ORAL TESTOSTERONE ESTER FORMULATIONS AND METHODS OF TREATING TESTOSTERONE DEFICIENCY COMPRISING SAME

FIELD OF THE INVENTION

[0001] The present invention relates generally to oral formulations of testosterone esters for the treatment of testosterone deficiency. More particularly, the present invention relates to pharmaceutical composition comprising testosterone undecanoate (TU) with enhanced and extended absorption and pharmacokinetics.

BACKGROUND OF THE INVENTION

[0002] Testosterone (T) is a primary androgenic hormone produced in the interstitial cells of the testes and is responsible for normal growth, development and maintenance of male sex organs and secondary sex characteristics (*e.g.*, deepening voice, muscular development, facial hair, etc.). Throughout adult life, testosterone is necessary for proper functioning of the testes and its accessory structures, prostate and seminal vesicle; for sense of well-being; and for maintenance of libido, erectile potency.

[0003] Testosterone deficiency—insufficient secretion of T characterized by low serum T concentrations—can give rise to medical conditions (*e.g.*, hypogonadism) in males. Symptoms associated with male hypogonadism include impotence and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, decreased muscle mass, and increased fat mass. Furthermore, hypogonadism in men is a risk factor for osteoporosis, metabolic syndrome, type II diabetes and cardiovascular disease.

[0004] Various testosterone replacement therapies are commercially available for the treatment of male hypogonadism. Pharmaceutical preparations include both testosterone and testosterone derivatives in the form of intramuscular injections, implants, oral tablets of alkylated T (*e.g.*, methyltestosterone), topical gels, or topical patches. All of the current T therapies, however, fail to adequately provide an easy and clinically effective method of delivering T. For example, intramuscular injections are painful and are associated with significant fluctuations in serum T levels between

doses; T patches are generally associated with levels of T in the lower range of normal (*i.e.*, clinically ineffective) and often cause substantial skin irritation; and T gels have been associated with unsafe transfer of T from the user to women and children. As well, the sole "approved" oral T therapy, methyltestosterone, is associated with a significant occurrence of liver toxicity. Over time, therefore, the current methods of treating testosterone deficiency suffer from poor compliance and thus unsatisfactory treatment of men with low T.

[0005] Testosterone and its esters are poorly bioavailable—owing to extensive first pass intestinal and hepatic metabolism—or ineffective—due to an inability of the body to liberate testosterone from its testosterone prodrug. For example, testosterone and testosterone esters with side chains of less than 10 carbons in length are primarily absorbed via the portal circulation resulting in substantial, if not total, first pass metabolism. Fatty acid esters of long carbon chains (*i.e.*, 14 or more carbons) may be absorbed by intestinal lymphatics, but the longer the fatty acid chain length, the slower the rate and extent of hydrolysis of the ester by esterases to liberate testosterone thus resulting in poor (*i.e.*, clinically ineffective) pharmacological activity.

[0006] Other than selection of a testosterone ester, the formulation of the testosterone ester presents unique challenges. The gastrointestinal environment is decidedly aqueous in nature, which requires that drugs must be solubilzed for absorption. However, testosterone and particularly its esters are extremely insoluble in water and aqueous media, and even if the T or T ester is solubilized initially in the formulation, the formulation must be able to maintain the drug in a soluble or dispersed form without precipitation or, otherwise, coming out of solution *in vivo* (although such a property can be tested *in vitro*, for example, by mixing the contents of a formulation in simulated intestinal fluid). Furthermore, an oral T formulation must, effectively release T or T ester according to a desired release profile. Hence, an effective formulation of T or T ester must balance good solubility with optimum release and satisfaction of a targeted plasma or serum concentration profile.

[0007] For these reasons, among others, no oral formulation of testosterone or testosterone esters has been approved by the United States Food and Drug Administration (FDA) to date. In fact, the only oral testosterone product ever approved to date by the FDA is methyltestosterone (in which a methyl group covalently bound to a testosterone "nucleus" at the C-17 position to inhibit hepatic metabolism; note, also, that methyltestosterone is not a prodrug of testosterone) and this approval occurred several decades ago. Unfortunately, use of methyltestosterone has been associated with a significant incidence of liver toxicity, and it is rarely prescribed to treat men with low testosterone.

[0008] As noted above, fatty acid esters of testosterone provide yet another mode of potential delivery of testosterone to the body (*i.e.*, as a "prodrug"). Once absorbed, testosterone can be liberated from its ester via the action of non-specific tissue and plasma esterases. Furthermore, by increasing the relative hydrophobicity of the testosterone moiety and the lipophilicity of the resulting molecule as determined by its n-octanol-water partition coefficient (log P) value, such prodrugs can be absorbed, at least partially, via the intestinal lymphatics, thus reducing first-pass metabolism by the liver. In general, lipophilic compounds having a log P value of at least 5 and oil solubility of at least 50 mg/mL are transported primarily via the lymphatic system.

[0009] Despite their promise, prodrugs of testosterone, including testosterone esters, have not been formulated in a manner to achieve effective and sustained serum testosterone levels at eugonadal levels (*i.e.*, average serum T concentration falling in the range of about 300-1100 ng/dL). In fact, an orally administered pharmaceutical preparation of a testosterone prodrug, including testosterone esters, has yet to be approved by the FDA.

[0010] Hence, there remains a need for an oral formulation of a testosterone ester, which provides optimum serum testosterone levels that are clinically effective to treat hypogonadal men (*i.e.*, those with a serum T concentration of $\leq$ 300 ng/dL) over an extended period of time.

SUMMARY OF THE INVENTION

[0011] In one embodiment of the present invention, an oral pharmaceutical composition is provided comprising testosterone undecanote solubilized in a carrier comprising at least one lipophilic surfactant and at least one hydrophilic surfactant in a total lipohilic surfactant to total hydrophilic surfactant ratio (w/w) falling in the range of about 6:1 to 3.5:1, which composition, upon once- or twice-daily oral administration, provides an average serum testosterone concentration at steady state falling in the range of about 300 to about 1100 ng/dL. The pharmaceutical composition provides a C_{max} that, when administered with a meal, does not exceed 2500 ng/dL, preferably does not exceed 1800 ng/dL, and most preferably does not exceed 1500 ng/dL.

[0012] According to a preferred embodiment, the at least one hydrophilic surfactant comprises Cremophor RH 40 (polyoxyethyleneglycerol trihydroxystearate); the at least one lipophilic surfactant comprises oleic acid. The pharmaceutical compositions of the invention may comprise 18 to 22 percent by weight of the solubilized testosterone undecanoate, and may further be substantially free of a monohydric alcohols such as ethanol.

[0013] In another embodiment of the invention, a dosage form of testosterone undecanoate is provided comprising testosterone undecanote solubilized in a carrier comprising at least one lipophilic surfactant and at least one hydrophilic surfactant, which dosage form, upon once- or twice-daily oral administration to a subject suffering from hypogonadism or its symptons, provides an average serum testosterone concentration at steady state falling in the range of about 300 to about 1100 ng/dL, while avoiding an occurrence of a C_{max} value that exceeds 2500 ng/dL, more preferably avoiding an occurrence of a C_{max} value that exceeds 1800 ng/dL, and most preferably avoiding an occurrence of a C_{max} value that exceeds 1500 ng/dL.

[0014] In yet another embodiment of the present invention, a pharmaceutical composition is provided comprising testosterone undecanoate solubilized in a carrier comprising at least one lipophilic surfactant and at least one hydrophilic surfactant, which composition, upon oral administration with a meal having a fat content ranging from as low as 20 wt% to as high as 50 wt%, provides an average serum testosterone

concentration that is statistically insignificant to that observed upon oral administration with a meal having a fat content of about 30 wt%.

[0015] In still yet another embodiment of the invention, a pharmaceutical composition is provided comprising testosterone undecanote solubilized in a carrier comprising at least one lipophilic surfactant and at least one hydrophilic surfactant in a total lipohilic surfactant to total hydrophilic surfactant ratio (w/w) falling in the range of about 6:1 to 3.5:1, which composition, upon once- or twice-daily oral administration, provides a serum testosterone rapid phase half-life of about 5 hours and a serum testosterone terminal high-life of about 29 hours.

[0016] In still yet another embodiment of the invention, a pharmaceutical composition is provided comprising testosterone undecanote solubilized in a carrier comprising at least one lipophilic surfactant and at least one hydrophilic surfactant in a total lipophilic surfactant to total hydrophilic surfactant ratio (w/w) falling in the range of about 6:1 to 3.5:1, which composition, upon once- or twice-daily oral administration to a subject suffering from testosterone deficiency or its symptoms, provides a mean serum testosterone concentration at day 30 of a daily treatment regimen, which is substantially the same as that observed on day 7. According to the invention, the mean serum testosterone concentration obtained at day 30 of a daily treatment regimen may also be substantially the same as that observed on day 60.

