TESTOSTERONE GEL COMPOSITIONS AND RELATED METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 61/915,742, filed December 13, 2013, and to U.S. Nonprovisional Patent Application No. 14/177,765, filed February 11, 2014, the entire contents of which are incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to gel compositions containing active pharmaceutical ingredient such as testosterone, solvent, and gel-forming polymer (a.k.a. thickener), useful for transdermal administration of the active ingredient to a patient, and related methods.

BACKGROUND

Male hypogonadism is a common hormone deficiency in men that involves decreased functional activity of the gonads. Male hypogonadism results from a variety of conditions in which testosterone concentration is diminished below the normal range. The hypogonadic condition is sometimes linked with a number of physiological changes, such as diminished interest in sex, impotence, reduced lean body mass, decreased bone density, affected mood, and reduced energy levels.

In the United States, men of all ages are treated for hypogonadism using testosterone replacement therapy. Various methods of delivering testosterone have been considered and developed to provide suitable replacement therapies. Examples include intramuscular injections, pellet implants, transdermal patches, and hydroalcoholic testosterone gels. Commercial testosterone gels include AndroGel® testosterone gel from AbbVie, Inc., and Testim® testosterone gel from Auxilium, each of which is a one-percent testosterone gel that is administered by application of the gel to external skin surfaces whereafter testosterone in the gel passes through the skin. AndroGel® is also commercially available in a 1.62-percent testosterone gel product.

A testosterone gel is a medicinal formulation that can be applied externally to a patient's skin and deliver testosterone transdermally. These gels are designed to provide a combination of useful rheological, tactile, and functional (testosterone delivery) properties, preferably including desired pharmaceutical stability, and

without undesirable odor, texture, or appearance. Rheological properties such as gel viscosity should allow a gel to be applied externally to skin and thereafter remain at that location of application for a period of uptake of the testosterone through the skin. Tactile properties relate to the feel and texture of the gel when touched and applied by a user, with preferred gels exhibiting a smooth feel. Good delivery properties (*e.g.*, uptake) allow an effective amount of testosterone from the applied gel to be absorbed through skin during the time that the gel remains located at the skin surface.

Certain specific ingredients are included in commercial testosterone gel products to achieve desired properties of viscosity and uptake, such as enhancers, that is, a material which is capable of increasing the rate of passage of an androgen through a body membrane. For example, Testim® testosterone gel includes the chemically complex, cyclic oxacyclohexadecane-2-one.

Doctors and patients continue to need improved testosterone gel products having good stability, cosmetic properties, and efficacy, especially such products that also benefit from cost advantages or improved performance relative to current available product options.

SUMMARY

The following description relates to pharmaceutical compositions, such as compositions in the form of a gel ("gel compositions"), that include an active pharmaceutical ingredient ("active ingredient") that can be applied to the skin to transdermally administer the active ingredient to a patient. The active ingredient can be any that is desired for transdermal administration, though gel compositions of the invention that include testosterone as the active ingredient have been found to exhibit particularly useful or advantageous properties compared to other testosterone gel compositions currently marketed.

Examples of gel compositions as described can include a combination of ingredients that includes a solvent, cosolvent, polyol, gel-forming polymer (*i.e.*, "thickener"), and optional pH adjusting ingredient (pH-modifier), to provide bioavailability of the active ingredient that is as good as, equivalent to, or better than certain currently-available commercial products such as Testim® testosterone gel and Androgel® testosterone gel. Advantageously, the gel compositions described

herein can achieve useful, desirable, or improved functional and cosmetic properties without the need for certain complicated (also potentially expensive) or cosmetically undesirable (*e.g.*, due to odor) ingredients present in one or more of those commercial products. The ingredients used in the presently described gel compositions (solvent, cosolvent, polyol, gel-forming polymer, and pH-modifier) are relatively simple and inexpensive, well known, and widely available.

Advantageously, the pharmaceutical compositions as described do not require and can preferably exclude a "Hsieh enhancer" such as oxacyclohexadecane-2-one as described in United States Patent Numbers 7,320,968 and 5,023,252(The entirety of these two patent documents, and other patent documents legally related thereto based on a common priority, are incorporated herein by reference). Pharmaceutical compositions of the present description can exclude the presence of any one or more of these "Hsieh enhancers" described in U.S. Patent Number 7,320,968 (and its family members) or 5,023,252. Such enhancers are said to be lipophilic, and certain specific Hsieh enhancers are said to be "macrocyclic" meaning a cyclic compound having at least 12 carbon atoms in the cyclic ring. Examples of macrocyclic enhancers include: (A) macrocyclic ketones, for example, 3-methylcyclopentadecanone (muscone), 9-cycloheptadecen-1-one (civetone), cyclohexadecanone, and cyclopentadecanone (normuscone); and (B) macrocyclic esters, for example, pentadecalactones such as oxacyclohexadecan-2-one (cyclopentadecanolide; omega-pentadecalactone).

As another example, the commercially available AndroGel® testosterone gel composition includes isopropyl myristate as an enhancer. The presently-described pharmaceutical compositions do not require and can optionally exclude isopropyl myristate.

A testosterone gel composition as described herein, having useful or advantageous performance, does not require and specifically excludes any significant amount of a "Hseih enhancer" and/or any significant amount of a isopropyl myristate. A testosterone gel composition as described herein may be prepared with ingredients that are generally available commercially, and by relatively simple manufacturing steps and methods. Embodiments of the resultant

gel composition do not exhibit an undesired odor that can arise from the presence of a "Hseih enhancer."

Data show that testosterone gel compositions described herein can exhibit transdermal absorption of testosterone that is as good as, *e.g.*, equivalent to, or better than absorption of testosterone associated with commercial products such as the Testim® testosterone gel and Androgel® testosterone gel products. The testosterone gel compositions can also be stable, and can have desirable cosmetic, tactile properties (*e.g.*, texture), rheological properties including diminished, and reduced or suppressed undesirable odor, preferably an absence of any noticeable undesirable odor.

In one aspect, the invention relates to a pharmaceutical composition that contains: about 0.5 to about 10 weight percent testosterone; solvent comprising ethyl alcohol; cosolvent system comprising a cosolvent selected from diisopropyl adipate, methyl laurate, oleyl alcohol, and combinations thereof; polyol system comprising a polyol selected from glycerine, propylene glycol, polyethylene glycol, and combinations thereof; and gel-forming polymer, wherein the weight percent is based on total weight of the pharmaceutical composition.

In another aspect the invention relates to a pharmaceutical composition in the form of a gel, consisting essentially of: about 0.5 to about 10 weight percent testosterone; ethyl alcohol; diisopropyl adipate; methyl laurate; oleyl alcohol; glycerine; propylene glycol; polyethylene glycol polyol; gel-forming polymer; purified water; and optional pH- modifier, wherein the weight is based on total weight of the pharmaceutical composition.

In another aspect, the invention relates to a pharmaceutical composition in the form of a gel, consisting of: about 0.5 to about 10 weight percent testosterone; ethyl alcohol; cosolvent system consisting of diisopropyl adipate, methyl laurate, and oleyl alcohol; polyol system consisting of glycerine, propylene glycol, polyethylene glycol; gel-forming polymer; purified water; and optional pH-adjuster, wherein the weight percent is based on total weight of the pharmaceutical composition.

In yet another aspect, the invention relates to a package containing from 3 to 6 grams pharmaceutical composition. The composition contains: about 0.5 to about

10 weight percent testosterone; solvent comprising ethyl alcohol; cosolvent system comprising cosolvent selected from diisopropyl adipate, methyl laurate, oleyl alcohol, and combinations thereof; polyol system comprising polyol selected from glycerine, propylene glycol, polyethylene glycol, and combinations thereof; and gel-forming polymer, wherein the weight percent is based on total weight of the pharmaceutical composition.

