adhesion or the rate of drug delivery from the pressure-sensitive adhesive composition.
Additionally, the inhibition of crystallization in transdermal devices was reported by Biali et al. See, U.S. Pat. No. 6,465,005 in which it is described that the use of a steroid (estradiol for instance) as an additive in a process of manufacture or storage of a transdermal device acts as a crystallization inhibitor during storage of the device.

Further, transdermal delivery from semi-solid formulations faces opposite requirements. The drug delivery system should enable absorption of an extensive amount of active drug through the skin within the shortest period of time in order to prevent contamination of individuals, transfer to clothing or accidental removing. The drug delivery system should also provide sustained release of the active drug over 24 hours ideally, so that only once-daily application is required. This drug delivery system should also prevent drug crystallization at the application surface area.

Drug delivery systems having such properties may be achieved by combining various solvents. A volatile solvent may be defined as a solvent that changes readily from solid or liquid to a vapor, that evaporates readily at normal temperatures and pressures. Here below is presented data for some usual solvents, where volatility is reflected by the molar enthalpy of vaporization \( \Delta_{\text{vap}} H \), defined as the enthalpy change in the conversion of one mole of liquid to gas at constant temperature. Values are given, when available, both at the normal boiling point \( T_b \), referred to a pressure of 101.325 kPa (760 mmHg), and at 25°C. (From “Handbook of Chemistry and Physics, David R. Lide, 79th edition (1998–1999)—Enthalpy of vaporization (6-100 to 6-115). Stanislaus et al. (U.S. Pat. No. 4,704,406 on Oct. 9, 2001) defined as volatile solvent a solvent whose vapor pressure is above 35 mm Hg when the skin temperature is 32°C, and as non-volatile solvent a solvent whose vapor pressure is below 10 mm Hg at 32°C skin temperature. Examples of non-volatile solvents include, but are not limited to, propylene glycol, glycerin, liquid polyethylene glycol, or polyoxyalkylene glycols. Examples of volatile solvents include, but are not limited to, ethanol, propanol, or isopropanol.

### Table 1

<table>
<thead>
<tr>
<th>Solvent</th>
<th>( T_b ) (°C)</th>
<th>( \Delta_{\text{vap}} H ) (kJ mol(^{-1}))</th>
<th>( \Delta_{\text{vap}} H ) (25°C) (kJ mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>78.3</td>
<td>38.6</td>
<td>42.3</td>
</tr>
<tr>
<td>Propan-2-ol (isopropanol)</td>
<td>82.3</td>
<td>39.9</td>
<td>45.4</td>
</tr>
<tr>
<td>Propandiol</td>
<td>97.2</td>
<td>41.4</td>
<td>47.5</td>
</tr>
<tr>
<td>Butan-2-ol</td>
<td>90.5</td>
<td>40.8</td>
<td>40.7</td>
</tr>
<tr>
<td>Butan-1-ol</td>
<td>117.7</td>
<td>43.2</td>
<td>52.4</td>
</tr>
<tr>
<td>Ethylene glycol mono methyl ether</td>
<td>124.1</td>
<td>46.9</td>
<td>45.2</td>
</tr>
<tr>
<td>Ethylene glycol mono ethyl ether</td>
<td>135.0</td>
<td>39.2</td>
<td>48.2</td>
</tr>
<tr>
<td>Ethylene glycol mono propyl ether</td>
<td>149.8</td>
<td>41.4</td>
<td>52.1</td>
</tr>
<tr>
<td>1,2-Propylene glycol</td>
<td>187.6</td>
<td>52.4</td>
<td>Not available</td>
</tr>
<tr>
<td>Diethylene glycol mono methyl ether</td>
<td>193.0</td>
<td>46.6</td>
<td>Not available</td>
</tr>
<tr>
<td>Diethylene glycol mono ethyl ether</td>
<td>196.0</td>
<td>47.5</td>
<td>Not available</td>
</tr>
<tr>
<td>1,3-Propylene glycol</td>
<td>214.4</td>
<td>57.9</td>
<td>Not available</td>
</tr>
<tr>
<td>Glycerol</td>
<td>200.0</td>
<td>61.0</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Numerous authors have investigated evaporation and transdermal penetration from solvent systems. For Example, Spencer et al. (Thomas S. Spencer, “Effect of volatile penetrants on in vitro skin permeability”, AAPS workshop held in Washington D.C. on Oct. 31-Nov. 1, 1986) established that the relationship between volatility and penetration is not absolute and depends on many parameters such as for instance hydration of the tissue or the solubility of the penetrant in the tissue. Stinchcomb et al. reported that the initial uptake of a chemical (hydrocortisone, flurbiprofen) from a volatile solvent system (acetone) is more rapid than that from a non-volatile solvent system (aqueous solution). With an aqueous solution, close to the saturation solubility of the chemical, the driving force for uptake remains more or less constant throughout the exposure period. Conversely, for a volatile vehicle which begins evaporating from the moment of application, the surface concentration of the chemical increases with time up to the point at which the solvent has disappeared; one is now left with a solid film of the chemical from which continued uptake into the stratum corneum may be very slow and dissolution-limited.

Risk assessment following dermal exposure to volatile vehicles should pay particular attention, therefore, to the duration of contact between the evaporating solvent and the skin (Andra L. Stinchcomb, Fabrice Pinot, Gilles D. Tournaille, Annette L. Bunge, and Richard H. Guy, “Chemical uptake into human stratum corneum in vivo from volatile and non-volatile solvents”, Pharmaceutical Research, Vol. 16, No 8, 1999). Kondo et al. studied bioavailability of percutaneous nifedipine in rats from binary (acetone and propylene glycol PG or isopropyl myristate IPM) or ternary (acetone-PG-IPM) solvent systems, compared with the results from simple PG or IPM solvent systems saturated with the drug. (Kondo et al. S, Yamazaki C, Sugimoto J., “Enhancement of transdermal delivery by superfusible thermodynamic potential III. Percutaneous absorption of nifedipine in rats”, J Pharmaco Biodyn. 1987 December; 10(12):743-9).

U.S. Pat. No. 6,299,900 to Reed et al. discloses a non-occlusive, percutaneous, or transdermal drug delivery system—having active agent, safe and approved sunscreen as penetration enhancer, and optional volatile liquid. The invention describes a transdermal drug delivery system, which comprises at least one physiologically active agent or prodrug thereof and at least one penetration enhancer of low toxicity being a safe skin-tolerant ester sunscreen. The composition comprises an effective amount of at least one physiologically active agent, at least one non-volatile dermal penetration enhancer; and at least one volatile liquid.

U.S. Pat. No. 5,891,462 to Carrara discloses a pharmaceutical formulation in the form of a gel suitable for the transdermal administration of an active agent of the class of estrogens or of progestin class or of a mixture thereof, comprising lauryl alcohol, diethylene glycol mono ethyl ether and propylene glycol as permeation enhancers.


Williams et al. reports the effects of diethylene glycol mono ethyl ether (TRANSCUTOL™) in binary co-solvent systems with water on the permeation of a model lipophilic drug across human epidermal and silastic membranes (A. C. Williams, N. A. Megrab and B. W. Barry, “Permeation of oestriadiol through human epidermal and silastic membranes from saturated TRANSCUTOL®/water systems”, in Prediction of Percutaneous Penetration, Vol. 4B, 1996). Many references may also illustrate the effect of TRANSCUTOL™ as an intracutaneous drug depot builder well known to one skilled in the art.
[0028] U.S. Pat. No. 5,658,587 to Santus et al. discloses transdermal therapeutic systems for the delivery of alpha adrenoceptor blocking agents using a solvent enhancer system comprising diethyleneglycol mono ethyl ether and propylene glycol.