[0017] In another embodiment of the invention, a method of treating testosterone deficiency or its symptoms is provided comprising orally administering to a subject suffering from testosterone deficiency or its symptoms an effective amount of a pharmaceutical composition comprising testosterone undecanote solubilized in a carrier comprising at least one lipophilic surfactant and at least one hydrophilic surfactant in a total lipophilic surfactant to total hydrophilic surfactant ratio (w/w) falling in the range of about 6:1 to 3.5:1 to provide an average serum testosterone concentration at steady state falling in the range of about 300 to about 1100 ng/dL. The composition may be administered once daily or twice daily, and can give rise to a C_{max} value falling in the range of about 900 to 1100 ng/dL.

[0018] According to the method, the composition may be administered with a meal comprising at least 20 wt% fat. The method can give rise to substantially no diurnal

testosterone pharmacokinetic variation, an average serum T_{max} value falling in the range of about 3 to 7 hours after oral administration, and substantially no significant decline in steady state serum testosterone response is observed upon repeat dosing.

[0019] In a preferred embodiment of the present invention, a pharmaceutical composition is provided comprising:

(a) 15-25 percent by weight of a solubilized testosterone undecanoate;

(b) 12-18 percent by weight of at least one hydrophilic surfactant;

(c) 50-65 percent by weight of at least one lipophilic surfactant;

(d) 10-15 percent by weight of a mixture of borage oil and peppermint oil,

which composition may be free of monohydric alcohols generally, specifically, ethanol and, upon oral administration to a subject in need thereof, gives rise to a serum testosterone half-life ($T_{½}$) falling in the range of about 10 hours to about 18 hours. Cremophor RH40 is a preferred hydrophilic surfactant and a preferred lipophilic surfactant is oleic acid. Borage oil and peppermint oil are both considered lipophilic surfactants.

[0020] In a particularly preferred embodiment, the composition comprises:

(a) 18-22 percent by weight of a solubilized testosterone undecanoate;

(b) 15-17 percent by weight of at least one hydrophilic surfactant;

(c) 50-55 percent by weight of at least one lipophilic surfactant; and;

(d) 10-15 percent by weight of a mixture of borage oil and peppermint oil.

The ratio of borage oil to peppermint oil may range from 8:1 to 3:1; preferably from 6:1 to 5:1; most preferably from 5:1 to 4:1. In addition, to Cremophor RH40, Solutol HS-15, Tween 80 and TPGS are preferred hydrophilic surfactants; and, in addition to oleic acid, Glycerol monoleate, propylene glycol laurate and Capmul MCM are preferred lipophilic surfactants. Combinations of two or more lipophilic surfactants and two or more hydrophilic surfactants are also contemplated.

[0021] In another embodiment of the present invention, a method of treating testosterone deficiency is provided, the method comprising orally administering to a hypogonadal subject an effective amount of a pharmaceutical composition comprising:

(a) 15-25 percent by weight of a solubilized testosterone undecanoate;

(b) 12-18 percent by weight of one or more hydrophilic surfactants;

(c) 50-65 percent by weight of one or more lipophilic surfactants;

(d) 10-15 percent by weight of a mixture of borage oil and peppermint oil, and free of ethanol, whose once- or twice-daily oral administration gives rise to an average (or a mean) steady state serum testosterone concentration, C_{ave}, falling in the range of about 300 and about 1100 ng/dL in the subject. The composition may optionally be administered with a meal whose fat content ranges from about 15 wt% to about 25 wt% or more. According to the method, any one or all of the following pharmacokinetic parameters may be achieved in the subject:

(a) serum testosterone C_{max} within 900 and 1100 ng/dL in the subject;

(b) substantially no diurnal testosterone pharmacokinetic variation;

(c) serum T_{max} 3 to 7 hours after administering the composition; and

(d) substantially no decline in steady state serum testosterone response is observed upon repeat dosing.

[0022] In this respect, before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and to the arrangements of the components set forth in the following description or illustrated in the drawings. The invention is capable of embodiments in addition to those described and of being practiced and carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein, as well as the abstract, are for the purpose of description and should not be regarded as limiting.

[0023] As such, those skilled in the art will appreciate that the conception upon which this disclosure is based may readily be utilized as a basis for the designing of other moieties, methods and systems for carrying out the several purposes of the present invention. For example, some embodiments of the invention may combine TU with other active drugs, including other hormones, in an oral delivery system that, in part, prevents or alleviates symptoms associated with testosterone deficiency. It is important, therefore, that the claims be regarded as including such equivalent constructions, which do not depart from the scope and spirit of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] Figure 1 provides serum T levels over a 24 hour period of once or twice daily oral dosing of a TU formulation of the invention.

[0025] Figure 2 shows a serum T response over time in hypogonadal men upon administration of a formulation of the invention vs. a conventional oral TU formulation comprising TU in oleic acid (Restandol).

[0026] Figure 3 provides T_{max} values of serum T levels in subjects having consumed meals of varying fat content (as a percentage by weight) prior to oral administration of a TU formulation of the invention.

[0027] Figure 4 provides C_{max} values of serum T levels in subjects having consumed meals of varying fat content (as a percentage by weight) prior to oral administration of a TU formulation of the invention.

[0028] Figure 5 provides area under the curve (AUC) values of serum T levels in subjects having consumed meals of varying fat content (as a percentage by weight) prior to oral administration of a TU formulation of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0029] The present invention provides an oral pharmaceutical composition comprising TU, which when administered no more than twice a day to hypogonadal males, provides average steady state serum levels (concentrations) of testosterone in such males, which fall within a desired "normal" or eugonadal range (*i.e.*, about 300-1100 ng/dL) while avoiding the high C_{max} values that are considered by the United States Food and Drug Administration to be undesirable, if not unacceptable. For instance FDA approval guidelines state that less than 85% of treated subjects may have a C_{max} value of 1500 ng/dL or greater, and that none may have a C_{max} value exceeding 2500 ng/dL. Less than 5% of treated subjects may have a C_{max} value falling in the range of 1800 – 2500 ng/dL. Moreover, the formulations of the invention are designed to be self-emulsifying drug delivery systems (SEDDS) so that

a TU-containing emulsion (or dispersion) is formed upon mixing with intestinal fluids in the gastrointestinal tract.

[0030] In one embodiment of the present invention, testosterone and/or esters at the C-17 position of the testosterone molecule, alone or in combination with other active ingredients, may be orally delivered using the inventive formulation. For example, the combination of testosterone undecanoate with an orally active inhibitor of Type I or Type II 5α-reductase or the combination of testosterone undecanoate with a synthetic progestin may be preferable in some embodiments.

[0031] While many of the embodiments of the present invention will be described and exemplified with the undecanoate acid ester of testosterone (*i.e.*, TU), other esters of hydrophobic compounds, including T, can be adopted for oral delivery based on the teachings of the specification. In fact, it should be readily apparent to one of ordinary skill in the art from the teachings herein that the inventive drug delivery systems and compositions therefrom may be suitable for oral delivery of other testosterone esters, such as short-chain (C_2-C_6), medium-chain (C_7-C_{13}) and long-chain (C_{14}-C_{24}) fatty acid esters, preferably medium-chain fatty acid esters of testosterone.

[0032] The formulations of the present invention comprise a T-ester dissolved in a mixture comprising one or more lipophilic surfactants and one or more hydrophilic surfactants. A lipophilic surfactant as defined herein has a hydrophilic-lipophilic balance (HLB) value of less than 10, and preferably less than 5. A hydrophilic surfactant as defined herein has an HLB value of greater than 10. (HLB is an empirical expression for the relationship of the hydrophilic and hydrophobic groups of a surface active amphiphilic molecule, such as a surfactant. It is used to index surfactants and its value varies from about 1 to about 45 and includes both non-ionic and ionic surfactants. The higher the HLB, the more water soluble/dispersible the surfactant.)

[0033] According to one aspect of the present invention, each of the components of the delivery system (*i.e.*, the lipophilic and hydrophilic surfactants) individually have

solubilizing characteristics and contribute, in part, to solubilizing the active ingredient. Those lipophilic surfactants that contribute substantially to dissolving the drug are defined herein as "primary" solvent(s). It should be appreciated, however, that solubility can be affected by the temperature of the solvent/formulation. Formulations of the present invention comprising, for example, about 20% testosterone undecanoate, remain soluble at or above 30 °C, including in the range of 30 to about 40 °C.

[0034] A hydrophilic surfactant component may be necessary to achieve desirable dispersability of the formulation in the GI tract and release of the drug. That is, a hydrophilic surfactant, in addition to serving as a secondary solvent, may be required to release the drug from within the lipid carrier matrix, or primary solvent. In this respect, a high HLB surfactant, such as Cremophor RH40, can generally suffice. The levels (amounts) of the high HLB surfactant can be adjusted to provide optimum drug release without compromising the solubilization of the active ingredient.

[0035] Lipophilic surfactants suitable in drug delivery systems of the present invention include:

[0036] Fatty acids (C_6-C_{24}, preferably C_{10}-C_{24}, more preferably C_{14}-C_{24}), for example, octanoic acid, decanoic acid, undecanoic acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, and linolenic acid. Oleic acid is preferred.