In another aspect, the invention relates to a method for treating a condition associated with a deficiency of endogenous testosterone in a male patient. The method includes administering to the patient a pharmaceutical composition that contains: about 0.5 to about 10 weight percent testosterone; solvent comprising ethyl alcohol; cosolvent system comprising cosolvent selected from diisopropyl adipate, methyl laurate, oleyl alcohol, and combinations thereof; polyol system comprising polyol selected from glycerine, propylene glycol, polyethylene glycol, and combinations thereof; and gel-forming polymer, wherein the weight percent is based on total weight of the pharmaceutical composition.

In yet another aspect the invention relates to a method for transdermal delivery of testosterone to a patient. The method includes administering to the patient a pharmaceutical composition in the form of a gel, which contains: about 0.5 to about 10 weight percent testosterone; solvent comprising ethyl alcohol; cosolvent system comprising cosolvent selected from diisopropyl adipate, methyl laurate, oleyl alcohol, and combinations thereof; polyol system comprising polyol selected from glycerine, propylene glycol, polyethylene glycol, and combinations thereof; and gel-forming polymer, wherein the weight percent is based on total weight of the pharmaceutical composition.

In yet another aspect the invention relates to a method for treating hypogonadism in a patient. The method includes administering to the patient a pharmaceutical composition in the form of a gel, which contains: about 0.5 to about 10 weight percent testosterone; solvent comprising ethyl alcohol; cosolvent system comprising cosolvent selected from diisopropyl adipate, methyl laurate, oleyl alcohol, and combinations thereof; polyol system comprising polyol selected from glycerine, propylene glycol, polyethylene glycol, and combinations thereof; and gel-

forming polymer, wherein the weight percent is based on total weight of the pharmaceutical composition.

In yet another aspect the invention relates to a method for maintaining an effective concentration of testosterone in the blood serum of a male for treating hypogonadism. The method includes transdermally delivering to the male by applying to the skin a pharmaceutical composition in the form of a gel. The gel contains: about 0.5 to about 10 weight percent testosterone based on total weight of the pharmaceutical composition; solvent comprising ethyl alcohol; cosolvent system comprising a cosolvent selected from diisopropyl adipate, methyl laurate, oleyl alcohol, and combinations thereof; polyol system comprising a polyol selected from glycerine, propylene glycol, polyethylene glycol, and combinations thereof; and gel-forming polymer. The pharmaceutical composition is applied to skin of the male in the form of a unit dose that contains about 25 mg to about 200 mg of testosterone and is maintained on the skin for a period of time sufficient for delivery of the testosterone to the male's systemic circulation such that, following a single application of the unit dose to the skin, the amount of circulating testosterone (AUC_{0-24}) in blood serum of the male achieved in a 24-hour period following the application is about 1,000 to about 350,000 pg•h/mL (picogram- hour/milliliter) greater than the amount of circulating testosterone (AUC_{0-24}) in the blood serum of the male that would have been achieved in the same 24-hour period had the dose not been administered.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing flux of active ingredient of testosterone gel compositions, relative to time.

Figure 2 is a graph showing flux of active ingredient of testosterone gel compositions, relative to time.

DETAILED DESCRIPTION

While the present invention may be embodied in many different forms, the following description includes certain specific testosterone gel composition embodiments that particularly relate to treating hormone deficiency or

hypogonadism in males. The present description is not to be limited to these exemplary embodiments.

The following description relates to pharmaceutical compositions that may take the form of a gel (or "hydroalcoholic gel") composition useful for transdermal administration of an active pharmaceutical ingredient, for example testosterone. This description explains that the pharmaceutical composition may preferably take the form of a pharmaceutical gel composition. But while a gel composition may be an exemplary or preferred form of a described pharmaceutical composition, other various forms of transdermal pharmaceutical compositions described herein can also be useful, including creams, dispersions, emulsions, lotions, ointments, thickened solutions, etc.

The pharmaceutical composition contains the active ingredient such as testosterone in an amount and form effective to treat a condition of a patient. The pharmaceutical composition additionally contains various inactive (not pharmaceutically active) ingredients that in combination can produce a combination of desired properties including viscosity and other rheological properties, desired tactile (*e.g.*, feel and texture) properties, desirable (*e.g.*, non-offensive) odor properties, and useful or advantageous properties of effectively allowing transdermal passage of the active ingredient to the blood stream of a patient.

Exemplary pharmaceutical compositions as described herein can be in the form of a gel that includes: an active ingredient that can be an androgen suitable for transdermal administration, such as testosterone; solvent that includes a straight or branched lower alcohol (*e.g.*, a C_2, C_3, or C_4 alcohol) such as ethyl alcohol (ethanol) or isopropyl alcohol (isopropanol) or a combination of two or more such lower alcohols; cosolvent or a combination of cosolvents (a single cosolvent or combination of two or more cosolvents being referred to as a "cosolvent system") that can include one or more of diisopropyl adipate, methyl laurate, and a C_{14} to C_{22} alcohol (*e.g.*, oleyl alcohol); polyol or a combination of polyols (a single polyol or combination of two or more polyols being referred to as a "polyol system") that can include one or more of glycerine, propylene glycol, and polyethylene glycol; a gel-forming or "gelling" polymer (a.k.a., a "thickener") that affects viscosity of the

pharmaceutical composition; and an optional pH-modifier such as a base in an amount to desirably affect pH of the pharmaceutical composition.

The active ingredient can be an androgen such as testosterone, including any suitable form of testosterone such as 17-β-hydroxyandrost-4-en-3-one. The amount of active pharmaceutical ingredient (*e.g.*, testosterone) in a gel composition can be an amount to produce a desired dosage upon application of the gel composition to a patient in need thereof and to be treated, for example an amount in the range from 0.25 to 10 percent by weight testosterone (*e.g.*, 17-β-hydroxyandrost-4-en-3-one), *e.g.*, from 0.5 to 5 or from 0.5 to 2 percent by weight testosterone (*e.g.*, 17-β-hydroxyandrost-4-en-3-one), based on a total weight of the pharmaceutical composition. A concentration of testosterone that has been used for commercial testosterone gel compositions is about 1 percent by weight based on total weight of the testosterone gel composition.

In addition to the active ingredient, the described pharmaceutical compositions (*e.g.*, gels) include inactive ingredients to provide functional (*e.g.*, rheological and absorption) properties, tactile properties, and cosmetic (*e.g.*, odor, texture) properties. These inactive ingredients can include one or more solvent, cosolvent, gelling polymer, water, and optional base or other pH-adjusting or pH-modifying material. Additionally, the described pharmaceutical compositions may optionally include other minor ingredients or excipients such as a stabilizer, emollient, antimicrobial, fragrance, and the like, in a low amount such as below 1 percent, below about 0.5 percent, or below about 0.2 percent by weight based on total weight pharmaceutical composition.

Examples of useful solvents include lower alcohols capable of containing the active pharmaceutical ingredient in a dissolved form. Lower alcohols include saturated alkyl (straight or branched) alcohols having four or fewer (*e.g.*, 2, 3, or 4) carbon atoms, with particular examples including ethanol and isopropanol. A lower alcohol such as ethyl alcohol can be used as the solvent for testosterone as an active pharmaceutical ingredient. Testosterone is relatively soluble in ethyl alcohol, having a reported solubility of 0.17 grams per gram ethyl alcohol. A pharmaceutical gel composition can include any desired and useful amount of solvent (*e.g.*, lower alcohol such as ethyl alcohol), with amounts in the range from 70 to 90 weight

percent and from 75 to 85 weight percent (*e.g.*, about 77 or about 78 weight percent, such as 78.35 weight percent) ethyl alcohol being preferred for certain pharmaceutical gel compositions described herein that contain testosterone.