[0029] U.S. Pat. No. 5,662,890 to Punto et al. discloses alcohol-free cosmetic compositions for artificially tanning the skin containing a combination of diethyleneglycol mono ethyl ether and dimethyldisorbide as permeation enhancers.

[0030] U.S. Pat. No. 5,932,243 to Fricker et al. discloses a pharmaceutical emulsion or microemulsion preconcentrate for oral administration of macrolide containing a hydrophilic carrier medium consisting of diethyleneglycol mono ethyl ether, glycerol, 1,2-propylene glycol, or mixtures thereof.

[0031] U.S. Pat. Nos. 6,267,985 and 6,383,471 to Chen et al. disclose pharmaceutical compositions and methods for improved solubilization of triglycerides and improved delivery of therapeutic agents containing diethyleneglycol mono ethyl ether and propylene glycol as solubilizers of ionizable hydrophobic therapeutic agents.

[0032] U.S. Pat. No. 6,426,078 to Bauer et al. discloses an oil-in-water microemulsion containing diethyleneglycol mono ethyl ether or propylene glycol as co-emulsifier of lipophilic vitamins.


[0034] Thus there remains a need to provide a pharmaceutically acceptable transdermal or transmucosal pharmaceutical formulation or drug delivery system that exhibits the advantages of both occlusive systems (high thermodynamic activity) and non-occlusive systems (low irritation and sensitization potential, and excellent skin tolerance) while overcoming the disadvantages of these systems. The novel transdermal or transmucosal pharmaceutical formulation of the present invention satisfies this need.

[0035] The present invention is directed to the transdermal administration of 5-alpha reductase inhibitors. 5-alpha reductase is an enzyme that converts testosterone, the male sex hormone, into the more potent dihydrotestosterone (DHT). The 5-alpha reductase exists as two isoenzymes, namely the steroid 5-alpha reductase 1 (SRD5A1) and the steroid 5-alpha reductase 2 (SRD5A2). The second isoenzyme is deficient in 5-alpha-reductase deficiency which leads to a form of intersexuality.

[0036] The enzyme 5-alpha reductase is produced only in specific tissues of the male human body, namely the skin, seminal vesicles, prostate and epididymis. Inhibition of 5-alpha reductase results in decreased production of DHT, increased levels of testosterone and possibly increased levels of estradiol.

[0037] 5-alpha-reductase inhibitor drugs are clinically used in the treatment of conditions which are exacerbated by dihydrotestosterone, such as mild-to-moderate benign prostatic hyperplasia (BPH), prostate cancer and androgenetic alopecia (also known as male-pattern baldness). In benign prostatic hyperplasia, dihydrotestosterone acts as a potent cellular androgen and promotes prostate growth—inhbiting the enzyme reduces the excessive prostate growth. In alopecia, male-pattern baldness is one of the effects of androgen receptor activation. Reducing the levels of DHT thus reduces alopecia. Finasteride inhibits the function of only one of the isoenzymes (type 2), while dutasteride inhibits both forms. These drugs decrease the levels of available 5α-reductase prior to testosterone binding with the enzyme, thus reducing levels of DHT that derives from such a bond.

[0038] Adverse drug reactions experienced with 5α-reductase inhibitors are generally dose-dependent. Common adverse drug reactions include impotence, decreased libido, decreased ejaculate volume. Rare adverse drug reactions include: breast tenderness and enlargement (gynecomastia), and allergic reaction.

[0039] Thus there is a need for optimized delivery of 5-alpha-reductase inhibitor drug enhancing therapeutic effects while reducing occurrence and or importance of adverse drug reactions associated with treatment with 5α-reductase inhibitor drugs.

[0040] A variety of patents have disclosed compositions containing 5α-reductase inhibitor drugs such as finasteride or dutasteride: see, e.g., U.S. Pat. Nos. 6,998,138; 6,974,569; 6,818,226; 6,733,776; 6,649,155; 6,630,164; 6,451,300; 6,271,246; 6,090,409; the entire content of which are incorporated herein as reference.

[0041] No admission is made that any reference, including any patent or patent document, cited in this specification constitutes prior art. In particular, it will be understood that, unless otherwise stated, reference to any document herein does not constitute an admission that any of these documents forms part of the common general knowledge in the art in United States of America or in any other country. The discussion of the references states what their authors assert, and the applicant reserves the right to challenge the accuracy and pertinency of any of the documents cited herein.

[0042] In view of the aforementioned, there remains a need to provide a pharmaceutically acceptable transdermal or transmucosal pharmaceutical formulation or drug delivery
system containing 5-alpha-reductase inhibitors or pharmaceutically acceptable salts thereof or pharmaceutically acceptable derivatives thereof that exhibit the advantages of both occlusive systems (high thermodynamic activity) and non-occlusive systems (low irritation and sensitization potential, and excellent skin tolerance) while overcoming the disadvantages of these systems. The novel transdermal or transmucosal pharmaceutical formulation of the present invention satisfies this need.

SUMMARY OF THE INVENTION

[0043] In one aspect, the present invention relates to non-occlusive compositions for pharmaceutical drug delivery. In one embodiment, the composition may be formulated to be suitable for transdermal application. The composition typically comprises a therapeutically effective amount of 5-alpha-reductase inhibitors. Further, the composition may be a lotion or a low-viscosity, medium-viscosity, or high-viscosity gel. The composition typically comprises a primary vehicle comprising a mixture of a mono alkyl ether of diethylene glycol, a glycol, at least one short-chain alcohol, water. Optionally, the composition also comprises a fatty permeation enhancer. Preferred fatty permeation enhancers are selected from the group of saturated fatty alcohols or fatty acids, or mixtures thereof, and having the formula CH₃(CH₂)ₙ−CH₂OH or CH₃(CH₂)ₙ−H₂COOH, respectively, in which n is an integer from 8 to 22, preferably 8 to 12, most preferably 10; Some other preferred fatty permeation enhancers are selected from the group of unsaturated fatty alcohols or fatty acids, or mixtures thereof, and having the formula CH₃(CH₂ₙ−OH or CH₃(CH₂ₙ−COOH, respectively, in which n is an integer from 8 to 22. Most preferred fatty permeation enhancers are lauryl alcohol and lauric acid, myristyl alcohol and myristic acid, and oleyl alcohol and oleic acid, or mixtures thereof.

[0044] In another embodiment of the present invention, the compositions may include further components as described herein, for example, the hydroalcoholic vehicle described herein above may further comprise additional solvent(s), antioxidant(s), cosolvent(s), penetration enhancer(s), buffering agent(s), and/or gelling agent(s). The apparent pH of the composition is usually between about pH 4.5 and about pH 8.5, and the composition is designed for application to the surface of skin or of the scalp.

[0045] Preferred embodiments of the present invention are low- to medium-viscosity gel formulations for non-occlusive therapeutic applications, with a viscosity ranging from 1,000 to 20,000 centipoises.

[0046] The formulations of the present invention may be provided, for example, in unit dose container(s) or multiple dose containers e.g., metering-dose dispensers.