[0037] Mono- and/or di-glycerides of fatty acids, such as Imwitor 988 (glyceryl mono-/di-caprylate), Imwitor 742 (glyceryl mono-/di-caprylate/caprate), Imwitor 308 (glyceryl mono-caprylate), Imwitor 191 (glyceryl mono-stearate), Softigen 701 (glyceryl mono-/di-ricinoleate), Capmul MCM (glyceryl mono-/di-caprylate/caprate), Capmul MCM(L) (liquid form of Capmul MCM), Capmul GMO (glyceryl mono-oleate), Capmul GDL (glyceryl dilaurate), Maisine (glyceryl mono-linoleate), Peceol (glyceryl mono-oleate), Myverol 18-92 (distilled monoglycerides from sunflower oil) and Myverol 18-06 (distilled monoglycerides from hydrogenated soybean oil), Precirol ATO 5 (glyceryl palmitostearate) and Gelucire 39/01 (semi-synthetic

glycerides, *i.e.*, C_{12-18} mono-, di- and tri-glycerides). The preferred members of this class of lipophilic surfactants are the partial glycerides of oleic, palmitic and stearic acids and blends thereof.

[0038] Acetic, succinic, lactic, citric and/or tartaric esters of mono- and/or di-glycerides of fatty acids, for example, Myvacet 9-45 (distilled acetylated monoglycerides), Miglyol 829 (caprylic/capric diglyceryl succinate), Myverol SMG (mono/di-succinylated monoglycerides), Imwitor 370 (glyceryl stearate citrate), Imwitor 375 (glyceryl monostearate/citrate/lactate) and Crodatem T22 (diacetyl tartaric esters of monoglycerides).

[0039] Propylene glycol mono- and/or di-esters of fatty acids, for example, Lauroglycol (propylene glycol monolaurate), Mirpyl (propylene glycol monomyristate), Captex 200 (propylene glycol dicaprylate/dicaprate), Miglyol 840 (propylene glycol dicaprylate/dicaprate) and Neobee M-20 (propylene glycol dicaprylate/dicaprate).

[0040] Polyglycerol esters of fatty acids such as Plurol oleique (polyglyceryl oleate), Caprol ET (polyglyceryl mixed fatty acids) and Drewpol 10.10.10 (polyglyceryl oleate).

[0041] Castor oil ethoxylates of low ethoxylate content (HLB<10) such as Etocas 5 (5 moles of ethylene oxide reacted with 1 mole of castor oil) and Sandoxylate 5 (5 moles of ethylene oxide reacted with 1 mole of castor oil).

[0042] Acid and ester ethoxylates formed by reacting ethylene oxide with fatty acids or glycerol esters of fatty acids (HLB<10) such as Crodet 04 (polyoxyethylene (4) lauric acid), Cithrol 2MS (polyoxyethylene (2) stearic acid), Marlosol 183 (polyoxyethylene (3) stearic acid) and Marlowet G12DO (glyceryl 12 EO dioleate).

Sorbitan esters of fatty acids, for example, Span 20 (sorbitan monolaurate), Crill 1 (sorbitan monolaurate) and Crill 4 (sorbitan mono-oleate).

[0043] Transesterification products of natural or hydrogenated vegetable oil triglyceride and a polyalkylene polyol (HLB<10), *e.g.* Labrafil M1944CS (polyoxyethylated apricot kernel oil), Labrafil M2125CS (polyoxyethylated corn oil) and Gelucire 37/06 (polyoxyethylated hydrogenated coconut). Labrafil M1944CS is preferred.

[0044] Alcohol ethyoxylates (HLB<10), *e.g.* Volpo N3 (polyoxyethylated (3) oleyl ether), Brij 93 (polyoxyethylated (2) oleyl ether), Marlowet LA4 (polyoxyethylated (4) lauryl ether).

[0045] Pluronics, for example, Polyoxyethylene-polyoxypropylene co-polymers and block co-polymers (HLB<10) *e.g.* Synperonic PE L42 (HLB = 8) and Synperonic PE L61 (HLB = 3).

[0046] Mixtures of suitable lipophilic surfactants, such as those listed above, may be used if desired, and in some instances are found to be advantageous.

[0047] Any pharmaceutically acceptable hydrophilic surfactant (*i.e.*, having an HLB value greater than 10) may be used in the present invention. Some non-limiting examples include:

[0048] Castor oil or hydrogenated castor oil ethoxylates (HLB>10), *e.g.* Cremophor EL (polyoxyethylene (35) castor oil), Cremophor RH40 (polyoxyethylene (40) hydrogenated castor oil), Etocas 40 (polyoxyethylene (40) castor oil), Nikkol HCO-60 (polyoxyethylene (60) hydrogenated castor oil), Solutol HS-15 (polyethylene glycol 660 hydroxystearate), Labrasol (caprylocaproyl macrogol-8 glycerides), α-tocopherol-polyethylene glycol-1000-succinate (TPGS) and ascorbyl-6 palmitate. Cremophor RH40 is preferred.

[0049] Polyoxyethylene sorbitan fatty acid derivates, *e.g.* Tween 20 (polyoxyethylene (20) monolaureate), Tween 80 (polyoxyethylene (20) monooleate), Crillet 4 (polyoxyethylene (20) monooleate) and Montanox 40 (polyoxyethylene (20) monopalmitate). Tween 80 (Polysorbate 80) is preferred.

[0050] Gelucires, preferably Gelucire 50/13 (PEG mono- and diesters of palmitic and stearic acids. (In reference to Gelucires, the first number (*i.e.*, 50) corresponds to the melting point of the material and the second (*i.e.*, 13) to the HLB number.)

[0051] Fatty acid ethoxylates (HLB>10), *e.g.* Myrj 45 (polyoxyethylene (8) stearate), Tagat L (polyoxyethylene (30) monolaurate), Marlosol 1820 (polyoxyethylene (20) stearate) and Marlosol OL15 (polyoxyethylene (15) oleate). Myrj 45 is preferred.

[0052] Alcohol ethoxylates (HLB>10), *e.g.* Brij 96 (polyoxyethylene (10) oleyl ether), Volpo 015 (polyoxyethylene (15) oleyl ether), Marlowet OA30 (polyoxyethylene (30) oleyl ether) and Marlowet LMA20 (polyoxyethylene (20) C_{12}–C_{14} fatty ether).

[0053] Polyoxyethylene-polyoxypropylene co-polymers and block co-polymers (HLB>10), that are commercially available under the trade name Pluronics or Poloxamers , such as Poloxamers 188 and 407 also known as Syperonic PE L44 (HLB = 16) and Syperonic F127 (HLB = 22), respectively.

[0054] Anionic surfactants, *e.g.* sodium lauryl sulphate, sodium oleate and sodium dioctylsulphosuccinate.

[0055] Alkylphenol surfactants (HLB>10), *e.g.* Triton N-101 (polyoxyethylene (9-10) nonylphenol) and Synperonic NP9 (polyoxyethylene (9) nonylphenol).

[0056] As mentioned, in one aspect of the present invention, each of the components of the delivery system (*i.e.*, the lipophilic and hydrophilic surfactants) individually has solvent characteristics and contributes, in part, to solubilizing the active ingredient. In this way, without being bound by or limited to theory, the present invention does not require additional solvents, such as cosolvents, but these may be optionally included in the inventive systems and formulations.

[0057] Optional cosolvents suitable with the instant invention are, for example, water, short chain mono-, di-, and polyhydric alcohols, such as ethanol, benzyl

alcohol, glycerol, propylene glycol, propylene carbonate, polyethylene glycol with an average molecular weight of about 200 to about 10,000, diethylene glycol monoethyl ether (*e.g.*, Transcutol HP), and combinations thereof. Preferably, such cosolvents, especially ethanol or other monoethanols, are excluded altogether.

[0058] Additional oils that may be incorporated in embodiments of the present invention include complete glycerol triesters of medium chain (C_7–C_{13}) or long chain (C_{14}–C_{22}) fatty acids with low molecular weight (up to C_6) mono-, di- or polyhydric alcohols. Some examples of oils for use in this invention thus include: vegetable oils (*e.g.*, soybean oil, safflower seed oil, corn oil, olive oil, castor oil, cottonseed oil, arachis oil, sunflower seed oil, coconut oil, palm oil, rapeseed oil, evening primrose oil, grape seed oil, wheat germ oil, sesame oil, avocado oil, almond, borage, peppermint and apricot kernel oils) and animal oils (*e.g.*, fish liver oil, shark oil and mink oil).

[0059] In other embodiments of the present invention, methods and compositions for modulating (*i.e.*, sustaining) the rate of available serum testosterone by incorporating component(s) that may biochemically modulate (1) TU absorption, (2) TU metabolism to T, and/or (3) metabolism of T to dihydrotestosterone (DHT). For example, the inclusion of medium to long chain fatty acid esters can enhance TU absorption. In this way, more TU may stave off hydrolysis in the gut and enter the blood stream. In other words, the fatty acid ester may competitively inhibit esterases that would otherwise metabolize TU. Examples of other esters or combinations thereof include botanical extracts or benign esters used as food additives (*e.g.*, propylparben, octylacetate and ethylacetate).