One or more additional solvent (*e.g.*, "cosolvent") can also be included in the pharmaceutical gel composition in combination with the active ingredient and lower alcohol (primary) solvent described above. According to preferred pharmaceutical gel compositions, a certain specific combination of cosolvents has been identified to provide desired or advantageous properties for a testosterone gel composition, the combination including diisopropyl adipate, methyl laurate, and an alkyl (branched, straight, unsaturated, or saturated) alcohol having from 14 to 22 carbon atoms such as oleyl alcohol. Extensive experimentation led to the unexpected discovery that testosterone gel compositions containing this combination of cosolvents, in combination with ethyl alcohol as the primary solvent, exhibit desired, effective (*e.g.*, bioequivalence with currently marketed products) and/or advantageous skin penetration properties. These same gel compositions did not exhibit an undue or undesirable odor and did exhibit useful or advantageous rheological and tactile properties. Extensive experimentation also identified useful and preferred amounts of total cosolvent (*i.e.*, useful amounts of the three cosolvents taken in total), and useful amounts of each of the three cosolvents (individually, and relative to each other) for use as a cosolvent system in a gel composition.

A total amount of the combination of three cosolvents in a preferred cosolvent system (diisopropyl adipate, methyl laurate, and oleyl alcohol) in a testosterone gel composition, can be any useful amount, with an exemplary range being from 1 to 12 weight percent of these three ingredients, in total, based on the total weight of the composition, more preferably from about 2 to about 10 weight percent, or from about 2 to about 8 weight percent, based on a total weight of the composition.

Within these ranges, amounts of each of the three cosolvents of the preferred cosolvent system can be selected as desired, and preferably as follows. Preferred amounts of diisopropyl adipate can be in the range from 0.5 to 5 weight percent, *e.g.*, from about 1 to about 3.5 weight percent or from 1 to 2 weight percent based on total weight pharmaceutical composition. Preferred amounts of methyl laurate

can be in the range from 0.1 to 3 weight percent, *e.g.*, from about 0.2 to about 2.5 weight percent, or from 0.2 to 0.4 weight percent based on total weight pharmaceutical composition. Preferred amounts of C_{14} to C_{22} (*e.g.*, oleyl) alcohol can be in the range from 0.5 to 5 weight percent, e.g., from about 1 to about 3.5 weight percent, or from 1 to 2 weight percent based on total weight pharmaceutical composition.

Relative amounts (by weight) of diisopropyl adipate to C_{14} to C_{22} (*e.g.*, oleyl) alcohol can be about 1 to 1, more generally within a range from 0.8 to 1.2 grams diisopropyl adipate per gram C_{14} to C_{22} (*e.g.*, oleyl) alcohol. A preferred amount (by weight) of methyl laurate relative to diisopropyl adipate (or, alternately, relative to the C_{14} to C_{22} (*e.g.*, oleyl) alcohol) can be an amount of methyl laurate (by weight) that is less than the amount of diisopropyl adipate (alternately C_{14} to C_{22} (*e.g.*, oleyl) alcohol), *e.g.*, an amount that is in a range from about 10 percent (by weight) to about 70 percent (by weight) of the amount of diisopropyl adipate (alternately C_{14} to C_{22} (*e.g.*, oleyl) alcohol). Relative amounts (by weight) of diisopropyl adipate to C_{14} to C_{22} (*e.g.*, oleyl) alcohol to methyl laurate can be (0.8-1.2):1:(0.1-0.7).

One particular cosolvent system of a pharmaceutical composition may contain about 1.5 weight percent diisopropyl adipate, about 0.25 weight percent methyl laurate, and about 1.5 weight percent oleyl alcohol, based on total weight pharmaceutical composition. Another particular cosolvent system of a pharmaceutical composition may contain a ratio of about 6:1:6 diisopropyl adipate to methyl laurate to oleyl alcohol.

Preferred pharmaceutical gel compositions also include one or a combination of two or more polyols (a polyol system) to provide desired or advantageous tactile properties in combination with desired functional properties. Examples of useful polyols include one or a combination of propylene glycol, polyethylene glycol (*e.g.* polyethylene glycol 1000; the "1000" stands for an approximate or average molecular weight of the polyethylene glycol), and glycerine. These three polyols, in combination, have been found to impart positive tactile attributes to a pharmaceutical gel composition as described. The use of one or more of these polyols at a reasonable level can impart a smooth, slippery skin feel when the gel composition is applied, as opposed to a sticky or tacky feel.

Based on extensive experimentation, pharmaceutical gel compositions that include testosterone as an active pharmaceutical ingredient, ethanol solvent, and a polyol system that includes a combination of propylene glycol, polyethylene glycol (*e.g.* polyethylene glycol 1000), and glycerine, can exhibit desired, effective, or advantageous functionality. These gel compositions have been determined to not exhibit undue or undesirable odor, while exhibiting useful or advantageous rheological, tactile, and cosmetic properties. Extensive experimentation also identified useful and preferred amounts of total amounts of polyol (*i.e.*, useful amounts of the three polyols taken in total), and useful amounts of each polyol (individually, and relative to each other) in a gel composition.

Polyols, including the described combination of polyols in the described amounts and relative amounts, can also contribute to stability of a testosterone gel composition, by providing a reduced freezing point and resistance to freezing, and resistance to testosterone degradation due to temperature cycling or freeze-thaw cycling.

A total amount of a polyol system containing the three identified polyols -- propylene glycol, polyethylene glycol (*e.g.* polyethylene glycol 1000), and glycerine -- in a testosterone gel composition, can be any useful amount, with an exemplary range being from 5 to 15 weight percent of these three polyols, in total, based on the total weight of the pharmaceutical gel composition, more preferably from 7 to 14 weight percent or from 8 to 12 weight percent.

Within these ranges, amounts of each polyol can be selected as desired, for example as follows. Preferred amounts of propylene glycol can be in the range from 2 to 8 weight percent, *e.g.*, from about 3 to about 7 weight percent. Preferred amounts of polyethylene glycol can be in the range from 0.2 to 0.8 weight percent, *e.g.*, from about 0.3 to about 0.7 weight percent. Preferred amounts of glycerine can be in the range from 2 to 8 weight percent, *e.g.*, from about 3 to about 7 weight percent. Relative amounts (by weight) of propylene glycol to glycerine can be about 1 to 1, more generally within a range from 0.8 to 1.2 grams propylene glycol to glycerine. A preferred amount (by weight) of polyethylene glycol relative to propylene glycol (or, alternately, relative to the glycerine) can be an amount of polyethylene glycol (by weight) that is less than fifty percent of the amount (by

weight) of propylene glycol (alternately glycerine), *e.g.*, an amount that is in the range from about 5 percent (by weight) to about 25 percent (by weight) polyethylene glycol to propylene glycol (alternately glycerine).

One particular polyol system of a pharmaceutical composition may contain about 0.5 weight percent polyethylene glycol (*e.g.*, PEG 1000), about 5.0 weight percent propylene glycol, and about 5.0 weight percent glycerine, based on total weight pharmaceutical composition.

The described pharmaceutical compositions also include a gel-forming polymer or "thickener" for use in increasing the viscosity of the composition. Increased viscosity retards the flow of the composition, thus allowing for improved surface cling. Increased viscosity retards also the movement of particles dispersed in the composition, allowing for compounds dispersed therein to remain suspended therein for relatively long periods of time. A pharmaceutical gel composition as described herein may have any desired or useful viscosity. Examples of gel-forming polymers include various natural and synthetic polymeric materials known in the pharmaceutical composition and dosage form arts for increasing viscosity of a pharmaceutical composition or dosage form, including: cellulosic polymers, for example, cellulose, hydroxyethylcellulose, carboxymethylcellulose, and hydroxypropylmethylcellulose; polyalkylene oxide polymers (*e.g.*, polyethylene oxide), polyvinyl alcohol, and acrylic polymers (*e.g.*, acrylic acid co-polymers and homopolymers).

In certain pharmaceutical composition embodiments, preferred gel-forming polymers can be carbomer polymers, for example non-linear polymers of acrylic acid cross-linked with a polyalkenyl polyether. Examples of carbomers useful in pharmaceutical compositions as described include carboxypolymethylene, carboxyvinyl polymer, and alkyl acrylates, for example, acrylic acid-alkyl methacrylate copolymers. Examples also include polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol such as those that make up the Carbopol® line of polymeric thickeners (*e.g.*, Carbopol® 980, Carbopol® 980 NF, Pemulen™ TR-1 (acrylic acid-alkyl methacrylate copolymer) polymers) and similar polymeric thickeners.