[0047] In another aspect the present invention comprises a composition for pharmaceutical drug delivery. Such compositions may, for example, comprise a therapeutically effective amount of 5-alpha-reductase inhibitors, or a pharmaceutically acceptable salt or derivative thereof, in a hydroalcoholic vehicle as described herein above. In such compositions the transdermal flux of the 5-alpha-reductase inhibitor in the hydroalcoholic vehicle of the present invention is greater than the transdermal flux of an equal concentration of dutasteride in an essentially equivalent time period, wherein the skin acts as the flux rate controlling membrane.

[0048] In yet another aspect the present invention comprises a composition for pharmaceutical drug delivery. Such compositions may, for example, comprise a therapeutically effective amount of a 5-alpha-reductase inhibitor, or a pharmaceutically acceptable salt or derivative thereof, in a hydroalcoholic vehicle. In such compositions the transdermal flux of the dutasteride in the hydroalcoholic vehicle of the present invention is independent from the apparent pH of said compositions.

[0049] The above-described compositions for pharmaceutical delivery may include further components as described herein, for example, the hydroalcoholic vehicle may further comprise additional solvent(s), antioxidant(s), cosolvent(s), penetration enhancer(s), buffering agent(s), and/or gelling agent(s).

[0050] The compositions of the present invention may be used, for example, for transdermal applications including application to the skin (for example, arms, shoulders, scalp, thumbs, abdomen) or to the mucosal tissues (for example, intranasally, intrabucally, as an ovule or as a suppository).

[0051] In yet another aspect, the present invention includes dosage forms for pharmaceutical delivery of a drug, preferably a 5-alpha-reductase inhibitor such as, for example, finasteride or dutasteride. In one embodiment, the dosage form is configured to provide steady-state delivery of finasteride or dutasteride with once-a-day dosing.

[0052] In a further aspect, the present invention includes methods of manufacturing the compositions described herein for pharmaceutical drug delivery.

[0053] In another aspect, the present invention includes methods for administering a 5-alpha-reductase inhibitor to a subject in need thereof. For example, the method may provide comprising providing a composition of the present invention for transdermal, pharmaceutical delivery of 5-alpha-reductase inhibitor. The 5-alpha-reductase inhibitor, and pharmaceutically salts or derivatives thereof, can be used for the treatment of a variety of conditions including, but not limited to, androgenetic alopecia, benign prostatic hyperplasia, or prostate cancer.

[0054] These and other embodiments of the present invention will readily occur to those of ordinary skill in the art in view of the disclosure herein.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

[0055] FIG. 1 shows data for equilibrium solubility of dutasteride over a 16 hour permeation in various pure solvents;

[0056] FIG. 2 shows data for equilibrium solubility of dutasteride over a 16 hour permeation in various hydro-alcoholic solvents;

[0057] FIG. 3 shows data for the effect of pH on equilibrium solubility of dutasteride over a 16 hour permeation;

[0058] Figs. 4 and 5 show data for equilibrium solubility of dutasteride over a 16 hour permeation in various drug carriers according to the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0059] All patents, publications, and patent applications cited in this specification are herein incorporated by reference as if each individual patent, publication, or patent application
was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. 0060. It is to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting. As used in this specification, description of specific embodiments of the present invention, and any appended claims, the singular forms “a,” “an” and “the” include plural references unless the context clearly dictates otherwise. Thus, for example, reference to “a cosolvent” includes two or more cosolvents, mixtures of cosolvents, and the like, reference to “a compound” includes one or more compounds, mixtures of compounds, and the like.

0061. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although other methods and materials similar, or equivalent, to those described herein can be used in the practice of the present invention, the preferred materials and methods are described herein.

0062. In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

0063. The term “dosage form” as used herein refers to a pharmaceutical composition comprising an active agent, such as a substance, and optionally containing inactive ingredients, e.g., pharmaceutically acceptable excipients such as suspending agents, surfactants, disintegrants, binders, diluents, lubricants, stabilizers, antioxidants, osmotic agents, colorants, plasticizers, coatings and the like, that may be used to manufacture and deliver active pharmaceutical agents.

0064. The term “gel” as used herein refers to a semi-solid dosage form that contains a gelling agent in, for example, an aqueous, alcoholic, or hydroalcoholic vehicle and the gelling agent imparts a threedimensional cross-linked matrix (“gelified”) to the vehicle. The term “semi-solid” as used herein refers to a heterogeneous system in which one solid phase is dispersed in a second liquid phase.

0065. The pH measurements for formulations and compositions described herein, wherein the formulations or compositions do not comprise a predominantly aqueous environment, are more aptly described as “apparent pH” values as the pH values are not determined in a predominantly aqueous environment. In such cases, the influence of, for example, organic solvents on the pH measurement may result in a shift of pH relative to a true aqueous environment.

0066. The term “carrier” or “vehicle” as used herein refers to carrier materials (other than the pharmaceutically active ingredient) suitable for transdermal administration of a pharmaceutically active ingredient. A vehicle may comprise, for example, solvents, cosolvents, permeation enhancers, pH buffering agents, antioxidants, gelling agents, additives, or the like, wherein components of the vehicle are nontoxic and do not interact with other components of the total composition in a deleterious manner.

0067. The phrase “non-occlusive, transdermal drug delivery” as used herein refers to transdermal delivery methods or systems that do not occlude the skin or mucosal surface from contact with the atmosphere by structural means, for example, by use of a patch device, a fixed application chamber or reservoir, a backing layer (for example, a structural component of a device that provides a device with flexibility, drape, or occlusivity), a tape or bandage, or the like that remains on the skin or mucosal surface for a prolonged period of time. Non-occlusive, transdermal drug delivery includes delivery of a drug to skin or mucosal surface using a topical medium, for example, creams, ointments, sprays, solutions, lotions, gels, and foams. Typically, non-occlusive, transdermal drug delivery involves application of the drug (in a topical medium) to skin or mucosal surface, wherein the skin or mucosal surface to which the drug is applied is left open to the atmosphere.

0068. The term “transdermal” delivery, as used herein refers to both transdermal (and “percutaneous”) and transmucosal administration, that is, systemic delivery by passage of a drug through a skin or a mucosal tissue surface and ultimately into the bloodstream.

0069. The term “topical” delivery, as used herein refers to local delivery of a drug into a skin surface or a mucosal tissue surface with minimal passage into the bloodstream.

0070. The phrase “therapeutically effective amount” as used herein refers to a nontoxic but sufficient amount of a drug, agent, or compound to provide a desired therapeutic effect, for example, one or more doses of 5-alpha-reductase inhibitor that will be effective in relieving androgenetic alopecia, benign prostate hyperplasia, or prostate cancer.

0071. The term “5-alpha-reductase inhibitor” as used herein refers to any of the conventional 5-alpha-reductase inhibitors. The preferred 5-alpha-reductase inhibitors of the present invention are azasteroid compounds. Even more preferred 5-alpha-reductase inhibitors of the present invention are finasteride, dutasteride, pharmaceutically acceptable salts thereof, pharmaceutically acceptable derivatives thereof, as well as mixtures thereof.

0072. The term “5-alpha-reductase inhibitor pharmaceutically acceptable salts” as used herein refers to formation of salts with acceptable salt formers such as, but not limited to, hydrochloride, sulphate, tosylate, mesylate, napsylate, besylate, maleate, phosphate, salicylate, turtrate, lactate, citrate, benzoate, succinate, acetate, pivalate, oxalate, picrate, phthalate, and the like.