[0060] Other components that can modulate TU absorption include "natural" and synthetic inhibitors of 5α-reductase, which is an enzyme present in enterocytes and other tissues that catalyzes the conversion of T to DHT. Complete or partial inhibition of this conversion may both increase and sustain increases serum levels of T after oral dosing with TU while concomitantly reducing serum DHT levels. Borage oil, which contains a significant amount of the 5α-reductase inhibitor, gamma-linolenic acid (GLA), is an example of a "natural" modulator of TU metabolism.

Other than within borage oil, of course, GLA could be added directly as a separate component of a TU formulation of the invention. Many natural inhibitors of 5α-reductase are known in the art (*e.g.*, epigallocatechin gallate, a catechin derived primarily from green tea and saw palmetto extract from berries of the *Serenoa repens* species), all of which may be suitable in the present invention. Non-limiting examples of synthetic 5α-reductase inhibitors suitable for use in the present invention include compounds such as finasteride, dutasteride and the like.

[0061] In addition to 5α-reductase inhibitors, the present invention contemplates the use of inhibitors of T metabolism via other mechanisms. One such point of inhibition may be the cytochrome P450 isozyme CYP3A4, which is present in enterocytes and in liver cells and thus capable of metabolizing testosterone. Accordingly, selected embodiments of the invention, include peppermint oil, which is known to contain components capable of inhibiting CYP3A4 activity.

[0062] Yet other optional ingredients which may be included in the compositions of the present invention are those which are conventionally used in oil-based drug delivery systems, *e.g.,* antioxidants such as tocopherol, tocopherol acetate, ascorbic acid, butylhydroxytoluene (BHT), ascorbyl palmitate, butylhydroxyanisole and propyl gallate; pH stabilizers such as citric acid, tartaric acid, fumaric acid, acetic acid, glycine, arginine, lysine and potassium hydrogen phosphate; thickeners/suspending agents such as hydrogenated vegetable oils, beeswax, colloidal silicon dioxide, mannitol, gums, celluloses, silicates, bentonite; flavoring agents such as cherry, lemon and aniseed flavors; sweeteners such as aspartame, acesulfane K, sucralose, saccharin and cyclamates; etc.

[0063] The present inventors have learned that relative proportions of the one or more lipophilic surfactants and one or more hydrophilic surfactants can be critical to achieving the desired pharmacokinetics of the present invention. More specifically, the inventors have discovered a ratio of total lipophilic surfactant and total hydrophilic surfactant, which is not only able to solubilize a relatively large amount of T-ester (*e.g.*, greater than 15%, 18%, 20%, 22%, or 25%) but one that is also able to provide optimum release of the T-ester from within the formulation. Preferably, the

total oil (*e.g.*, oleic acid + borage oil + peppermint oil, all of which are considered lipophilic surfactants) to hydrophilic surfactant ratio (w/w) falls in the range of about 6:1 to 1:1, 6:1 to 3.1, 6:1 to 3.5:1, or 6:1 to 4:1; and more preferably, from about 5:1 to 3:1, and most preferably, from about 4:1 to 3:1.

[0064] The following relative concentrations, by weight, are preferred (the percentages are based on the total weight of the formulation):

Hydrophilic surfactant: 10-20%, more preferably 12-18%, and most preferably 15-17%.

Lipophilic surfactant: 50-70%, more preferably 50-65%, and most preferably 50-55%

Other oils: 5-15%, more preferably 7-15%, and most preferably 10-13%

Drug: 10-30%, more preferably 15-25%, and most preferably 18-22%.

[0065] The formulations of the present invention have self-emulsifying properties, forming a fine emulsion upon dilution with aqueous media or intestinal fluids *in vivo*. In other words, the formulations may have high surfactant and lipid content designed for optimum dispersion upon mixing with an aqueous medium. Qualitative description of the self-emulsification property of the inventive formulations can be visually observed during the dissolution of same *in vitro*. On the other hand, quantitative measurements may be taken of the particle size of the emulsified droplets using laser light scattering and/or turbidity measurements in the dissolution medium by UV/VIS spectrophotometer. Any of these methodologies are available and known to one of ordinary skill in the art.

[0066] The pharmaceutical compositions according to the present invention are preferably liquid or semi-solid at ambient temperatures. Furthermore, these pharmaceutical compositions can be transformed into solid dosage forms through adsorption onto solid carrier particles, such as silicon dioxide, calcium silicate or magnesium aluminometasilicate to obtain free- flowing powders which can be either filled into hard capsules or compressed into tablets. *See, e.g.*, US 2003/0072798, the disclosure of which is incorporated in its entirety by reference. Hence, the term "solubilized" herein, should be interpreted to describe an active pharmaceutical

ingredient (API), which is dissolved in a liquid solution or which is uniformly dispersed in a solid carrier. Also sachet type dosage forms can be formed and used.

[0067] The instant invention preferably comprises an API that is solubilized in the presence of lipid surfactant excipients (*e.g.*, any combination of the lipophilic and hydrophilic surfactants noted above). Accordingly, the melting point of the surfactants used is one factor that can determine whether the resulting composition will be liquid or semi-solid at ambient temperature. Particularly preferred compositions of the present invention are liquid oral unit dosage forms, more preferably filled into hard or soft capsules, *e.g.* gelatin or non-gelatin capsules such as those made of cellulose, carrageenan, or pollulan. The technology for encapsulating lipid-based pharmaceutical preparations is well known to one of ordinary skill in the art. As the inventive delivery systems and formulations described herein are not limited to any one encapsulation method, specific encapsulation techniques need not be discussed further.

[0068] The drug carrier systems and pharmaceutical preparations according to the present invention may be prepared by conventional techniques for lipid-based drug carrier systems. In a typical procedure for the preparation of the preferred carrier systems of this invention, a lipophilic surfactant component is weighed out into a suitable stainless steel vessel and a hydrophilic surfactant component is then weighed and added to the container along with any additional components. In a preferred method, the hydrophobic drug may be first added to a lipophilic surfactant component (*e.g.*, oleic acid) and completely dissolved before adding a hydrophilic surfactant component. In any case, mixing of the components may be effected by use of a homogenizing mixer or other high shear device and high temperature particularly when high melting point surfactants are used to ensure that all components are in homogenous liquid state before or after the addition of the drug.

[0069] In a situation in which a hydrophobic drug is weighed and added to a combined lipid mixture, mixing is continued, preferably at high temperature, until a homogenous solution is prepared. The formulation may be de-aerated before encapsulation in either soft or hard capsules. In some instances the fill formulation

may be held at elevated temperature using a suitable jacketed vessel to aid processing. Also, in some instances, the homogenous solution may be filtered (*e.g.*, through a 5 micron filter) before filling into capsules.

[0070] Returning now to the delivery of testosterone, the pharmaceutical compositions of the present invention may be suitable for testosterone therapy. Testosterone is the main endogenous androgen in men. Leydig cells in the testes produce approximately 7 mg of testosterone each day resulting in serum concentrations ranging from about 300 to about 1100 ng/dL. Women also synthesize testosterone in both the ovary and adrenal gland, but the amount is about one-tenth that observed in eugonadal men. The majority ($\geq$ 98%) of circulating testosterone is bound to sex hormone binding globulin and albumin and is biologically active only when released in the free form. The term "free" is thus defined as not being bound to or confined within, for example, biomolecules, cells and/or lipid matrices of the inventive formulations described herein. Generally, "free" medicaments described herein refer to medicament that is accessible to metabolic enzymes circulating in serum.

[0071] While the present invention should not be limited to the delivery of testosterone or any particular ester thereof, TU has been found to offer unique chemical and physical characteristics that make its use preferable in some embodiments. The present inventors have learned that the undecanoate acid ester of testosterone, in particular, can yield superior bioavailability to that found with other equivalent esters (*e.g.*, testosterone enanthate (TE)).

[0072] What is more, the use of TU in the formulations of the present invention is associated with a substantially lower serum DHT to T ratio than has been reported for other forms of T replacement – including oral formulations of TU (**Table 1**). Testosterone interacts with androgen receptors either directly or following its conversion to DHT via the action of 5α-reductase. DHT is a more potent androgen than testosterone and its elevated levels are thought by some scientists to increase the risk of prostate cancer. In this way, the present invention provides yet another unexpected advantage over other known testosterone delivery vehicles.

Table 1: Comparison of Serum DHT and DHT:T Ratios Observed in Response to T-Replacement by Various Routes of Administration

Form of Androgen Replacement/Dose	Length of Exposure	Avg. Serum DHT (ng/dL)	Avg. DHT:T Ratio	Multiple of Clarus DHT:T Ratio	Reference
Oral TU in SEDDS [200 mg T (as TU), BID]	7-Days	107	0.24	1	
Oral TU in SEDDS [200 mg T (as TU), BID]	30-Days	109	0.25	1	
Scrotal T-Patch (4 – 6 mg, QD) (Testoderm®)	8 years	175	0.42	1.75	Atkinson *et al* (1998)[1]
Transdermal T-Gel (5-10 g, QD) (AndroGel®)	3 years	130-210	0.25-0.30	1 - 1.25	Swerdloff *et al* (2000)[2], Wang *et al* (2004)[3]
Oral TU (Andriol) [50 mg T (as TU), BID]	Several Months	93	0.40	1.7	Houwing *et al* (2003)[4]
Oral TU (Andriol) [50 mg T (as TU), BID]	10 years	90	0.50	2.1	Gooren *et al* (1994)[5]

[1] Atkinson, LE, Chang, Y-L and Synder, PJ. (1998) Long-term experience with testosterone replacement through scrotal skin. In: *Testosterone: Action, Deficiency and Substitution* (Nieschlag, E and Behre, HM, eds). Springer-Verlag, Berlin, pp. 365-388

[2] Swerdloff, RS, et a (2000). Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. *J. Clin. Endocrinol. Metab*. 85: 4500-4510.