These and other useful gel-forming polymers can be a homopolymer or copolymer having a polymeric backbone made up of polymerized acrylic acid monomers, which may become crosslinked. Exemplary such polyacrylate gel-forming polymers contain long polymer chains having pendant carboxylic acid functionalities, crosslinked, *e.g.*, with polyalkenyl polyethers.

Certain presently preferred testosterone gel compositions of the present description include a gel-forming polymer as described. Examples of preferred amounts of carbomer gel-forming polymer (*e.g.*, polyacrylate) in a gel composition can be useful to achieve desired viscosity and other functional and cosmetic properties, with amounts in the range from 0.1 to 10 percent by weight (based on the total weight of the pharmaceutical gel composition) being useful, and preferred amounts being in the range from 0.2 to 6 or from 0.3 to 3 weight percent based on total weight pharmaceutical composition.

In pharmaceutical compositions that contain acidic materials, *e.g.*, an acidic gel-forming polymer such as a carbomer, a pH-modifier may be included. A pH-modifier can be a basic ingredient that affects pH such as by neutralizing an acidic component of the gel composition. In particular, certain of the preferred gel composition described herein can include gel-forming polymer that includes pendant acidic (carboxylic acid) groups and a pH-modifier (base) to neutralize such pendant acid groups and impart a desired pH (or "apparent pH") to the gel.

The type of base useful in a gel composition can be any base useful to affect pH as desired, such as to neutralize acid functionalities of a polyacrylate gel-forming polymer, and that also is not incompatible with the gel composition generally. Examples of useful bases include sodium hydroxide (*e.g.*, 0.1 normal (N) sodium hydroxide), tromethamine, and others. A preferred base for certain pharmaceutical gel compositions may be tromethamine. The amount of base included in pharmaceutical gel composition can be any desired amount, such as an amount sufficient to affect pH as desired, such as to neutralize acid functionalities of a polyacrylate gel-forming polymer.

In selecting a combination of base chemistry and concentration, these may preferably be selected to result in a gel composition that is physically stable and clear (not cloudy). For example, when 4.75% of 0.1N sodium hydroxide was used

in a system with ethanol as solvent, a resulting sodium salt precipitated in the ethanol system, evident as cloudiness. Gel compositions using tromethamine remained clear and colorless while maintaining a consistent viscosity and stability.

A base may be added to a pharmaceutical composition to provide a desired pH reading using a standard pH meter. As used herein, the term "apparent pH" refers a result of a measurement made using a standard pH meter by placing the electrode into a pharmaceutical gel composition as described, as if to measure pH of the pharmaceutical gel composition. The pH meter can be any standard pH meter, and the measurement can be performed at standard conditions of testing for pH of an aqueous liquid. A pharmaceutical composition as described herein may include some amount of water, but may sometimes include a relatively low amount of water and a high amount of non-water solvent and cosolvent, along with other non-water ingredients such as polyol, gelling polymer, and solids. As a consequence, a value obtained by taking a measurement of a pharmaceutical gel composition as described using a pH meter, may not necessarily be a measure of a concentration of hydrogen ions in the composition. Still, a standard pH meter is capable of taking a measured reading from the composition when the electrode is placed in the pharmaceutical composition as if taking a pH measurement. If the reading of the pH meter is not considered a true pH of the pharmaceutical composition, due to its relatively low water content, the measurement is still considered to be an "apparent pH" of the pharmaceutical composition for purposes of the present description and claims.

According to certain examples of pharmaceutical gel composition as described, an apparent pH of these compositions may be in a range from 4.5 to 6.5, *e.g.*, from 5.5 to 6.5. Still, compositions having an apparent pH outside of these identified ranges may still be useful pharmaceutical compositions.

According to certain particularly preferred testosterone gel compositions, combinations of certain preferred ingredients can be included in amounts also described, to provide preferred properties such as preferred skin penetration properties, preferred viscosity, and preferred tactile properties. The ingredients of the particularly preferred pharmaceutical gel compositions include the lower alcohol solvent ethanol; a cosolvent system (including diisopropyl adipate, methyl laurate, and oleyl alcohol); and a polyol system (including propylene glycol, polyethylene

glycol, and glycerine) each in amounts as described herein. Exemplary gel compositions can also contain these ingredients along with an active pharmaceutical ingredient, gel-forming polymer, optional pH-modifier, and water, in the absence or substantial absence of other ingredients. Such compositions are considered to consist of or consist essentially of these ingredients. A substantial absence of other ingredients can allow for a small amount of such other ingredients, *e.g.*, less than 1, 0.5, or 0.2 weight percent of other added ingredients based on a total weight of the pharmaceutical composition.

A pharmaceutical composition described as "consisting of" a group of specific ingredients is a composition made by combining the specified ingredients and no other identifiable ingredient. The pharmaceutical composition may include other (non-ingredient) materials only to the extent that the other materials were useful or appurtenant to preparation of one of the recited ingredients, such as the gel-forming polymer, solvent, cosolvent, polyol, active ingredient, or pH-modifier, and then only in a functionally insignificant amount.

A pharmaceutical composition described as "consisting essentially of" a group of specific ingredients is a composition made by combining the specified ingredients and no other identifiable ingredient other than optional minor (*e.g.*, "excipient") ingredients such as a stabilizer, emollient, antimicrobial agent, coloring agent, fragrance, and the like, in a low amount, such as, by way of example, below about 1, 0.5 percent, or below about 0.2 percent by weight total such additional ingredients based on a total weight of the pharmaceutical composition.

The pharmaceutical composition of the present description may be formulated and prepared using conventional methods and equipment known in the pharmaceutical arts, such as by relatively simple combining, mixing, and stirring steps using known types of equipment. Standard glassware or stainless steel mixing vessels may be used. The composition can be formulated typically at room temperature, *e.g.*, at or around 25°C, or slightly above and at atmospheric pressures.

For purposes of a single example, a preferred pharmaceutical composition as described can be prepared by a method that includes steps useful to prepare known versions of alcohol gels, including combining ingredients in a manner to result in a stable and effective transdermal gel. Useful methods can include steps that ensure

desired functionality of a gel-forming polymer, such as by an order of addition of ingredients that hydrates and optionally neutralizes a gel-forming carbomer polymer (if used). An example of a method useful to prepare a one-percent testosterone gel composition can include a step of hydrating gel-forming polymer or polymers (*e.g.*, Carbopol® and Pemulen™ (acrylates) ingredients) in a portion of ethanol solvent. Testosterone, USP, is dissolved in a separate portion of ethanol. The gel-forming polymer is then combined with the ethanolic solution of testosterone.

With the exception of aqueous tromethamine as a pH-modifier, the remaining ingredients of the pharmaceutical composition can be added to this combined ethanolic mixture either in a single subsequent step of adding a mixture of the remaining ingredients, or in multiple steps of adding multiple ingredients singly. For example, a system of cosolvents may be added together in one step and one or more polyols of a polyol system may be added separately or together. A tromethamine solution can be added in a final step. All ingredients are miscible in ethanol. Thus, after each component addition the result remains a solution.

A pharmaceutical composition as described may be contained in a tube, a sachet, a metered pump, or another useful dispensing device. Such a tube or sachet may contain one unit dose of the composition, *e.g.*, 5 grams of testosterone gel which can contain 50 mg of testosterone. A metered pump may be capable of dispensing one metered dose of the composition per actuation, which metered dose may or may not contain a unit dose.

As one example, a gel composition can be dispensed from a hand-held metered-dose pump capable of delivering a metered dose of the gel, such as about 1.25 grams (g) of the testosterone gel with each actuation, *e.g.*, with four pump actuations, a total of 5 grams (a single unit dose) of the testosterone gel may be delivered. In another embodiment, the gel composition can be packaged in foil packet. For example, each packet can hold a single unit dose of the gel, such as an amount of about 5 grams of testosterone gel. A patient can tear the packet along a perforated edge to remove the gel. As another alternative, a gel composition as described can be dispensed from a rigid multi-dose container (*e.g.*, with a hand pump) having a foil packet of the composition inside the container. Any useful dispensing option, as described or otherwise, can allow a user to deliver an accurate

amount of a desired dosage of the gel composition, by mass or volume, (*e.g.*, 5.0 g, 7.5 g, 10 g, *etc*).