0073. The phrase “short-chain alcohol” as used herein refers to a C2-C4 alcohol, for example, ethanol, propanol, butanol, isopropanol, and/or mixtures thereof.

0074. The phrase “volatile solvent” refers to a solvent that changes readily from solid or liquid to a vapor, and that evaporates readily at normal temperatures and pressures. Examples of volatile solvents include, but are not limited to, ethanol, propanol, butanol, isopropanol, and/or mixtures thereof. The term “non-volatile solvent” as used herein refers to a solvent that does not change readily from solid or liquid to a vapor, and that does not evaporate readily at normal temperatures and pressures. Examples of non-volatile solvents include, but are not limited to, propylene glycol, glyc erin, liquid polyethylene glycols, polyoxyalkylene glycols, and/or mixtures thereof. Stanislaus, et al., (U.S. Pat. No. 4,704,406) defined “volatile solvent” as a solvent whose vapor pressure is above 35 mm Hg when skin temperature is 32°C, and a “non-volatile” solvent as a solvent whose vapor pressure is below 10 mm Hg at 32°C, skin temperature. Solvents used in the practice of the present invention are typically physiologically compatible and used at non-toxic levels.

0075. The phrase “monoalkylether of diethylene glycol” means a chemical having general formula CnH2n+2O(C2H2O)n wherein n=1-4. Further, the term “glycol” encompasses a broad range of chemicals including but not limited to propylene glycol, dipropylene glycol, butylene glycol, and poly-
The phrase “permeation enhancer” or “penetration enhancer” as used herein refers to an agent that improves the rate of transport of a pharmacologically active agent (e.g., detergent) across the skin or mucosal surface. Typically a penetration enhancer increases the permeability of skin or mucosal tissue to a pharmacologically active agent. Penetration enhancers, for example, increase the rate at which the pharmacologically active agent permeates through skin and enters the bloodstream. Enhanced permeation effected through the use of penetration enhancers can be observed, for example, by measuring the flux of the pharmacologically active agent across animal or human skin as described in the Examples herein below. An “effective” amount of a permeation enhancer as used herein means an amount that will provide a desired increase in skin permeability to provide, for example, the desired depth of penetration of a selected compound, rate of administration of the compound, and amount of compound delivered.

The phrase “contamination” or “transfer” as used herein means the unintended presence of harmful substances in individuals or surfaces by direct contact between individuals, between surfaces, or between individuals and surfaces (and reciprocally).

The phrase “synergy”, “synergism”, “synergistic effect” or “synergistic action” as used herein means an effect of the interaction of the actions of two agents such that the result of the combined action is greater than expected as a simple additive combination of the two agents acting separately.

The phrase “modulate”, “regulate” or “control” as used herein means to adjust, or maintain, with respect to a desired rate, degree, or condition, as to adjust permeation rate, crystallization speed, and repartition of an active pharmaceutical ingredient in the layers of the skin.

The phrase “effective” or “adequate” permeation enhancer or combination as used herein means a permeation enhancer or a combination that will provide the desired increase in skin permeability and correspondingly, the desired depth of penetration, rate of administration, and amount of drug delivered.

The phrase “thermodynamic activity” of a substance means the energy form involved in skin permeation of this substance. The chemical potential of a substance is defined in thermodynamics as the partial molar free energy of the substance. The difference between the chemical potentials of a drug outside and inside the skin is the energy source for the skin permeation process.

The phrase “stratum corneum” as used herein refers to the outer layer of the skin. The stratum corneum typically comprises layers of terminally differentiated keratinocytes (made primarily of the proteinaceous material keratin) arranged in a brick and mortar fashion wherein the mortar comprises a lipid matrix (containing, for example, cholesterol, ceramides, and long chain fatty acids). The stratum corneum typically creates the rate-limiting barrier for diffusion of the active agent across the skin.

The phrase “intradermal depot” as used herein refers to a reservoir or deposit of a pharmaceutically active compound within or between the layers of the skin (e.g., the epidermis, including the stratum corneum, dermis, and associated subcutaneous fat), whether the pharmaceutically active compound is intracellular (e.g., within keratinocytes) or intercellular.

The term “subject” as used herein refers to any warm-blooded animal, particularly including a member of the class Mammalia such as, without limitation, humans and non human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs, and the like. The term does not denote a particular age or sex.

The term “sustained release” as used herein refers to predetermined continuous release of a pharmaceutically active agent to provide therapeutically effective amounts of the agent over a prolonged period. In some embodiments of the present invention, the sustained release occurs at least in part from an intradermal depot of a pharmaceutically active compound.

The term “prolonged period” as used herein typically refers to a period of at least about 12 hours, more preferably at least about 18 hours and more preferably at least about 24 hours.

The term “sustained release dosage form” as used herein refers to a dosage form that provides an active agent, e.g., detergent, substantially continuously for several hours, typically for a period of at least about 12 to about 24 hours.

The term “delivery rate” as used herein refers to the quantity of drug delivered, typically to plasma, per unit time, for example, nanograms of drug released per hour (ng/hr) in vivo.

In the context of plasma blood concentration of active agent, the term “C” as used herein refers to the concentration of drug in the plasma of a subject, generally expressed as mass per unit volume, typically nanograms per milliliter (this concentration may be referred to as “plasma drug concentration” or “plasma concentration” herein which is intended to be inclusive of drug concentration measured in any appropriate body fluid or tissue). The plasma drug concentration at any time following drug administration is typically referred to as Ct ime as in C 10h or C20h, etc. The term “Cmax” refers to the maximum observed plasma drug concentration following administration of a drug dose, and is typically monitored after administration of a first dose and/or after steady-state delivery of the drug is achieved. The following terms are used herein as follows: “Cavg” refers to average observed plasma concentration typically at steady state, Cav at steady state is also referred to herein as “Css”; “Cmin” refers to minimum observed plasma concentration typically at steady state.

The term “tmax” as used herein refers to the time to maximum plasma concentration and represents the time that elapses between administration of the formulation and a maximum plasma concentration of drug (i.e., a peak in a graph of plasma concentration vs. time). Tmax values may be determined during an initial time period (for example, related to administration of a single dose of the drug) or may refer to the time period between administration of a dosage form and the observed maximum plasma concentration during steady state.

The term “steady state” as used herein refers to a pattern of plasma concentration versus time following consecutive administration of a constant dose of active agent at predetermined intervals (for example, once-a-day dosing).
During "steady state" the plasma concentration peaks and plasma concentration troughs are substantially the same within each dosing interval.

[0092] One of ordinary skill in the art appreciates that intradermal concentrations or plasma drug concentrations obtained in individual subjects will vary due to inter-subject variability in many parameters affecting, for example, drug absorption, distribution, metabolism, and excretion. Accordingly, mean values obtained from groups of subjects are typically used for purposes of comparing plasma drug concentration data and for analyzing relationships between in vitro dosage assays and in vivo plasma drug concentrations.