[3] Wang, C et al (2004). Long-term testosterone gel (AndroGel®) treatment maintains beneficial effects on sexual function and mood, lean and fat mass and bone mineral density in hypogonadal men. *J. Clin. Endocrinol. Metab.* 89:2085-2098.

[4] Houwing, NS et al (2003). Pharmacokinetic study in women of three different doses of a new formulation of oral testosterone undecanoate, Andriol Testocaps. *Pharmcotherapy*: 23: 1257-1265.

[5] Gooren, LJG (1994). A ten-year safety study of the oral androgen testosterone undecanoate. *J. Androl.* 15: 212-215.

[0073] Specific embodiments of the instant invention will now be described in non-limiting examples. **Table 2** provides composition details of various formulations of TU, in accordance with the teachings of the instant invention. For calculation purposes, 1 mg of T is equivalent to 1.58 mg T-undecanoate.

[0074] The compositions details of **Table 2** (mg/capsule and wt. percentage) are based on an approximate fill weight of 800 mg fill weight per '00' hard gelatin capsule. However, at testosterone-ester amounts less than about 100 mg/capsule, the formulations may be proportionally adjusted for smaller total fill weights that would permit use of smaller hard gelatin capsules (*e.g.*, size '0' or smaller size if needed).

[0075] As well, it should be apparent to one of ordinary skill in the art that many, if not all, of the surfactants within a category (*e.g.*, lipophilic, hydrophilic, etc.) may be exchanged with another surfactant from the same category. Thus, while Table 1 lists formulations comprising oleic acid, one of ordinary skill in the art should recognize other lipophilic surfactants (*e.g.*, those listed above) may be suitable as well. Similarly, while Table 1 lists formulations comprising Cremophor RH40 (HLB = 13), one of ordinary skill in the art should recognize other hydrophilic surfactants (*e.g.*, those listed above) may be suitable. Borage oil, peppermint oil, BHT, and ascorbyl palmitate may be substituted for chemically similar substances or eliminated.

Table 2

F.	Composition % w/w (mg/ "00" capsule)[1]							Fill Wt. (mg)[2]
	TU	Oleic Acid	Cremophor RH40	Borage Oil	Peppermint Oil	BHT	Ascorbyl Palmitate	
1	20 (158)	51.5 (413)	16 (128.5)	10 (80)	2.5 (20)	0.06 (0.5)	-	800
2	15 (120)	54.5 (436)	18 (144)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
3	17 (136)	52.5 (420)	18 (144)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
4	19 (152)	50.5 (404)	18 (144)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
5	21 (168)	50 (400)	16.5 (132)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
6	23 (184)	50 (400)	14.5 (116)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
7	25 (200)	50 (400)	12.5 (100)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
8	16 (128)	53.5 (428)	18 (144)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
9	18 (144)	51.5 (413)	18 (144)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6

10	22 (176)	50 (400)	15.5 (124	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
11	24 (192)	50 (400)	13.5 (108)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
12	15 (120)	55.5 (444)	17 (136)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
13	17 (136)	53.5 (428)	17 (136)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
14	19 (152)	51.5 (412)	17 (136)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
15	15 (120)	56.5 (452)	16 (128)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
16	17 (136)	54.5 (436)	16 (128)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
17	19 (152)	52.5 (420)	16 (128)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
18	21 (168)	50.5 (404)	16 (128)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
19	20 (160)	50.5 (404)	17 (136)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
20	20 (160)	51.5 (412)	16 (128)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
21	15 (120)	57.5 (460)	15 (120)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
22	16 (128)	56.5 (452)	15 (120)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
23	17 (136)	55.5 (444)	15 (120)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
24	18 (144)	(54.5 (436)	15 (120)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
25	19 (152)	53.5 (428)	15 (120)	10 (80)	2.5 (20)	0.02 (0.2)	0.8 (6.4)	806.6
26	20 (158)	51.5 (413)	16 (128.5)	9.4 (75)	3.1 (25)	0.06 (0.5)	-- --	800
27	20 (158)	51.5 (413)	16 (128.5)	10.6 (85)	1.9 (15)	0.06 (0.5)	-- --	800
28	20 (158)	51.5 (413)	16 (128.5)	11.2 (90)	1.2 (10)	0.02 (0.2)	0.8 (6.4)	806.1
29	20 (158)	51.5 (413)	16 (128.5	11.8 (95)	0.6 (5)	0.02 (0.2)	0.8 (6.4)	806.1
30	25 (200)	50 (400)	12.5 (100)	10.6 (85)	1.9 (15)	0.06 (0.5)	-- --	800.5

[1] Milligram weights rounded to nearest whole number; 800 (±10%)

[2] ± 8 mg

[0076] Preferred formulations of TU filled into size "00" capsules in accordance with the present invention are:

Formulation A

Ingredients	mg/capsule	%, w/w
Testosterone Undecanoate	158.3	19.8
Oleic Acid	413.1	51.6
Cremophor RH 40	128.4	16.1
Borage Seed Oil	80.0	10
Peppermint Oil	20.0	2.5
BHT	0.2	0.03
Total	**800**	**100**

Formulation B

Ingredients	mg/capsule	%, w/w
Testosterone Undecanoate	158.3	19.8
Oleic Acid	412.5	51.6
Cremophor RH 40	128.4	16.0
Peppermint Oil	20.0	2.5
Borage Seed Oil + 0.03% BHT	80.0	10
Ascorbyl Palmitate	0.8	0.1
Total	**800**	**100**

[0077] *In vivo* and *in vitro* performance data of the formulations in keeping with the invention will next be described. However, the scope of the invention should not be limited to the following examples nor the specific formulations studied in the examples.

Example 1 – Single-Day study

[0078] Formulation B was studied for its single-day pharmacokinetic profile upon once- or twice-daily administration to hypogonadal men. The study was designed as an open-label, single-day dosing, sequential, cross-over, pharmakokinetic study. Twelve (12) hypogonadal men were enrolled after giving written informed consent, and all 12 subjects completed the study. Each subject received a daily dose of Formulation B as follows:

1. 200 mg T (as TU) QD, *i.e.*, 2 capsules/dose
2. 200 mg T (as TU) BID (100 mg/dose), *i.e.*, 1 capsule/dose
3. 400 mg T (as TU) BID (200 mg/dose)

[0079] The doses were administered as capsules to subjects five minutes after a meal (breakfast for QD, and breakfast and dinner for BID).

Table 3 provides the relevant PK parameters from the study:

Table 3. Single-Day Pharmacokinetic Parameters for T, DHT, and DHT:T Ratio

Pharmacokinetic Parameter (unit)	Means (Standard Deviations) of Pharmacokinetic Parameters[a]		
	Regimen 1 (TU QD 200 mg[b])	Regimen 2 (TU BID 100 mg[b])	Regimen 3 (TU BID 200 mg[b])
T			
AUC_{24} (ng•hr/dL)	5907 (1840)	6751 (2145)	9252 (3173)
C_{avg} (ng/dL)	246 (77)	281 (89)	385 (132)
$T_{1/2}$ (hr)[a]	15.5 (7.0-24.0)	15.1 (4.5-43.4)	8.0 (4.2-16.3)
C_{max} (ng/dL)	0-24 hrs: 557 (252)	0-12 hrs: 470 (247) 12-24 hrs: 466 (160)	0-12 hrs: 626 (267) 12-24 hrs: 718 (333)
T_{max} (hr)[a]	0-24 hrs: 4.0 (2.0-8.0)	0-12 hrs: 4.0 (2.0-12.0) 12-24 hrs: 16.0 (14.0-20.0)	0-12 hrs: 4.0 (2.0-12.0) 12-24 hrs: 16.0 (14.0-20.0)
DHT			
AUC_{24} (ng•hr/dL)	1097 (387)	1400 (758)	1732 (859)
C_{avg} (ng/dL)	45.7 (16.1)	58.3 (31.6)	72.2 (35.8)
C_{max} (ng/dL)	0-24 hrs: 122 (66)	0-12 hrs: 81.3 (40.3) 12-24 hrs: 97.9 (51.2)	0-12 hrs: 108 (59) 12-24 hrs: 114 (58)
T_{max} (hr)[a]	0-24 hrs: 4.0 (1.0-8.0)	0-12 hrs: 4.0 (1.0-12.0) 12-24 hrs: 16.0 (13.0-20.0)	0-12 hrs: 4.0 (1.0-12.0) 12-24 hrs: 16.0 (14.0-20.0)
DHT:T Ratio			
R_{avg} (ng/dL)	0.189 (0.070)	0.233 (0.137)	0.198 (0.041)

[a] Values shown for half-life and time to maximum concentration are median and the range.