A condition in a patient related to below-normal androgen concentration in blood serum of the patient may be treated by administering to the patient a pharmaceutical composition as described, such as a topically-delivered, transdermal gel composition as described. A pharmaceutical gel composition may be applied and rubbed onto skin of the patient, such as intact, clean, and dry skin of the shoulder, upper arm, axilla, the upper torso, or thigh, and maintained thereon for a period of time sufficient for delivery of androgen to the blood serum of the patient.

The dosage amount will depend upon the condition to be treated, the frequency of administration of the dose, and the amount of androgen in the gel composition. Without limitation, a pharmaceutical gel composition as described can be applied to skin of a patient in the form of a unit dose that contains from about 25 milligrams (mg) to about 200 mg of testosterone. A single unit dose of the testosterone gel composition can be in a range from 2.5 grams (which at a 1% concentration contains 25 mg of testosterone) to 20 grams (which at a 1% concentration contains 200 mg of testosterone). As particular examples, a single unit dose of the testosterone gel composition can be 5 grams (containing 50 mg of testosterone) or 10 grams (containing and 100 mg of testosterone).

For the purpose of treating male hypogonadism, a preferred once daily dosage amount (*e.g.*, unit dose) of a gel composition of the present invention (containing 1 percent testosterone) can be from about 1 to about 10 grams of the gel composition, and preferably about 5 to about 10 grams of the gel composition. The unit dose can be maintained on the skin for a period of time sufficient for delivery of the testosterone to the patient's systemic circulation such that, following a single application of the unit dose to the skin, the amount of circulating testosterone ($AUC_{0\text{-}24}$) in blood serum of the patient achieved in a 24-hour period following the application is a useful or desired amount, such as an amount that is about 46,000 to about 95,000 pg•h/mL (picogram-hour/milliliter) (*e.g.*, about 53,000 to about 82,800 pg•h/mL; about 50,000 to about 88,000 pg•h/mL, such as about 66,250 pg•h/mL) greater than the amount of circulating testosterone ($AUC_{0\text{-}24}$) in the blood serum of

the patient that would have been achieved in the same 24-hour period had the dose not been administered.

In situations where a unit dose is applied, one or more of such unit doses may be administered to a patient, depending upon the condition to be treated, the amount of androgen to be delivered, and the frequency of administration. The number of such unit doses may be increased or decreased as needed, depending upon, as stated above, whether a desired clinical effect has been achieved and the concentration of androgen in the blood serum of the patient treated.

If, after a period of time has passed following the initial administration of a testosterone gel composition (for example, about 14 days), a desired clinical response has not been achieved or if the androgen concentration in the blood serum of the patient is determined and found to remain below the normal adult concentration thereof, *i.e.*, below about 250 to about 300 ng•h/dL (nanogram-hour per deciliter) (*i.e.*, 2,500 to about 3,000 pg•h/mL), the amount of the dose, the frequency of the dose, and/or the number of applications of the dose may be increased. Similarly, if, after a period of time has passed following the initial administration of the gel composition (for example, about 14 days), the androgen concentration in the blood serum of the patient is determined and found to be above the normal adult concentration thereof, the amount of the dose, the frequency of the dose, and/or the number of applications of the dose may be decreased.

Example 1

Gel compositions that can be used as a topical gel for delivery of testosterone, including certain pharmaceutical compositions of the invention, were prepared according to the following Tables. The ingredients and amounts of ingredients used in each example are given in percent by weight relative to the total weight of the composition.

Table 1 Testosterone Gel 1% Formulations (Examples 1-1 through 1-11)

Ingredient	1-1	1-2	1-3	1-4	1-5	1-6	1-7	1-8	1-9	1-10	1-11
Testosterone, USP	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ethyl alcohol, anhydrous, USP	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	67.0	67.5	67.0	67.0	q.s. to 100
Glycerin, 99.7%, USP	5.0	5.0	5.0	5.0	5.0	5.0	-	-	-	-	5.0
Carbomer 980	1.5	1.5	1.5	1.5	1.5	1.5	0.9	0.9	0.9	0.9	1.5
Pemulen™ TR-1	0.3	0.3	0.3	0.3	0.3	0.3	-	-	-	-	0.3
PEG 1000, NF	0.5	0.5	0.5	0.5	0.5	0.5	-	-	-	-	0.5
Tromethamine, USP	0.1	0.1	0.1	0.1	0.1	0.1					0.1
Sodium hydroxide (0.1 N)	-	-	-	-	-	-	4.72	4.72	4.72	4.72	-
Propylene Glycol, USP	5.0	5.0	5.0	13.0	5.0	6.0	-	-	8.0	-	8.0
Pentadecalactone	8.0	-	-	-	-	-	-	-	-	-	-
dl-limonene	-	-	-	-	-	2.0	-	-	-	-	-
Diisopropyl adipate	-	-	-	-	3.0	-	-	-	-	-	-
Lauryl alcohol	-	-	-	-	-	3.0	-	-	-	-	2.0
Methyl laurate	-	-	-	-	2.0	2.0	-	-	-	-	1.0
Isopropyl myristate	-	8.0	-	-	-		0.5	-	-	-	-
Oleyl alcohol	-	-	-	-	3.0	-	-	-	-	3.0	-
Propylene glycol dicaprylate / dicaprate (Miglyol 840)	-	-	-	-	-	-	-	-	-	3.0	-
PG-dipelargonate	-	-	-	-	-	-	-	-	-	0.6	-
Purified Water, USP	5.0	5.0	13.0	5.0	5.0	5.0	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	5.0
Apparent pH	5.3	5.2	5.2	5.4	5.5	5.0	5.1	5.4	5.5	5.3	5.7
Viscosity, cP at 25°C	978	763	1,383	1,531	1,017	732	275	494	1,102	766	1,436
Visual appearance	Clear	Clear	Clear	Clear	NA	NA	Clear	Clear	Clear	NA	Clear

Based on the *in vitro* performance results of the Examples of Table 1, Example 1-5 had desired performance. Additional examples (1-5A, 1-5B, 1-5C, and 1-5D) were prepared having formulations similar to but different from the Example 5 formulation. The formulations of Examples 1-5A, 1-5B, 1-5C, and 1-5D varied in terms of the ratios and overall levels of cosolvents of the diisopropyl adipate, methyl laurate, oleyl alcohol cosolvent system. See Table 2 below.

Table 2 Testosterone Gel 1% Formulations (the "5-series")

Example	1-5	1-5A	1-5B	1-5C	1-5D
Ingredient					
Testosterone, USP	1.0	1.0	1.0	1.0	1.0
Ethyl alcohol, anhydrous, USP	q.s. to 100	75.1	q.s. to 100	77.3	78.3
Glycerin, 99.7%, USP	5.0	5.0	5.0	5.0	5.0
Carbomer 980	1.5	1.5	1.5	1.5	1.5
Acrylates (Pemulen TR-1)	0.3	0.3	0.3	0.3	0.3
PEG 1000, NF	0.5	0.5	0.5	0.5	0.5
Tromethamine, USP	0.1	0.1	0.1	0.1	0.1
Propylene Glycol, USP	5.0	5.0	5.0	5.0	5.0
Diisopropyl adipate	3.0	2.5	2.0	2.0	1.5
Methyl laurate	2.0	1.5	1.0	0.25	0.25
Oleyl alcohol	3.0	2.5	2.0	2.0	1.5
Purified Water, USP	5.0	5.0	5.0	5.0	5.0

The performance of the "5-Series" Example formulations compared well to the commercial Testim® testosterone gel product. Figure 2 illustrates performance data of the "5-series" compared to a Testim® testosterone gel product.