[0093] Before describing the present invention in detail, it is to be understood that this invention is not limited to particular embodiments described herein, for example, particular solvent(s), antioxidant(s), cosolvent(s), penetration enhancer(s), buffering agent(s), and/or gelling agent(s), and the like, as use of such particulars may be selected in view of the teachings of the present specification by one of ordinary skill in the art. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

[0094] In one aspect, the present invention relates to a nonocclusive composition for pharmaceutical drug delivery. The composition may be formulated to be suitable for systemic application, for example, transcutaneous and/or transmucosal applications. The composition typically comprises a therapeutically effective amount of 5-alpha-reductase inhibitor or a pharmaceutically acceptable salt or derivative thereof. The composition typically comprises at least one short-chain alcohol, a monooalkylether of diethylene glycol, and a glycol. The composition may optionally comprise other inactive ingredients without departing from the scope of the present invention. In one embodiment, the 5-alpha-reductase inhibitor is dutasteride or finasteride. In other embodiments, the dutasteride or finasteride is a pharmaceutically acceptable salt or a pharmaceutically acceptable derivative salt of dutasteride or finasteride. A preferred concentration range of the 5-alpha-reductase inhibitor is about 0.01 to about 5 weight percent, more preferred is a concentration of about 0.05 to about 1 weight percent.

[0095] The short-chain alcohol in formulations of the present invention may be, for example, ethanol, propanol, butanol, isopropanol, and mixtures thereof. A preferred concentration range of the short-chain alcohol, for example, ethanol, is a concentration of about 5 to about 75 weight percent where the water is present at a concentration of about 10 to about 60 weight percent. Water can be added quantum sufficient (q.s.) amounts may vary as can be determined by one of ordinary skill in the art in view of the teachings of the present specification. A more preferred concentration range of the short-chain alcohol, for example, ethanol, is about 30 to about 70 weight percent where the water is present at a concentration of about 10 to about 40 weight percent.

[0096] The formulations of the present invention further comprise a combination of a monooalkylether of diethylene glycol (for example mono ethyl ether of diethylene glycol) and a pharmaceutically acceptable glycol. In one embodiment the glycol is propylene glycol. A preferred concentration range of the monooalkylether of diethylene glycol and of the pharmaceutically acceptable glycol is a concentration of about 1 to about 30 weight percent, more preferred is a concentration of about 2.5 to about 20 weight percent. More preferred formulations of the present invention comprise combination wherein the monooalkylether of diethylene glycol to the pharmaceutically acceptable glycol ratio ranges from about 10:1 to about 1:10, and wherein the monooalkylether of diethylene glycol and the pharmaceutically acceptable glycol are present in combination in a cumulative amount of not less than 15 weight percent and not more than 60 weight percent of the total composition.

[0097] Further, the formulations of the present invention may further comprise a gelling or thickening agent(s). Exemplary gelling agents include, but are not limited to, carbomer, carboxyethylcellulose or polyacrylic acid such as carbomer 980 or 940 NF, 981 or 941 NE, 1382 or 1342 NF, 5984 or 934 NF, ETD 2020, 2050, 934P NF, 934P NF, carbopol polymers such as PEMULEN TR1 NF or PEMULEN TR2 NF, carbomer interpolymer networks such as CARBOPOL ETD 2020 NF, CARBOPOL ETD 2050 NF, CARBOPOL ULTRA EZ 10, etc.; cellulose derivatives such as ethylcellulose, hydroxypropylmethylcellulose (HPMC), ethylhydroxyethylcellulose (EHEC), carboxymethylcellulose (CMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), etc.; natural gums such as arabic, xanthan, guar gums, alginites, etc.; polyvinylpyrrolidone derivatives; polyethylene glycol poloxamer copolymers, etc.; others like chitosan, polyvinyl alkohols, pectins, veegum grades, and the like. Other suitable gelling agents to apply the present invention include, but are not limited to, carbomers. Alternatively, other gelling agents or viscousant known by those skilled in the art may also be used. The gelling agent or thickener is present from about 0.2 to about 30% w/w depending on the type of polymer, as known by one skilled in the art. A preferred concentration range of the gelling agent(s), for example, hydroxypropyl cellulose or carbomer, is a concentration of between about 0.5 and about 5 weight percent, more preferred is a concentration of between about 1 and about 3 weight percent.

[0098] The formulations of the present invention may also further comprise a permeation enhancer (penetration enhancer). Permeation enhancers include, but are not limited to, sulfur compounds such as dimethyl sulfoxide and decamethyl syloxide; surfactants such as sodium laurate, sodium lauryl sulfate, ceteth-10 methylammonium bromide, benzalkonium chloride, poloxamer (231, 182, 184), tween (20, 40, 60, 80) and lecithin; the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecylacycloheptan-2-one; fatty alcohols such as lauryl alcohol, myristyl alcohol, cetyl alcohol and the like; fatty acids such as lauric acid, oleic acid and erucic acid; fatty acid esters such as isopropyl myristate, isopropyl palmitate, methylpropionate, and ethyl oleate; polyols and esters thereof such as propylene glycol, ethylene glycol, glycerol, butanediol, polyethylene glycol, and polyethylene glycol monolaureate, amides and other nitrogenous compounds such as urea, dimethylacetamide (DMA), dimethylformamide (DMF), 2-pyrroldione, 1-methyl-2-pyrroldione, ethanalamine, diethanolamine and triethanolamine, terpenes; alkanones, and organic acids, particularly salicylic acid and salicylates, citric acid and succinic acid. As noted earlier herein, "Percutaneous Penetration Enhancers", eds. Smith et al. (CRC Press, 1995), which is incorporated herein by reference thereto, provides an excellent overview of the field and further information concerning possible secondary enhancers for use in conjunction with the present invention.
More permeation enhancer(s) suitable to be used with the present invention may be known by those skilled in the art. The permeation enhancer is present from about 0.1 to about 30% w/w depending on the type of compound. Preferred permeation enhancers are fatty alcohols and fatty acids. More preferred permeation enhancers are fatty alcohols. Preferably, the fatty alcohols have the formula the CH₃(CH₂)n(CH₃)₂CH₂OH wherein n ranges from (8-n) to (16-n) and m=0-2. A preferred concentration range of the penetration enhancer (s) is, depending on the type of penetration enhancer, a concentration of between about 0.1 and about 10 weight percent, as known by one skilled in the art. In one preferred embodiment, the penetration enhancer comprises myristyl alcohol in a concentration of between about 0.1 and about 2 weight percent.

[0099] A preferred concentration range of the antioxidant (s) of the formulations of the present invention, for example, tocopherol and derivatives, ascorbic acid and derivatives, butylated hydroxyanisole, butylated hydroxytoluene, fumaric acid, malic acid, propyl gallate, sodium metabisulfite and derivatives, is a concentration of about 0.01 to about 5 weight percent; more preferred is a concentration of about 0.1 to about 0.5 weight percent, depending on the type of antioxidant used, as known by the one skilled in the art.

[0100] A preferred concentration range of the buffering agent(s) of the formulations of the present invention, for example, carbonate buffers, citrate buffers, phosphate buffers, acetate buffers, hydrochloric acid, lactic acid, tartaric acid, inorganic and organic bases, is a concentration of about 1 to about 10 weight percent, more preferred is a concentration of about 2 to about 5 weight percent, depending on the type of buffering agent(s) used, as known by the one skilled in the art. The preferred concentration range of said buffering agents are those enabling design of compositions having a pH close to the physiologic pH of the skin, about between pH 4.5 and about pH 8.5, preferably between about pH 4.5 and about pH 8.5, and even more preferably between pH 5.5 and pH 6.5. Concentrations of the buffering agent(s) may vary, however, as known by the one skilled in the art. The buffering agent may replace up to 100% of the water amount within the composition.