[b] Doses indicated are in T equivalents. Each TU capsule contained 158.3 mg TU, which corresponds to 100 mg T equivalents.

[0080] Mean serum T concentration during the 24-hour period post-dose (C_{avg}) indicated positive increases in serum T levels for all regimens studied, with the best

response obtained in Regimen 3 (C_{avg} 385 ng/dL). Mean peak serum T concentration observed in response to the oral T-ester preparations evaluated in this study never exceeded the upper limit of normal (*i.e.*, 1100 ng/dL). And while some individual subjects did have C_{max} T values above the normal upper limit, the vast majority of these peaks were in the range of 1200 to 1400 ng/dL. No subject in any treatment arm experienced a C_{max} in excess of 1500 ng/dL.

[0081] Median serum T half-life ($T_{1/2}$) was approximately 15 hours for Regimens 1 and 2; for Regimen 3, $T_{1/2}$ was 8 hours. In each regimen, serum DHT concentrations increased in concert with serum T levels. The mean DHT:T ratios (R_{avg}) in all periods were modestly above the normal ranges as determined by liquid chromatography-mass spectroscopy (LC/MS/MS) (*i.e.*, 0.03-0.1), but were clinically insignificant.

[0082] TU dosed at 200 mg T equivalents, BID with food yielded the most promising results with 75% of the subjects achieving a serum T C_{avg} above 300 ng/dL (lower normal eugonadal limit). Similarly, 75% of the subjects achieved an average serum T within the normal range (*i.e.*, 0.03 – 0.1 ng/dL). Those subjects that did not achieve a C_{avg} of at least 300 ng/dL were all above 200 ng/dL, indicating that a modest increase in the TU dose would have been effective oral T replacement therapy in these subjects.

[0083] Serum T and DHT concentrations increased in concert in the majority of subjects regardless of T-ester dose with excellent dose linearity for oral TU was observed when data were corrected for serum T at baseline. Although DHT:T ratios were modestly elevated, any elevation was considered clinically insignificant. Less inter-subject variability was observed with the formulation than equivalent formulations of other T-esters (*e.g.,* TE). Furthermore, in the "BID" dosing regimens, there was no difference in mean peak serum T concentrations or in the 12-hour AUCs between the morning and evening dose.

[0084] Concerning safety, although headache was reported as an adverse effect, in each treatment regimen, no adverse event was reported by more than one subject. No serious adverse events or deaths occurred during the study, and no subjects

prematurely discontinued the study due to adverse events. Hence, all adverse events were considered to be of mild intensity.

Example 2 – Seven-Day study

[0085] Formulation B was studied for its acute tolerability and steady-state serum pharmacokinetic profile at two doses administered twice-daily to hypogonadal men. The study was designed as an open-label, repeat dose, cross-over, pharmacokinetic study (with food effect examined in one arm).

[0086] Twenty nine (29) hypogonadal men were enrolled after giving written informed consent, 24 of which completed the study. Each subject who completed the study received a regimen of Formulation B as follows:

1. 7 daily doses of 600 mg T as TU BID (300 mg/dose), *i.e.*, 3 capsules/dose
2. 8 daily doses of 400 mg T as TU BID (200 mg/dose)

[0087] Doses were administered as capsules to subjects 30 minutes after initiation of meals (breakfast and dinner), except for Day 8, when the morning dose was administered fasting.

[0088] Peak exposure (C_{max}) to T and total exposure (AUC) to T were dose proportional after correction for the endogenous baseline T. The time of peak T concentrations (T_{max}) occurred at approximately 4 hours post-dose with each of the treatments. As well, the serum concentrations of both TU and DHTU rise and fall within the dosage interval with concentrations at the beginning and end of the dosing interval being less than 20% of the peak concentration for TU and less than 25% of the peak concentration for DHTU. Baseline T concentrations due to endogenous T production decreased progressively for each treatment. The observation is consistent with a progressive and persistent suppression of gonadotropins by exogenous T, thereby resulting in a decreased production of endogenous T. At least partial suppression was maintained over a 14-day washout period.

[0089] Again, serum T pharmacokinetics did not show diurnal variation with serum T concentrations. The night dose (administered at approximately 8 PM) produced a

similar concentration-time profile as the morning dose (administered at approximately 8 AM) (**Figure 1**). On account of the similarity between concentrations after AM and PM dosing (assessed in Regimen 1), 12-hour PK data from Regimen 2 (fed) were used to accurately predict a full 24-hour PK profile in response to 200 mg T (as TU), BID dosing. The simulated results indicated that (a) 77% of the subjects achieved a serum T C_{avg} in the eugonadal range over the 24-hour period based on AUC thereby meeting the current FDA efficacy requirement of 75% for a T-replacement product; and (b) none of the subjects experienced a C_{max} in excess of 1500 ng/dL, which is exceeds current FDA criteria that less than 85% of subjects have a C_{max} of greater than 1500 ng/dL for a T-replacement product. Hence, also consistent with current FDA mandated efficacy endpoints, no subjects had a C_{max} in excess of 2500 ng/dL and less than 5% of the subjects studied had a C_{max} in the range of 1800 - 2500 ng/dL. It is noteworthy that these results were achieved in the absence of any dose adjustment.

[0090] **Table 4** provides a comparison of steady state AM and PM pharmacokinetics of T with BID Dosing:

Table 4.	Treatment Regimen 1 300 mg T, as TU, BID	
	AM Dose Mean ± SEM	PM Dose Mean ± SEM
C_{max} (ng/dL)	1410 ± 146	1441 ± 118
T_{max} (hr, time after dose)	4.50 ± 0.39	5.9 ± 0.5
C_{min} (ng/dL)	305 ± 30	324 ± 36
AUC_{0-12} (ng•hr/dL)	9179 ± 754	9830 ± 659
C_{avg} (ng/dL)	765 ± 63	819 ± 55
FI ratio	1.37 ± 0.09	1.36 ± 0.09
C_{min}/C_{max} ratio	0.256 ± 0.029	0.243 ± 0.022

[0091] Administration of TU with a high-fat meal produced a similar serum T-concentration-time profile as administration with a standard meal. In contrast, administration of TU under fasting conditions resulted in greater than 50% decrease in

serum T exposures (C_{max} and AUC). **Table 5**. In all cases, a strong correlation between the observed C_{max} and the calculated C_{avg} was observed, suggesting that targeting of a particular C_{avg} with the oral T-ester formulation can result in predictable peak T levels after dosing.

Table 5.	After High Fat Breakfast		While Fasting		Geometric Mean of Individual Ratios
	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean	
C_{max} (ng/dL)	955	854	394	365	0.426
AUC_{0-12} (ng•hr.dL)	6217	5682	2894	2692	0.471
Administration under fed conditions (high fat breakfast) was used as the reference					

[0092] DHT concentrations tracked T concentrations, although DHT concentrations were only 11-34% of the T concentrations. Conversion of T to DHT showed a slight nonlinearity, increasing at a less than a concentration-proportional rate compared to T. The DHT/T ratio was least when T concentrations were highest, and the DHT/T ratio prior to starting TU treatment was approximately 0.1, while during treatment, at steady-state, the mean ratio was 0.24 and ranged from approximately 0.1 to 0.35 depending on the time of sampling after oral TU was administered.

[0093] Mean estradiol concentration prior to starting the oral TU treatment was approximately 11 pg/mL, and ranged from 19 pg/mL to 33 pg/mL on Day 7 of the various treatments (pre-dose concentrations). Pre-dose steady-state estradiol concentrations were approximately 20-30 pg/mL.

Example 3 – Four-Week study

[0094] Formulation B was also studied was to determine the time required to reach steady-state when hypogonadal men are treated for 28 days with twice daily dosing of 200 mg T (as TU) (*i.e.*, 2 capsules/dose). The study was designed as an open-label, repeat dose, pharmacokinetic study.

[0095] Fifteen (15) hypogonadal men were enrolled after giving written informed consent, and all completed the study. Each subject received twice-daily doses of 200 mg T as TU for 28 days.

[0096] For each subject, the "Day 28" serial PK sampling day was scheduled for Day 32 of the study. Therefore, each dose-compliant subject received a total of 31 daily doses of 400 mg T as TU (*i.e.*, 200 mg T, BID), and a final morning dose of 200 mg T as TU. Doses were administered as capsules, with subjects instructed to take doses 30 minutes after initiation of meals (breakfast and dinner).