Example 2 – *In Vitro* Evaluation of Percutaneous Absorption of Testosterone

To characterize the percutaneous absorption pharmacokinetics of testosterone in the various Example formulations of Table 1 and Table 2, absorption was measured in human cadaver skin *in vitro*, using the finite dose technique and Franz diffusion cell (Franz, J. Invest. Dermatol., 65:190-195 (1975). Results are depicted at Figure 1 and Figure 2.

The example testosterone gel formulations described in Table 1 were initially screened in an *in-vitro* skin penetration study. The graph at Figure 1 illustrates the results for *in-vitro* human skin penetration studies of Examples 1-through 1-11. The example testosterone gel formulations described in Table 2 were also tested in an *in vitro* skin penetration study. The graph at Figure 2 illustrates the results for *in vitro* human skin penetration studies of Examples 1-5A-through 1-5D.

Example 3

The testosterone gel formulation shown in Table 3 is bioequivalent to Testim® testosterone gel, possesses good long term stability, can be manufactured with consistency, and is cosmetically pleasing to a patient, including a lack of undesirable odor.

Table 3

1% Testosterone Gel Formulation	
Component	Percent by weight
Ethyl alcohol, anhydrous, USP	78.35
Testosterone, USP	1.00
Glycerin, 99.7%, USP	5.00
Diisopropyl adipate	1.50
Methyl laurate	0.25
Oleyl alcohol, NF	1.50
Carbomer Homopolymer Type C*, NF (Carbomer 980)	1.50
Carbomer Copolymer Type B*, NF (Pemulen TR-1, Acrylates)	0.30
Propylene glycol, USP	5.00
Polyethylene glycol 1000, USP	0.50
Purified Water, USP	5.00
Tromethamine, USP	0.10

*(allyl pentaerythritol crosslinked)

Claims:

1. A pharmaceutical composition, comprising:

about 0.5 to about 10 weight percent testosterone;

solvent comprising ethyl alcohol;

cosolvent system comprising a cosolvent selected from diisopropyl adipate, methyl laurate, oleyl alcohol, and combinations thereof;

polyol system comprising a polyol selected from glycerine, propylene glycol, polyethylene glycol, and combinations thereof; and

gel-forming polymer, wherein the weight percent is based on total weight of the pharmaceutical composition.

2. A pharmaceutical composition according to claim 1, wherein the composition is a gel.

3. A pharmaceutical composition according to claim 1 or 2 comprising about 0.5 to about 2 weight percent testosterone.

4. A pharmaceutical composition according to any of claims 1 through 3 comprising from about 75 to about 85 weight percent ethyl alcohol.

5. A pharmaceutical composition as according to any of claims 1 through 4 comprising about 1 to about 12 weight percent cosolvent system, wherein the cosolvent system comprises diisopropyl adipate, methyl laurate, and oleyl alcohol.

6. A pharmaceutical composition according to any of claims 1 through 5 comprising about 7 to about 14 weight percent polyol system, wherein the polyol system comprises glycerine, propylene glycol, and polyethylene glycol.

7. A pharmaceutical composition according to any of claims 1 through 6 wherein the gel-forming polymer is a carbomer comprising pendant acrylic acid groups.

8. A pharmaceutical composition according to any one of claims 1 through 7 further comprising a pH-modifier.

9. A pharmaceutical composition according to claim 8 wherein the pH-modifier is tromethamine.

10. A pharmaceutical composition according to any of claims 1 through 9, comprising:

about 0.5 to about 2 weight percent testosterone;

about 75 to about 85 weight percent ethyl alcohol;

about 2 to about 10 weight percent cosolvent system comprising diisopropyl adipate, methyl laurate, and oleyl;

about 7 to about 14 weight percent polyol system comprising glycerine, propylene glycol, polyethylene glycol, and combinations thereof; and

about 0.5 to about 3 weight percent carbomer gel-forming polymer.

11. A pharmaceutical composition according to any of claims 1 through 9, comprising:

1 weight percent testosterone;

75 to 85 weight percent ethyl alcohol;

cosolvent system comprising 1 to 2 weight percent diisopropyl adipate,

0.2 to 0.4 weight percent methyl laurate, and 1 to 2 weight percent oleyl alcohol;

polyol system comprising 3 to 7 weight percent glycerine, 3 to 7 weight percent propylene glycol, and

0.3 to 0.7 weight percent polyethylene glycol; and

1 to 3 weight percent gel-forming polymer.

12. A pharmaceutical composition according to any of claims 1 through 11 further comprising purified water.

13. A pharmaceutical composition according to any of claims 1 through 12, comprising:

about 1 weight percent testosterone;

about 78 weight percent ethyl alcohol;

cosolvent system comprising about 1.5 weight percent diisopropyl adipate, about 0.25 weight percent methyl laurate, and about 1.5 weight percent oleyl alcohol;

polyol system comprising about 5 weight percent glycerine, about 5 weight percent propylene glycol, and about 0.5 weight percent polyethylene glycol;

1.8 weight percent weight percent carbomer gel-forming polymer;

about 4 weight percent purified water; and

about 0.1 weight percent tromethamine.

14. A pharmaceutical composition according to any of claims 1 through 13 wherein the polyethylene glycol comprises polyethylene glycol 1000.

15. A pharmaceutical composition according to any of claims 1 through 14 comprising:

1.0 weight percent (wt %) testosterone;

78.4 wt % ethyl alcohol;

cosolvent system comprising 1.5 wt % diisopropyl adipate, 0.25 wt % methyl laurate, and 1.5 wt % oleyl alcohol;

polyol system comprising 5.0 wt % glycerin, 5.0 wt % propylene glycol, and 0.50 wt % polyethylene glycol 1000;

1.5 wt% carbomer homopolymer,

0.30 wt % carbomer copolymer,

0.10 wt% tromethamine; and

5.0 wt % purified water.

16. A pharmaceutical composition according to any one of claims 1 through 15 comprising:

1.00 weight percent (wt %) testosterone;

78.35 wt % ethyl alcohol;

cosolvent system comprising 1.50 wt % diisopropyl adipate, 0.25 wt % methyl laurate, and 1.50 wt % oleyl alcohol;

polyol system comprising 5.00 wt % glycerin, 5.00 wt % propylene glycol, and 0.50 wt % polyethylene glycol 1000;

1.50 wt% carbomer homopolymer,

0.30 wt % carbomer copolymer,

0.10 wt% tromethamine; and

5.00 wt % purified water.

17. A pharmaceutical composition according to any of claims 1 through 16, with the proviso that the composition excludes a Hseih enhancer.

18. A pharmaceutical composition according to any of claims 1 through 17, with the proviso that the composition excludes oxacyclohexadecane-2-one.

19. A pharmaceutical composition according to any of claims 1 through 18, with the proviso that the composition excludes isopropyl myristate.

20. A pharmaceutical composition according to any of claims 1 through 19 wherein the pharmaceutical composition can be applied to skin of a patient in the form of a unit dose that contains about 25 mg to about 200 mg of testosterone, and maintained on the skin for a period of time sufficient for delivery of the testosterone to the patient's systemic circulation such that, following a single application of the unit dose to the skin, the amount of circulating testosterone (AUC_{0-24}) in blood serum of the patient achieved in a 24-hour period following the application is about 46,000 to about 95,000 pg•h/mL (picogram-hour/milliliter) greater than the amount of circulating testosterone (AUC_{0-24}) in the blood serum of the patient that would have been achieved in the same 24-hour period had the dose not been administered.

21. A pharmaceutical composition in the form of a gel, consisting essentially of:

about 0.5 to about 10 weight percent testosterone;

ethyl alcohol;
diisopropyl adipate;
methyl laurate;
oleyl alcohol;
glycerine;
propylene glycol;
polyethylene glycol polyol;
gel-forming polymer;
purified water; and
optional pH- modifier, wherein the weight is based on total weight of the pharmaceutical composition.

22. A pharmaceutical composition according to claim 21 wherein the testosterone is present in a range from about 0.5 to about 2 weight percent.

23. A pharmaceutical composition according to claim 21 or 22 wherein the ethyl alcohol is present in a range from about 75 to about 85 weight percent.