[0101] The transdermal or topical pharmaceutical formulation of the present invention may also further include preservatives such as benzalkonium chloride and derivatives, benzoic acid, benzyalcohol and derivatives, bronabans, centrimide, chlorhexidine, cresol and derivatives, imidurea, phenol, phenoxethanol, phenylethyl alcohol, phenylmercuric salts, thimerosal, sorbic acid and derivatives. The preservative is present from about 0.01 to about 10% w/w depending on the type of compound used, as known by the one skilled in the art.

[0102] The transdermal or topical pharmaceutical formulation of the present invention may also further include humectants, sequestering agents, moisturizers, surfactants, emollients, colorants, fragrances, flavors, or any combination thereof.

[0103] In one embodiment, a gel formulation of the present invention comprises a therapeutically effective amount of a 5-alpha-reductase inhibitor, or a pharmaceutically acceptable salt or derivative thereof, of between about 0.01 to about 5 weight percent. The primary vehicle may comprise between about 10 to about 60 weight percent of water, between about 30 to about 70 weight percent ethanol, between about 15 and about 60 weight percent of a 10:1 to 1:10 (weight to weight) mixture of diethylene glycol mono ethyl ether and propylene glycol, and between about 0.1 and about 2 weight percent of lauryl alcohol, myristyl alcohol, oleyl alcohol, laurie acid, myristic acid, or oleic acid. The primary vehicle may be gellified with between about 0.5 and about 5 weight percent of hydroxypropylecellose. The apparent pH of the gel is between about pH 4.5 and about pH 8.5, or preferably between about pH 5.5 and pH 6.5.

[0104] Preferred embodiments of the present invention are gel formulations for non-occlusive therapeutic, transdermal or topical applications. In such embodiments transdermal delivery methods or systems do not occlude the skin or mucosal surface from contact with the atmosphere by structural means, for example, there is no backing layer used to retain the gel formulation in place on skin or mucosal surface.

[0105] The formulations of the present invention may be provided in a unit dose container(s). Such containers typically comprise inner and outer surfaces, wherein the formulation of the present invention is contained by the inner surface of the container. In selected embodiments, the container is a packet or a vial, and the inner surface of the container may further comprise a liner. For example, in one embodiment, the container is a flexible, foil packet and the liner is a polyethylene liner. Alternatively, in or addition, the formulations of the present invention may be provided in a multiple dose container(s). Such multiple dose containers typically comprise inner and outer surfaces, wherein the gel for pharmaceutical drug delivery is contained by the inner surface of the container. Multiple dose containers may, for example, dispenses fixed or variable metered doses. Multiple dose containers may, for example, be a stored-energy metered dose pump or a manual metered dose pump.

[0106] In another aspect the present invention comprises a composition for pharmaceutical drug delivery, comprising a therapeutically effective amount of 5-alpha-reductase inhibitor, or a pharmaceutically acceptable salt or derivative thereof, in a hydroalcoholic vehicle comprising water, a short chain alcohol, a monoalcohol ether of diethylene glycol, a pharmaceutically acceptable glycol, and an optional fatty permeation enhancer. In such compositions the pH of the composition is typically between about pH 4.5 and about pH 8.5. Furthermore, the transdermal flux (for example, instant flux) of the 5-alpha-reductase inhibitor, in the hydroalcoholic vehicle, across skin is greater than the transdermal flux of an equal concentration of 5-alpha-reductase inhibitor in an alcoholic solution (that is, an anhydrous solution without the propylene glycol, without the diethylene glycol mono ethyl ether, without the optional fatty permeation enhancer) of essentially equivalent pH over an essentially equivalent time period, wherein the skin is the flux rate controlling membrane. These compositions for pharmaceutical delivery may include further components as described herein, for example, the hydroalcoholic vehicle may further comprise a permeation enhancer. Such compositions may be formulated in a variety of ways including wherein the hydroalcoholic vehicle is gellified. These compositions may be used, for example, for transdermal applications including application to skin surfaces (arm, shoulder, abdomen, scalp, thigh) and mucosal tissues (for example, intranasally, intrabucally, as a vaginal ovule or as a suppository).

[0107] In yet another aspect the present invention comprises a composition for pharmaceutical drug delivery, comprising a therapeutically effective amount of 5-alpha-reductase inhibitor, or a pharmaceutically acceptable salt or
derivative thereof, in a hydroalcoholic vehicle comprising water, a short chain alcohol, a monoalkyl ether of diethylene glycol, a pharmaceutically acceptable glycol, and an optional fatty permeation enhancer. These compositions for pharmaceutical delivery may include further components as described herein, for example, the hydroalcoholic vehicle may further comprise a cosolvent(s), a penetration enhancer(s), a buffering agent(s), a preservative(s), an emollient(s), an humectant(s), and/or a gelling agent(s). Such compositions may be formulated in a variety of ways including wherein the hydroalcoholic vehicle is gellified. These compositions may be used, for example, for transdermal applications including application to skin surfaces (arm, shoulder, abdomen, scalp, thigh) and mucosal tissues (for example, intranasally, intrabucally, as a vaginal ovoe or as a suppository).

[0108] In a further aspect, the present invention includes methods of manufacturing the compositions described herein for pharmaceutical drug delivery. In one embodiment, the method of manufacturing comprises mixing the components to yield a homogeneous gel, wherein the pH of the gel is between about pH 4.5 and about pH 8.5 (exemplary components include, but are not limited to the following: a therapeutically effective amount of 5-alpha-reductase inhibitor, or a pharmaceutically acceptable salt or derivative thereof, a primary vehicle comprising water, at least one short-chain alcohol, a monoalkyl ether of diethylene glycol, a pharmaceutically acceptable glycol, an optional fatty permeation enhancer). These methods may include addition of further components as described herein, for example, the hydroalcoholic vehicle may further comprise cosolvent(s), penetration enhancer(s), buffering agent(s), preservative(s), emollient(s), humectant(s), and/or gelling agent(s). The method provides a gel suitable for pharmaceutical systemic or intradermal delivery of 5-alpha-reductase inhibitor. Further, a method of manufacturing may further include dispensing the pharmaceutical composition into one or more containers (for example, a unit dose container (e.g., a flexible foil pack, further comprising a liner) or a multiple dose container).

[0109] In another aspect, the present invention includes methods for administering 5-alpha-reductase inhibitors to a human subject in need thereof. For example, the method may comprise providing a composition of the present invention for transdermal or topical pharmaceutical delivery of 5-alpha-reductase inhibitors. Doses of the compositions of the present invention may, for example, be a gel applied to the surface of skin (arm, shoulder, thigh, abdomen, scalp). Further, doses of the compositions of the present invention may be applied in a single or in divided doses. In one embodiment, the composition is applied as one or more daily dose of the gel to a skin surface of the subject in an amount sufficient for the 5-alpha-reductase inhibitor to achieve therapeutic concentration in the bloodstream or in the dermis of the subject, wherein up to about 5 grams of the gel is applied daily to a skin surface area of between about 10 to about 1000 cm². 5-alpha-reductase inhibitors, and pharmaceutical salts or derivatives thereof, can be used for the treatment of a variety of conditions including benign prostate hyperplasia, prostate cancer, and androgenetic alopecia.