[0097] **Table 6** provides the relevant PK data from the study:

Table 6.[a]	T	DHT	DHT/T	E_2
C_{max} or R_{max}[b]	995 ± 436 (43.9%) ng/dL	151 ± 75 (49.5%) ng/dL	0.380 ± 0.181 (47.7%) ratio	30.6 ± 14.9 (48.7%) pg/mL
T_{max}	4.87 ± 1.96 (40.3%) hr	5.87 ± 2.80 (47.7%) hr	5.87 ± 6.02 (102.7%) hr	6.67 ± 3.09 (46.3%) hr
C_{min} or R_{min}[b]	199 ± 108 (54.2%) ng/dL	64.6 ± 47.6 (73.8%) ng/dL	0.131 ± 0.047 (36.0%) ratio	15.4 ± 9.2 (59.9%) pg/mL
C_{avg} or R_{avg}[b]	516 ± 226 (43.7%) ng/dL	109 ± 61 (55.8%) ng/dL	0.245 ± 0.077 (31.5%) ratio	22.0 ± 10.9 (49.8%) pg/mL
AUC_{0-12}	6197 ± 2708 (43.7%) ng•hr/dL	1312 ± 732 (55.8%) ng•hr/dL	2.94 ± 0.93 (31.5%) hr	264 ± 131 (49.8%) pg•hr/mL
C_{min}/C_{max} or R_{min}/R_{max}[b]	23.5% ± 16.2% (69.0%) %	41.5% ± 17.0% (40.9%) %	37.3% ± 11.5% (30.8%) %	50.2% ± 15.1% (30.0%) %
Absolute Change in $C_{baseline}$[c]	-168 ± 188 (112.2%) ng/dL	3.50 ± 16.80 (480.1%) ng/dL	0.197 ± 0.116 (59.0%) ratio	-0.405 ± 5.345 (1320.8%) pg/mL
Percent Change in $C_{baseline}$[c]	-53.4% ± 79.5% (148.8%) %	18.8% ± 95.0% (506.6%) %	267% ± 170% (63.8%) %	-1.9% ± 41.5% (2224.6%) %
Fluctuation Index	156% ± 64% (40.8%) %	84.7% ± 30.6% (36.1%) %	96.0% ± 29.7% (30.9%) %	74.5% ± 41.6% (55.9%) %
λ_z	0.0726 ± 0.0676 (93.1%) 1/hr	0.0793 ± 0.0373 (47.1%) 1/hr	NA	0.0544 ± 0.0176 (32.4%) 1/hr
$T_{1/2}$	29.0 ± 32.7 (112.8%) hr	10.8 ± 5.8 (53.6%) hr	NA	14.0 ± 5.3 (37.8%) hr

[a] Results expressed as mean ± SEM. Co-efficient over variation is expressed as % in parentheses.

[b] R_{max}, R_{min}, R_{avg} are the Maximum ratio, the Minimum ratio and the Time Averaged ratio, respectively for the DHT/T ratio (analogous to C_{max}, C_{min} and C_{avg})

[c] Change in Baseline determined as concentration (or ratio) in the final sample of Day 28 – concentration (or ratio) in the pre-treatment sample (Day 0).

[0098] 86.7% of subjects achieved serum T C_{avg} within the normal range, with no subjects having C_{max} concentrations greater than 1800 ng/dL, and with just 13.3% of subjects having C_{max} concentrations greater than 1500 ng/dL. (Note: No dosing adjustments were made during the conduct of this study to titrate subjects to be within the targeted efficacy and safety ranges.) The half-life of T in response to TU in the

formulation tested was appreciably longer than has been reported for T alone or for TU given orally in prior art formulations. For example, in clinical studies of an oral TU formulation consistent with the invention described herein, an elimination half-life (α phase) of about approximately 5 hours was observed compared to a value estimated to be roughly half that (*i.e.*, 2 to 3 hours) based on published serum T profiles after oral dosing of a prior art formulation of TU. A long elimination (*i.e.*, terminal) half-life of 29 hrs was also observed with the inventive oral TU formulation. Endogenous T production was suppressed, however, by the administration of exogenous T, with only limited suppression occurring for the first 3 days, and requiring 5-7 days of continued treatment for maximal suppression.

[0099] Concentrations of T and DHT reached steady state by Day 7 of treatment. Concentrations of T and DHT were greater on Day 3 than on Day 5, indicating that a period of time was required for the exogenously administered T to suppress endogenous T production thus enabling achievement of steady-state in response to oral TU. Indeed, addition of the exogenous T suppressed endogenous T levels from 276 ng/dL pretreatment to 108 ng/dL after 28 days of supplementary T treatment.

[0100] Significantly, however, once steady state was achieved for serum T in response to twice-daily oral TU, little to no decline in serum T response was observed over time (*i.e.*, no trend toward lower serum T level with continued TU dosing). For example, the C_{avg} at Day 15 was substantially similar to the C_{avg} observed at day 28 (**Figure 2**). By contrast, oral TU formulations in the art have been reported to trend toward a lower mean T over time (Cantrill, J. A. *Clinical Endocrinol* (1984) 21: 97-107). In hypogonadal men treated with a formulation of oral TU, known in the art, it has been reported that the serum T response observed after 4 weeks of therapy was about 30% less than that observed on the initial day of therapy in hypogonadal men--most of whom had a form of primary hypogonadism and thus low baseline levels of serum T (*e.g.*, <100 ng/dL), so the decrease in T cannot be explained by suppression of endogenous T alone].

[0101] Serum DHT concentrations closely tracked T concentrations, with DHT and DHT/T values increasing 4 to 7 fold during treatment. Average DHT/T ratio over a

12-hour dosing interval was 0.245, although values over the dosing interval ranged from a mean maximum ratio of 0.380 to a mean minimum ratio of 0.131. DHT concentrations returned to pretreatment levels within 36 hours of discontinuing treatment with oral TU. However, T concentrations did not return to pretreatment levels as quickly, ostensibly because of the suppression of endogenous T production/release is not as rapidly reversed.

[0102] Concentrations of estradiol (E2) showed a monotonic, progressive increase to the steady state, which was also reached by Day 7 of treatment. E2 concentrations also showed systematic variation over the dosing interval that tracked the changes in T. The mean C_{max}, C_{avg}, and C_{min} values for E2 were 30.6 pg/mL, 22.0 pg/mL and 15.5 pg/mL, respectively. E2 concentrations returned to pretreatment levels within 36 hours of discontinuing treatment with oral TU.

[0103] Mean C_{max}, C_{avg}, and C_{min} concentrations at steady state (morning dose of Day 28) for T were 995 ng/dL, 516 ng/dL and 199 ng/dL, respectively. Median Tmax for T occurred at 5.0 hours post dose. C_{min} averaged 23.5% of C_{max}, resulting in a Fluctuation Index of 156%. The elimination half-life of T could only be evaluated in about half the subjects, and its median value in those subjects was 18.4 hours (mean $T_{1/2}$ was 29 hours).

Example 4 – Food Effects study

[0104] Any effect of dietary fat on the pharmacokinetics of Formulation B in hypogonadal men was studied in an open-label, two-center, five-way crossover study. After a washout period of 4–10 days, a single dose of 300 mg of T (475mg TU, 3 capsules of Formulation B) was administered to sixteen hypogonadal men with serum a baseline T level 205.5±25.3 ng/dL (mean ± SE, range 23-334.1 ng/dL). Subjects were randomized to receive the drug in the fasting state or 30 minutes after consumption of meals containing ~800 calories with specific amounts of fat (wt %): very low fat (6-10%); low fat (20%); "normal" diet fat (30%); or high fat (50%). The "normal" diet was, *a priori*, established as the comparator (*i.e.*, reference diet) for purposes of statistical comparisons. Serial blood samples were collected for a total of

24 hours after drug administration to determine serum testosterone and dihydrotestosterone (DHT) levels by liquid chromatography-mass spectroscopy (LC/MS/MS).

[0105] Pharmacokinteic parameters (**Table 7, Figures 3-5**) observed for serum T in response to a single, high-dose of oral TU were found to be similar for a low-fat and normal fat diet – in fact so much so that they were bioequivalent (i.e., the 90% confidence interval was between 85 – 125%). Similar serum T PK parameters were also observed when the normal- and high-fat meals were compared. And although the high-fat meal yielded a greater serum T response (albeit not statistically different), the mean ratio of least square means fell within 70-143% when compared to the normal-fat meal – a clinically insignificant difference of <30%.

Table 7.	**Serum T pharmacokinetic parameters (mean ± SD) in response to oral TU administered with different diets**				
	Fasting	**6-10% Fat**	**20% Fat**	**30% Fat**	**50% Fat**
C_{Avg}[1] (ng/dL)	526±324	781±385	884±505	1010±356	1260±477
C_{Max} (ng/dL)	948±798	1370±732	1520±711	1760±598	2140±901
T_{Max} (hr)	4.1±0.96	4.9±1.8	6.3±3.9	5.1±1.5	6.4±4.9
AUC (ng*h/dL)	7796±3673	10855±4285	12477±5028	13639±3773	16464±5584

[1] C_{Avg} is calculated as $AUC_{0-\infty}/\tau$ (τ = dosing interval = 12 hours for BID dosing)

[0106] Variability in PK response appeared to be highest following the first dose, or first few doses of oral TU, and decreased as therapy continued. Consequently, any impact of dietary fat across the range of low-normal-high on serum T PK parameters is likely to be insignificant during chronic dosing. This stance is consistent with the PK findings from the 7-day treatment (Example 2) and from the 30-day treatment (Example 3), where repeat dose studies of oral TU where the PK under the differing meal conditions still showed similar results for Cmax and Cavg distributions [both studies administered 200 mg T (as TU), BID].