24. A pharmaceutical composition according to any of claims 21 through 23 wherein the pH-modifier is tromethamine.

25. A pharmaceutical composition according to any of claims 21 through 24, wherein the gel-forming polymer is a carbomer polymer.

26. A pharmaceutical composition according to claim 25, wherein the carbomer polymer is present in a range from about 0.5 to about 3 weight percent.

27. A pharmaceutical composition according to any of claims 21 through 26, consisting essentially of:
1 weight percent testosterone;
75 to 85 weight percent ethyl alcohol;
1 to 2 weight percent diisopropyl adipate;

0.2 to 0.4 weight percent methyl laurate;
1 to 2 weight percent oleyl alcohol;
3 to 7 weight percent glycerine;
3 to 7 weight percent propylene glycol;
0.3 to 0.7 weight percent polyethylene glycol;
1 to 3 weight percent gel-forming polymer; and
pH-modifier.

28. A pharmaceutical composition according to any of claims 21 through 25, consisting essentially of:

1 weight percent testosterone;
75 to 85 weight percent ethyl alcohol;
1 to 2 weight percent diisopropyl adipate;
0.2 to 0.4 weight percent methyl laurate;
1 to 2 weight percent oleyl alcohol;
3 to 7 weight percent glycerine;
3 to 7 weight percent propylene glycol;
0.3 to 0.7 weight percent polyethylene glycol;
1 to 3 weight percent weight percent gel-forming polymer;
purified water; and
pH-modifier.

29. A pharmaceutical composition according to any of claims 21 through 25, consisting essentially of:

about 1 weight percent testosterone;
about 78 weight percent ethyl alcohol;
about 1.5 weight percent diisopropyl adipate;
about 0.25 weight percent methyl laurate;
about 1.5 weight percent oleyl alcohol;
about 5 weight percent glycerine,
about 5 weight percent propylene glycol,
about 0.5 weight percent polyethylene glycol;

1.8 weight percent weight percent carbomer gel-forming polymer;
about 4 weight percent purified water; and
about 0.1 weight percent tromethamine.

30. A pharmaceutical composition according to claim 21, consisting essentially of:

1.0 weight percent (wt %) testosterone;
78.4 wt % ethyl alcohol;
1.5 wt % diisopropyl adipate;
0.25 wt % methyl laurate;
1.5 wt % oleyl alcohol;
5.0 wt % glycerin;
5.0 wt % propylene glycol;
0.50 wt % polyethylene glycol 1000;
1.5 wt% carbomer homopolymer;
0.30 wt % carbomer copolymer;
0.10 wt% tromethamine; and
5.0 wt % purified water.

31. A pharmaceutical composition according to claim 21, consisting essentially of:

1.00 weight percent (wt %) testosterone;
78.35 wt % ethyl alcohol;
1.50 wt % diisopropyl adipate;
0.25 wt % methyl laurate;
1.50 wt % oleyl alcohol;
5.00 wt % glycerin;
5.00 wt % propylene glycol;
0.50 wt % polyethylene glycol 1000;
1.50 wt% carbomer homopolymer;
0.30 wt % carbomer copolymer;
0.10 wt% tromethamine; and

5.00 wt % purified water.

32. A pharmaceutical composition according to any of claims 21 through 31 wherein the polyethylene glycol comprises polyethylene glycol 1000.

33. A pharmaceutical composition according to any of claims 20 through 30, with the proviso that the composition excludes Hseih enhancer.

34. A pharmaceutical composition according to any of claims 21 through 31, with the proviso that the composition excludes oxacyclohexadecane-2-one.

35. A pharmaceutical composition according to any of claims 21 through 34, with the proviso that the composition excludes isopropyl myristate.

36. A pharmaceutical composition according to any of claims 21 through 35 wherein the pharmaceutical composition can be applied to skin of a patient in the form of a unit dose that contains about 25 mg to about 200 mg of testosterone, and maintained on the skin for a period of time sufficient for delivery of the testosterone to the patient's systemic circulation such that, following a single application of the unit dose to the skin, the amount of circulating testosterone (AUC_{0-24}) in blood serum of the patient achieved in a 24-hour period following the application is about 46,000 to about 95,000 pg•h/mL (picogram-hour/milliliter) greater than the amount of circulating testosterone (AUC_{0-24}) in the blood serum of the patient that would have been achieved in the same 24-hour period had the dose not been administered.

37. A pharmaceutical composition in the form of a gel, consisting of:

about 0.5 to about 10 weight percent testosterone;

ethyl alcohol;

cosolvent system consisting of diisopropyl adipate, methyl laurate, and oleyl alcohol;

polyol system consisting of glycerine, propylene glycol, polyethylene glycol;

gel-forming polymer;

purified water; and

optional pH-adjuster, wherein the weight percent is based on total weight of the pharmaceutical composition.

38. A pharmaceutical composition according to claim 37 wherein the testosterone is present in a range from about 0.5 to about 2 weight percent.

39. A pharmaceutical composition according to claim 37 or 38 wherein the ethyl alcohol is present in a range from about 75 to about 85 weight percent.

40. A pharmaceutical composition according to any of claims 37 through 39 wherein the cosolvent system is present in a range from about 1 to about 12 weight percent.

41. A pharmaceutical composition according to any of claims 37 through 40 wherein the polyol system is present in a range from about 7 to about 14 weight percent.

42. A pharmaceutical composition according to any of claims 37 through 41 wherein pH-modifier is present and is tromethamine.

43. A pharmaceutical composition according to any of claims 37 through 42, wherein the gel-forming polymer is a carbomer polymer.

44. A pharmaceutical composition according to any of claims 37 through 43, consisting of:

about 0.5 to about 2 weight percent testosterone;

about 75 to about 85 weight percent ethyl alcohol;

about 2 to about 10 weight percent cosolvent system, wherein the cosolvent system consists of diisopropyl adipate, methyl laurate, and oleyl;

about 7 to about 14 weight percent polyol system, wherein the polyol system consists of glycerine, propylene glycol, and polyethylene glycol;

about 0.5 to about 3 weight percent carbomer gel forming polymer; and

pH-modifier.

45. A pharmaceutical composition according to any of claims 37 through 43, consisting of:

1 weight percent testosterone;

75 to 85 weight percent ethyl alcohol;

cosolvent system consisting of 1 to 2 weight percent diisopropyl adipate,

0.2 to 0.4 weight percent methyl laurate, and

1 to 2 weight percent oleyl alcohol;

polyol system consisting of 3 to 7 weight percent glycerine,

3 to 7 weight percent propylene glycol, and

0.3 to 0.7 weight percent polyethylene glycol;

1 to 3 weight percent gel-forming polymer; and

pH-modifier.

46. A pharmaceutical composition according to any of claims 37 through 43, consisting of:

1 weight percent testosterone;

75 to 85 weight percent ethyl alcohol;

cosolvent system consisting of 1 to 2 weight percent diisopropyl adipate,

0.2 to 0.4 weight percent methyl laurate, and

1 to 2 weight percent oleyl alcohol;

polyol system consisting of 3 to 7 weight percent glycerine,

3 to 7 weight percent propylene glycol, and

0.3 to 0.7 weight percent polyethylene glycol;

1 to 3 weight percent weight percent gel-forming polymer;

purified water; and
pH-modifier.

47. A pharmaceutical composition according to any of claims 37 through 43, consisting of:
about 1 weight percent testosterone;
about 78 weight percent ethyl alcohol;
cosolvent system consisting of about 1.5 weight percent diisopropyl adipate,
about 0.25 weight percent methyl laurate, and
about 1.5 weight percent oleyl alcohol;
polyol system consisting of about 5 weight percent glycerine,
about 5 weight percent propylene glycol, and
about 0.5 weight percent polyethylene glycol;
1.8 weight percent weight percent carbomer gel-forming polymer;
about 4 weight percent purified water; and
about 0.1 weight percent tromethamine.