[0110] From the foregoing, it is apparent that the invention provides a non-occlusive dosage form with a profile that permits once daily dosing of 5-alpha-reductase inhibitors.

[0111] Further, although preferred dosage forms are described herein, further dosage forms of the compositions of the present invention can be determined by one of ordinary skill in the art in view of the teachings presented herein.

[0112] Exemplary methods of making or manufacturing the compositions of the present invention are described herein below in the Materials and Methods section. Variations on the methods of making the compositions of the present invention will be clear to one of ordinary skill in the art in view of the teachings contained herein.

[0113] The manufacturing process for formulations of the present invention is straightforward and is typically carried out in a closed container with appropriate mixing equipment. For example, ethanol, propylene glycol, diethylene glycol mono ethyl ether are mixed in a primary container (reaction vessel) under a slight vacuum and nitrogen blanketing until a clear solution forms. In parallel, a water-soluble 5-alpha-reductase inhibitor is dissolved in a portion of water in a separate container and then added to the primary solution to prepare a hydro-alcoholic solution. On the contrary, organosoluble 5-alpha-reductase inhibitors are dissolved in the primary solution. The pH is then brought to its desired value (e.g., approximately pH 5.5 to 6.5) by adding a fixed amount of buffering agent, if required. The solution may be gellified by addition of hydroxypropylcellulose and is then stirred until the hydroxypropylcellulose is completely swollen.

[0114] The compositions of the present invention may be applied to a skin surface or a mucosal membrane using a variety of means, including, but not limited to a pump-pack, a brush, a swab, a finger, a hand, or other applicator.

[0115] The methods of manufacturing of the present invention may include dispensing compositions of the present invention into appropriate containers. The compositions of the present invention may be packaged, for example, in unit dose or multi-dose containers. The container typically defines an inner surface that contains the composition. Any suitable container may be used. The inner surface of the container may further comprise a liner or be treated to protect the container surface and/or to protect the composition from adverse affects that may arise from the composition being in contact with the inner surface of the container. Exemplary liners or coating materials include, but are not limited to high density polyethylene, low density polyethylene, very low density polyethylene, polyethylene copolymers, thermoplastic elastomers, silicon elastomers, polyurethane, polypropylene, polyethylene terephthalate, nylon, flexible polyvinylchloride, natural rubber, synthetic rubber, and combinations thereof. Liners or coating material are typically substantially impermeable to the composition and typically to the individual components of the composition.

[0116] A number of types of containers are known in the art, for example, packets with rupturable barriers (see, for example, U.S. Pat. Nos. 3,913,789, 4,759,472, 4,872,556, 4,890,744, 5,131,760, and 6,379,069), single-use packets (see, for example, U.S. Pat. Nos. 6,228,375, and 6,360,916), tortuous path seals (see, for example, U.S. Pat. Nos. 2,707,581, 4,491,245, 5,018,646, and 5,839,609), and various sealing valves (see, for example, U.S. Pat. Nos. 3,184,121, 3,278,085, 3,635,376, 4,328,912, 5,529,224, and 6,244,468). One example of a unit dose container is a flexible, foil packet with a polyethylene liner.

[0117] Containers/delivery systems for the compositions of the present invention may also include a multi-dose container providing, for example a fixed or variable metered dose application. Multi-dose containers include, but are not limited to, a metered dose aerosol, a stored-energy metered dose pump, or
a manual metered dose pump. In preferred embodiments, the container/delivery system is used to deliver metered doses of the compositions of the present invention for application to the skin of a subject. Metered dose containers may comprise, for example, an actuator nozzle that accurately controls the amount and/or uniformity of the dose applied. The delivery system may be propelled by, for example, a pump pack or by use of propellants (e.g., hydrocarbons, hydro fluorocarbons, nitrogen, nitrous oxide, or carbon dioxide). Preferred propellants include those of the hydrofluorocarbon (e.g., hydrofluoroalkanes) family, which are considered more environmentally friendly than the chlorofluorocarbons. Exemplary hydrofluoroalkanes include, but are not limited to, 1,1,1,2-
tetrafluoroethane (HFC-134a), 1,1,1,2,3,3,3-heptafluoropropane (HFC-227), difluoromethane (HFC-32), 1,1,1-trifluoroethane (HFC-143a), 1,1,2,2-tetrafluoroethane (HFC-134a), 1,1-difluoroethane (HFC-152a), as well as combinations thereof. Particularly preferred are 1,1,1,2-tetrafluoroethane (HFC-134a), 1,1,1,2,3,3,3-heptafluoropropane (HFC-227), and combinations thereof. Many pharmaceutically acceptable propellants have been previously described and may be used in the practice of the present invention in view of the teachings presented herein. The delivery system should provide dose uniformity. In a preferred embodiment, airless packaging with excellent barrier properties is used to prevent degradation of 5-alpha-reductase inhibitors, for example, airless metered-close pumps wherein the composition comprising 5-alpha-reductase inhibitors is packaged in collapsible aluminum foils. Accurate dosing from such pumps ensures reproducibility of dose.

The present invention further includes methods for administering a composition of the present invention to a subject in need thereof. Compositions of the present invention comprising 5-alpha-reductase inhibitors can be employed, for example, for the treatment of a variety of conditions and/or disease states which have been historically treated by oral doses of 5-alpha-reductase inhibitors.

The 5-alpha-reductase inhibitors compositions of the present invention may be self-applied by a subject in need of treatment or the composition may be applied by a caregiver or health care professional.

The following examples are illustrative of embodiments of the present invention and should not be interpreted as limiting the scope of the invention.

EXPERIMENTAL

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the formulations, methods, and devices of the present invention, and are not intended to limit the scope of what the inventors regard as the invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Materials and Methods

A. Pharmaceuticals and Reagents.

The pharmaceuticals and reagents used in the following examples meet the strict specifications for content and purity required for pharmaceutical products.
solution. The 5-alpha-reductase inhibitor was then added to the solution and the solution mixed to obtain a homogeneous, clear active organic solution. Water was then added quantum sufficit (q.s.). If desired, the pH was then adjusted to a specified pH. In some cases, water was added and pH was adjusted before the addition of dutasteride so that the 5-alpha-reductase inhibitor was not exposed to high local pH variations; although timing of the pH adjustment was not an issue. Some compositions were purged of air by nitrogen bubbling before the 5-alpha-reductase inhibitor was dissolved; however, as noted above, such nitrogen or argon sparging was not required. As noted above, the components may be added in essentially any order during manufacturing processes.

One exemplary method of manufacturing is as follows. The organo-soluble 5-alpha-reductase inhibitor is dissolved in ethanol, propylene glycol, diethylene glycol mono ethyl ether and myristyl alcohol. The organic solution is mixed until homogenized using mechanical mixing (e.g., magnetic stirring). The resulting organic solution was clear and homogeneous. Water is added to the 5-alpha-reductase inhibitor organic solution prepared and mixed until the solution was homogenized. Then the resulting clear and homogeneous hydro-alcoholic solution may be further gellified by means of cellulose derivatives thoroughly selected by the man skilled in the art of formulating pharmaceutical topical products.

The examples herein below exemplifies a variety of compositions that can be prepared thanks to this manufacturing process.