[0107] Statistical comparisons of the serum T response observed after oral TU was taken without food or with a very low fat, low fat, or high fat diet versus a normal fat diet (*i.e.*, reference diet) revealed that there was no statistically significant difference at the $p<0.05$ level between the low-fat or high-fat diets versus the normal diet. Conversely, administration of oral TU as a SEDDS formulation while fasting or with a very low-fat breakfast yielded serum T PK parameters significantly different (*i.e.*, lower) from a normal diet. Accordingly, the fat content of meals taken with the inventive formulations can differ substantially from "normal", without a clinically significant impact on the levels of T obtained. Thus, a patient is permitted flexibility in eating habits from meal to meal, and from day to day, which could not have been heretofore possible with known oral TU formulations. Oral TU formulations known in the art have heretofore been unable to achieve any meaningful serum T levels in the fasted state.

Example 5 – *In vitro* dissolution tests

[0108] Dissolution studies of formulations of the present invention were studied *in vitro* to assess their correlation with the PK profiles observed *in vivo*. In a first study, the dissolution of Formulation B was studied. Andriol Testocaps® (40 mg TU per softgel dissolved in a mixture of castor oil and propylene glycol laurate) was included for comparison. The study was conducted with essentially equivalent doses of TU, *i.e.*, 1 capsule of Formulation B (158.3 mg TU) and 4 softgels of Testocaps (4x40 mg = 160 mg TU). The dissolution (*i.e.*, the release of TU from the respective formulations) was studied in Fed State Simulated Intestinal Fluid (FeSSIF) medium, which simulates intestinal fluid upon stimulation by a meal. FeSSIF contains sodium hydroxide, glacial acetic acid, potassium chloride, lecithin, and sodium taurocholate. The final emulsion is adjusted to pH 5.0.

[0109] That data are presented in **Tables 8 and 9** demonstrate that the inventive formulation released approximately 40% TU within the first 30 minutes and about 60% of the total capsule after 4 hours. For the Testocaps®, however, there is little to no drug released (1%) for the entire 4 hours. The observed major difference in the dissolution of TU from these two formulations can be attributed, at least in part, to the

presence of the hydrophlic surfactant, *e.g.*,. Cremophor RH40, in Formulation B. In contrast, Andriol Testocaps® (incorporate an oil (Castor Oil) and a lipophilic surfactant (Propylene Glycol Laureate) only.

Table 8. % Release of TU from Formulation B

Time (Hours)	% Released			
	1	2	3	Average
0.5	39.3	39.2	34.6	**37.7**
1	46.2	43.6	44.3	**44.7**
2	52.8	50.9	49.8	**51.2**
4	62.7	61.7	61.3	**61.9**
Infinity	96.0	100.1	90.9	**95.6**

Table 9. % Release of TU from Andriol Testocaps®

Time (Hours)	% Released			
	1	2	3	Average
0.5	0.0	0.0	0.0	**0.0**
1	0.0	0.0	0.0	**0.0**
2	0.0	0.9	0.0	**0.3**
4	1.3	1.1	1.3	**1.3**
Infinity	3.9	3.6	1.5	**3.0**

[0110] In a second study, Formulation A was subjected to a similar assay, but using a 5% Triton X100 potassium phosphate buffer (pH 6.8) as a dissolution medium. The results are provided in **Table 10** below. In this study, 98% of the TU from the inventive formulation was released within the first 15 minutes of dissolution and once again the presence of the hydrophilic surfactant Cremophor RH40 has certainly facilitated this fast dissolution and TU release.

Table 10. % Release of TU from Formulation A							
Time	**% Released**						
(M)	**1**	**2**	**3**	**4**	**5**	**6**	**Average**
0	0.0	0.0	0.0	0.0	0.0	0.0	**0.0**
.25	98.9	96.9	97.7	95.7	96.6	101.0	**97.8**
0.5	98.9	97.8	98.4	98.3	97.5	100.0	**98.5**
1.0	99.5	98.2	98.0	98.4	98.1	100.2	**98.7**

[0111] In yet another embodiment of the present invention, the pharmaceutical compositions disclosed herein may also be suitable for ameliorating some of the side-effects of certain strategies for male contraception. For example, progestin-based male contraception substantially suppresses luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and thereby suppresses spermatogenesis, resulting in clinical azoospermia (defined as less than about 1 million sperm/mL semen for 2 consecutive months). However, administration of progestins also has the undesirable side-effect of significantly reducing steady-state serum testosterone levels.

[0112] In such situations, for example, it may be preferable to provide preparations of progestin concomitantly with testosterone or a testosterone derivative (*e.g.*, TU). More preferably, a pharmaceutical preparation according to the invention is provided, comprising progestin—in an amount sufficient to substantially suppress LH and FSH production—in combination with testosterone. In some embodiments, the pharmaceutical preparation is for once-daily, oral delivery.

[0113] Formulations of the present invention can provide extended release formulations that can deliver testosterone into the serum over several hours. Indeed, the half-life of serum testosterone according to the invention is between 3 and 7 hours, preferably greater than 4, 5, or 6 hours. The serum half-life of testosterone in men, by contrast, is considered to be in the range of 10 to 100 minutes.

[0114] Without being bound by or limited to theory, it is believed that the inventive formulations achieve these results, in one aspect, by enhancing absorption of a medicament therein by the intestinal lymphatic system rather than by way of portal circulation. In another aspect, again without being bound by or limited to theory, it is believed that by using an ester of testosterone, the time required for de-esterification to occur contributes to a longer T half-life.

[0115] Oral dosages of the present invention can be taken by a patient in need of testosterone therapy once every about twelve hours to maintain desirable levels of serum testosterone. In a more preferred embodiment, oral dosages are taken by a patient in need of testosterone therapy once every about twenty four hours. In general, "desirable" testosterone levels are those levels found in a human subject characterized as not having testosterone deficiency.

[0116] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or alterations of the invention following. In general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth and as follows in the scope of the appended claims.

Claims

1. An oral pharmaceutical composition comprising testosterone undecanoate solubilized in a carrier comprising at least one lipophilic surfactant and at least one hydrophilic surfactant in a total lipohilic surfactant to total hydrophilic surfactant ratio (w/w) falling in the range of about 6:1 to 3.5:1, wherein said solubilized testosterone undecanoate comprises 18 to 22 percent by weight of the composition, which composition upon once or twice daily oral administration, provides an average serum testosterone concentration at a steady state falling in the range of about 300 to about 1100 ng/dL.

2. The oral pharmaceutical composition of claim 1 in which the at least one hydrophilic surfactant comprises Cremophor RH 40 (polyoxyethyleneglycerol trihydroxystearate).

3. The oral pharmaceutical composition of claim 1 in which the at least one lipophilic surfactant comprises oleic acid.

4. The oral pharmaceutical composition of claim 1 in which the testosterone undecanoate is solubilized in a carrier substantially free of ethanol.

5. The oral pharmaceutical composition of claim 1 which comprises 15 to 17 percent by weight of the at least one hydrophilic surfactant.

6. The oral pharmaceutical composition of claim 1 which comprises 50 to 55 percent by weight of the at least one lipophilic surfactant.

7. A pharmaceutical composition comprising testosterone undecanoate solubilized in a carrier comprising at least one lipophilic surfactant and at least one hydrophilic surfactant in a total lipophilic surfactant to total hydrophilic surfactant ratio (w/w) falling in the range of about 6:1 to 3.5:1 to provide an average serum testosterone concentration at steady state falling in the range of about 300 to about 1100 ng/dL, wherein said solubilized testosterone undecanoate comprises 18 to 22 percent by weight of the composition, the composition for use in a method of treating testosterone deficiency or its symptoms comprising orally administering to a subject suffering from testosterone deficiency or its symptoms an effective amount of the pharmaceutical composition.

8. The pharmaceutical composition for use in the method of claim 7 in which the composition is administered once daily.

9. The pharmaceutical composition for use in the method of claim 7 in which the composition is administered twice daily.

10. An oral pharmaceutical composition comprising:

a. 18-22 percent by weight of solubilized testosterone undecanoate;

b. 50-55 percent by weight of at least one lipophilic surfactant; and;

c. 15-17 percent by weight of at least one hydrophilic surfactant;

d. 10-15 percent by weight of a mixture of borage seed oil and peppermint oil.

11. The composition as recited in claim 10 wherein said hydrophilic surfactant is Cremophor RH 40.

12. The composition as recited in claim 10 wherein said lipophilic surfactant is oleic acid.

13. The oral pharmaceutical composition as recited in claim 10 comprising:

a. 19.8 percent by weight of solubilized testosterone undecanoate;

b. 51.6 percent by weight of oleic acid;

c. 16.1 percent by weight of Cremophor RH 40;

d. 10 percent by weight of borage seed oil;

e. 2.5 percent by weight of peppermint oil; and

f. 0.03 percent by weight of BHT.

14. The composition as recited in Claim 10, wherein the ratio of lipophilic surfactants to hydrophilic surfactants is about 4:1.