48. A pharmaceutical composition according to claim 37 consisting of:
1.0 weight percent (wt %) testosterone;
78.4 wt % ethyl alcohol;
cosolvent system consisting of 1.5 wt % diisopropyl adipate,
0.25 wt % methyl laurate, and
1.5 wt % oleyl alcohol;
polyol system consisting of 5.0 wt % glycerin,
5.0 wt % propylene glycol, and
0.50 wt % polyethylene glycol 1000;
1.5 wt% carbomer homopolymer;
0.30 wt % carbomer copolymer;
0.10 wt% tromethamine; and
5.0 wt % purified water.

49. A pharmaceutical composition according to claim 37, consisting of:

1.00 weight percent (wt %) testosterone;

78.35 wt % ethyl alcohol;

cosolvent system consisting of 1.50 wt % diisopropyl adipate,

0.25 wt % methyl laurate, and

1.50 wt % oleyl alcohol;

polyol system consisting of 5.00 wt % glycerin,

5.00 wt % propylene glycol, and

0.50 wt % polyethylene glycol 1000;

1.50 wt% carbomer homopolymer;

0.30 wt % carbomer copolymer;

0.10 wt% tromethamine; and

5.00 wt % purified water.

50. A pharmaceutical composition according to any of claims 37 through 49 wherein the polyethylene glycol comprises polyethylene glycol 1000.

51. A pharmaceutical composition according to any of claims 37 through 50, with the proviso that the composition excludes Hseih enhancer.

52. A pharmaceutical composition according to any of claims 37 through 50, with the proviso that the composition excludes oxacyclohexadecane-2-one.

53. A pharmaceutical composition according to any of claims 37 through 52, with the proviso that the composition excludes isopropyl myristate.

54. A pharmaceutical composition according to any of claims 37 through 53 wherein the pharmaceutical composition can be applied to skin of a patient in the form of a unit dose that contains about 25 mg to about 200 mg of testosterone, and maintained on the skin for a period of time sufficient for delivery of the testosterone to the patient's systemic circulation such that, following a single application of the unit dose to the skin, the amount of circulating testosterone (AUC_{0-24}) in blood

serum of the patient achieved in a 24-hour period following the application is about 46,000 to about 95,000 pg•h/mL (picogram-hour/milliliter) greater than the amount of circulating testosterone (AUC_{0-24}) in the blood serum of the patient that would have been achieved in the same 24-hour period had the dose not been administered.

55. A package containing from 3 to 6 grams pharmaceutical composition according to any of claims 1 through 54.

56. A package containing from 3 to 6 grams pharmaceutical composition comprising:

about 0.5 to about 10 weight percent testosterone;

solvent comprising ethyl alcohol;

cosolvent system comprising cosolvent selected from diisopropyl adipate, methyl laurate, oleyl alcohol, and combinations thereof;

polyol system comprising polyol selected from glycerine, propylene glycol, polyethylene glycol, and combinations thereof; and

gel-forming polymer, wherein the weight percent is based on total weight of the pharmaceutical composition.

57. A package containing from 3 to 6 grams pharmaceutical composition according to any of claims 1 through 54, wherein the package is adapted for dispensing a single dose of the pharmaceutical composition.

58. A package containing from 3 to 6 grams pharmaceutical composition according to any of claims 1 through 54, wherein the package is adapted for dispensing a metered volume of the pharmaceutical composition.

59. A package according to claim 58, wherein the metered volume comprises multiple doses.

60. A package according to claim 58 or 59, wherein the package is a pump.

61. A pharmaceutical composition consisting essentially of:

about 0.5 to about 2 weight percent testosterone;

about 75 to about 85 weight percent ethyl alcohol;

about 2 to about 10 weight percent cosolvent system, wherein the cosolvent system consists of diisopropyl adipate, methyl laurate, oleyl alcohol, and combinations thereof;

about 7 to about 14 weight percent polyol system, wherein the polyol system comprises a polyol selected from glycerine, propylene glycol, polyethylene glycol, and combinations thereof;

about 0.5 to about 3 weight percent carbomer gel forming polymer; and

pH-modifier, wherein the weight percent is based upon the total weight of the pharmaceutical composition.

62. The pharmaceutical composition of claim 61 wherein the diisopropyl adipate, methyl laurate, and oleyl alcohol are present in the cosolvent system in a ratio from (0.8-1.2) to (0.1-0.7) to 1.

63. The pharmaceutical composition of claim 62, wherein the diisopropyl adipate, methyl laurate, and oleyl alcohol are present in the cosolvent system in a ratio from 6:1:6.

64. A pharmaceutical composition consisting essentially of:

about 0.5 to about 2 weight percent testosterone;

about 75 to about 85 weight percent ethyl alcohol;

about 1 to about 2 weight percent diisopropyl adipate;

about 0.2 to about 0.4 weight percent methyl laurate;

about 1 to about 2 weight percent oleyl alcohol;

about 3 to about 7 weight percent glycerine;

about 3 to about 7 weight percent propylene glycol;

about 0.3 to about 0.7 weight percent polyethylene glycol;

about 1 to about 3 weight percent weight percent gel-forming polymer; and

pH-modifier, wherein the weight percent is based upon the total weight of the pharmaceutical composition.

65. A pharmaceutical composition consisting essentially of:

about 0.5 to about 2 weight percent testosterone;

about 75 to about 85 weight percent ethyl alcohol;

about 1 to about 2 weight percent diisopropyl adipate;

about 0.2 to about 0.4 weight percent methyl laurate;

about 1 to about 2 weight percent oleyl alcohol;

about 3 to about 7 weight percent glycerine;

about 3 to about 7 weight percent propylene glycol;

about 0.3 to about 0.7 weight percent polyethylene glycol;

about 1 to about 3 weight percent weight percent gel-forming polymer;

purified water; and

pH-modifier, wherein the weight percent is based upon the total weight of the pharmaceutical composition.

66. A pharmaceutical composition consisting essentially of:

about 0.5 to about 2 weight percent testosterone;

about 75 to about 85 weight percent ethyl alcohol;

about 1 to about 2 weight percent diisopropyl adipate;

about 0.2 to about 0.4 weight percent methyl laurate;

about 1 to about 2 weight percent oleyl alcohol;

about 3 to about 7 weight percent glycerine;

about 3 to about 7 weight percent propylene glycol;

about 0.3 to about 0.7 weight percent polyethylene glycol;

about 1 to about 3 weight percent gel-forming polymer;

and

about 0.1 weight percent tromethamine , wherein the weight percent is based upon the total weight of the pharmaceutical composition.

67. A pharmaceutical composition according to any of claims 61 through 66 wherein the pharmaceutical composition can be applied to skin of a patient in the form of a unit dose that contains about 25 mg to about 200 mg of testosterone, and maintained on the skin for a period of time sufficient for delivery of the testosterone to the patient's systemic circulation such that, following a single application of the unit dose to the skin, the amount of circulating testosterone (AUC_{0-24}) in blood serum of the patient achieved in a 24-hour period following the application is about 46,000 to about 95,000 pg•h/mL (picogram-hour/milliliter) greater than the amount of circulating testosterone (AUC_{0-24}) in the blood serum of the patient that would have been achieved in the same 24-hour period had the dose not been administered.

68. A package containing a pharmaceutical composition consisting essentially of:

about 0.5 to about 2 weight percent testosterone;

about 75 to about 85 weight percent ethyl alcohol;

about 2 to about 10 weight percent cosolvent system, wherein the cosolvent system consists of diisopropyl adipate, methyl laurate, oleyl alcohol, and combinations thereof;

about 7 to about 14 weight percent polyol system, wherein the polyol system comprises a polyol selected from glycerine, propylene glycol, polyethylene glycol, and combinations thereof;

about 0.5 to about 3 weight percent carbomer gel forming polymer; and

pH-modifier, wherein the weight percent is based upon the total weight of the pharmaceutical composition.

69. A package according to claim 68, wherein the package is adapted for dispensing a single dose of the pharmaceutical composition.

70. A package according to claim 68, wherein the package is adapted for dispensing a metered volume of the pharmaceutical composition.

71. A package according to claim 69 or 70, wherein the package is a pump.

5