**ABBREVIATIONS**

- DUT: Dutasteride
- FIN: Finasteride
- EtOH: Ethanol
- IsOH: Isopropanol
- PG: Propylene glycol
- TC: Diethylene glycol mono ethyl ether
- LA: Lauryl alcohol
- MA: Myristyl alcohol
- OA: Oleyl alcohol
- LAc: Lauric acid
- MAc: Myristic acid
- OAc: Oleic acid
- CEl: cellulose
- CAR: carborner
- TEA: Triethanolamine
- DIPA: Diisopropylamine
- QS: quantum sufficit
- Percentages are expressed as percent weight by weight (w/w).

**Example 1**

DUT 0.05%, PG 15%, TC 15%, EtOH 50%, HCL 0.01M 0.25%, Water QS.

**Example 2**

DUT 0.05%, PG 25%, TC 5%, EtOH 50%, HCL 0.00M 0.25%, Water QS.

**Example 3**

DUT 0.05%, PG 5%, TC 25%, EtOH 50%, HCL 0.01M 0.25%, Water QS.

**Example 4**

DUT 0.05%, PG 15%, TC 15%, EtOH 50%, CAR 1.00%, Tea 0.20%, Water QS.

**Example 5**

DUT 0.5%, PG 15%, TC 15%, EtOH 50%, Water QS.

**Example 6**

DUT 0.5%, PG 15%, TC 15%, EtOH 50%, LAc 1%, Water QS.

**Example 7**

DUT 0.5%, PG 15%, TC 15%, EtOH 50%, MAc 1%, Water QS.

**Example 8**

DUT 0.5%, PG 15%, TC 15%, EtOH 50%, OAc 1%, Water QS.

**Example 9**

DUT 0.1%, PG 15%, TC 15%, EtOH 50%, MA 0.2%, CAR 1.00%, Tea 0.20%, Water QS.

**Example 10**

DUT 0.1%, PG 15%, TC 15%, EtOH 50%, MA 1%, CAR 1.00%, Tea 0.20%, Water QS.

**Example 11**

DUT 0.1%, PG 15%, TC 15%, EtOH 50%, MA 2%, CAR 1.00%, Tea 0.20%, Water QS.

**Example 12**

DUT 0.05%, PG 15%, TC 15%, EtOH 40%, MA 1%, CAR 1.00%, Tea 0.20%, Water QS.

**Example 13**

DUT 0.025%, PG 15%, TC 15%, EtOH 30%, MA 1%, CAR 1.00%, DIPA 0.20%, Water QS.

**Example 14**

DUT 1.0%, PG 5%, TC 10%, EtOH 70%, MA 2%, Water QS.

**Example 15**

**FIN 0.8%, PG 5%, TC 5%, EtOH 70%, MA 0.5%, Water QS.**

**Example 16**

Examples 1-15 are illustrations of preferred formulations according to the invention.

What is claimed is:

1. A transdermal or transmucosal non-occlusive, semi-solid pharmaceutical formulation comprising: at least one active ingredient which is a 5-alpha-reductase inhibitor; and a permeation enhancing solvent system present in an amount sufficient to solubilize the active ingredient and characterized in that it includes: (i) a pharmaceutically acceptable monoalkyl ether of diethylene glycol present in an amount of between about 1% and 30% by weight of the solvent system; (ii) a pharmaceutically acceptable glycol present in an
amount of between about 1% and 30% by weight of the solvent system, wherein the monoalkyl ether of diethylene glycol and the glycol in combination are present in an amount of at least 15% and no more than 60% by weight of the formulation; and (iii) a mixture of a C₄ to C₆ alcohol and water, which mixture is present in an amount of between about 40% and 98% by weight of the solvent system, wherein the C₄ to C₆ alcohol is present in an amount of about 5% to 80% by weight of the mixture, and the water is present in an amount of about 20% to 95% by weight of the mixture; so that, compared to formulations not containing the present permeation enhancing solvent system, the present formulation (a) inhibits crystallization of the at least one active ingredient on a skin or mucosal surface of a mammal, (b) reduces or prevents transfer of the formulation to clothing or to another being, (c) modulates biodistribution of the at least one active agent within different layers of skin, (d) facilitates absorption of the at least one active agent by a skin or a mucosal surface of a mammal, or (e) provides a combination of one or more of (a) through (d).

2. The pharmaceutical formulation of claim 1, wherein the monoalkyl ether of diethylene glycol and the glycol are present in a weight ratio of 10:1 to 1:10.

3. The pharmaceutical formulation of claim 1, wherein the monoalkyl ether of diethylene glycol is selected from the group consisting of diethylene glycol monoethyl ether, and diethylene glycol monomethyl ether or mixtures thereof.

4. The pharmaceutical formulation of claim 1, wherein the glycol is selected from the group consisting of propylene glycol, dipropylene glycol or mixtures thereof.

5. The pharmaceutical formulation of claim 1, wherein the C₂ to C₆ alcohol is selected from the group consisting of ethanol, propanol, isopropanol, 1-butanol, 2-butanol, or mixtures thereof.

6. The pharmaceutical formulation of claim 1, wherein the formulation further includes a saturated fatty alcohol or fatty acid, or mixtures thereof, wherein said fatty alcohol and/or said fatty acid have the formula CH₃—CH₂CH₂—OH or CH₃—CH(OH)CH₂—COOH, respectively, in which n is an integer from 8 to 22, preferably 8 to 12, most preferably 10; or an unsaturated fatty alcohol or fatty acid, or mixtures thereof, wherein said unsaturated fatty alcohol and/or fatty acid have the formula CH₃—(CH₂)n—COOH, respectively, in which n is an integer from 8 to 22.

7. The pharmaceutical formulation of claim 1, wherein the formulation further includes lauryl alcohol or myristyl alcohol present in an amount from 0.1 to 2% by weight of the total formulation.

8. The pharmaceutical formulation of claim 1, wherein the at least one active ingredient is an azasteroid compound.

9. The pharmaceutical formulation of claim 1, wherein the azasteroid compound is used to treat benign prostate hyperplasia; prostate cancer; and androgenetic alopecia.

10. The pharmaceutical formulation of claim 9, wherein the azasteroid compound is selected from the group consisting of dutasteride and pharmaceutically acceptable salts thereof.

11. The pharmaceutical formulation of claim 9, wherein the azasteroid compound is selected from the group consisting of dutasteride and pharmaceutically acceptable salts thereof.

12. The pharmaceutical formulation of claim 1, further comprising an agent selected from the group consisting of gelling agents; permeation enhancers; preservatives, antioxidants, buffers, humectants, sequestering agents, moisturizers, surfactants, emollients, film-forming agents, solubilizers, flavors, fragrances, stabilizers, solubilizers, and any combination thereof.

13. The pharmaceutical formulation of claim 1, comprising dutasteride in an amount of between about 0.01% and 5% by weight; a monoethyl ether of diethylene glycol in an amount of between about 1% and 30% by weight; propylene glycol in an amount of between about 1% and 30% by weight; a C₂ to C₆ alcohol in an amount of between about 10% and 70% by weight; a fatty permeation enhancer selected from the group of lauryl alcohol, myristyl alcohol, oleyl alcohol, lauric acid, myristic acid, or oleic acid in an amount of between about 0.1% to about 2% by weight; water; and an agent selected from the group consisting of gelling agents; permeation enhancers, preservatives, anti-oxidants, buffers, humectants, sequestering agents, moisturizers, surfactants, emollients, film-forming agents, solubilizers, flavors, fragrances, stabilizers, solubilizers, and any combination thereof.

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