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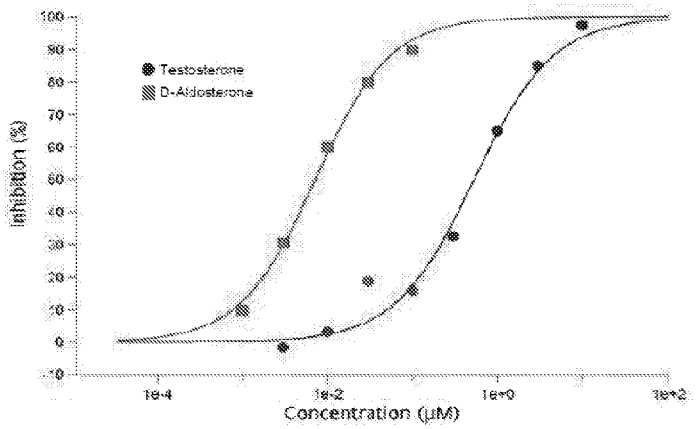
Figure 1.



(57) Abstract: Pharmaceutical products comprising an anti-hypertensive agent in combination with a testosterone replacement therapy, such as orally administered testosterone undecanoate are provided. Methods of safely treating a testosterone deficiency or its symptoms with the inventive pharmaceutical products are also provided.

WO 2020/210501 A1

ORAL PHARMACEUTICAL PRODUCTS AND METHODS OF USE COMBINING TESTOSTERONE ESTERS WITH ANTI-HYPERTENSIVE AGENTS

[0001] This application claims the benefit of priority of United States Provisional Application No. 62/833,189, filed April 12, 2019, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates generally to pharmaceutical products comprising formulations of testosterone esters for the treatment of testosterone deficiency, in combination with anti-hypertensive agents. More particularly, the present invention relates to formulations of testosterone undecanoate (TU) or testosterone enanthate (TE), in combination with an aldosterone antagonist and/or an epithelial Na-channel blocker.

BACKGROUND OF THE INVENTION

[0003] 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, the prostate and seminal vesicles; for sense of well-being; and for maintenance of libido and erectile potency.

[0004] 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 adult 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.

[0005] Various testosterone replacement therapies (TRTs) are commercially available for the treatment of male hypogonadism. Pharmaceutical preparations include both testosterone and testosterone derivatives in the form of intramuscular or subcutaneous injections, implants, oral tablets of alkylated T (*e.g.*, methyltestosterone), topical gels or solutions, 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 and solutions have been associated with unsafe transfer of T from the user to women and children. As well, the sole "approved" oral androgen 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.

[0006] Testosterone and its esters are poorly orally 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.

[0007] Other than selection of a testosterone ester, the formulation for oral delivery of the testosterone ester presents unique challenges. The gastrointestinal environment is decidedly aqueous in nature, which requires that drugs must be solubilized 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.

[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] Oral formulations of testosterone esters providing clinically-effective serum testosterone levels to treat hypogonadal men (*i.e.*, those with a serum T concentration of $\leq$ 300 ng/dL) over an

extended period of time are disclosed in WO2011129812, which is incorporated in its entirety by reference.

[0010] Some patients who are treated with TRTs, such as JATENZO® (see JATENZO package insert), Xyosted™ (see Xyosted package insert issued 09/2018), or Tlando (see Lipocine Announces ABPM Labeling Study Results Consistent with Recently Approved Testosterone Replacement Therapy on 27 March 2019) develop elevations of their BP.

[0011] Testosterone was shown to interact with the aldosterone receptor (e.g., mineralocorticoid receptor). These in vitro binding studies showed that T will displace radiolabeled aldosterone from the MR (see Eurofin Study AB78720). The IC50 for T is 0.53 microM.

[0012] The kidney plays an important role in BP regulation, in part thru the excretion of sodium. Aldosterone activates the mineralocorticoid receptors in the principal cells in the connecting and collecting tubules. Aldosterone, after combining with the cytosolic mineralocorticoid receptor, leads to enhanced sodium reabsorption and potassium secretion by increasing both the number of open sodium channels and the number of Na-K-ATPase pumps. The BP effect of aldosterone can be blocked, either by aldosterone antagonists which block activation of the mineralocorticoid receptors in the principal cells, or by blocking sodium channels.

[0013] Some patients receiving testosterone replacement therapy (TRT) have elevated blood pressure. TRT with concomitant administration of an anti-hypertensive agent such as an aldosterone antagonist can mitigate any T-induced increase in blood pressure. It is believed that T can interact with the mineralocorticoid receptor (MR). Activation of the MR can lead to renal sodium retention and thus edema and/or hypertension. Thus, aldosterone antagonists, such as spironolactone and eplerenone, that block the MR activation can prevent the elevated blood pressure associated with TRT in some patients.

[0014] Some patients receiving testosterone replacement therapy (TRT) have elevated blood pressure. It is believed that T can interact with the mineralocorticoid receptor (MR). Activation of the MR can activate epithelial sodium (Na) channels (ENaC) which leads to renal sodium retention and thus edema and/or hypertension. Thus, blockade of ENaC by epithelial Na-channel blockers, such as amiloride and triamterene, can prevent the elevated blood pressure associated with TRT in some patients.

[0015] Mineralocorticoid receptor antagonists such as aldosterone antagonists and epithelial Na-channel blockers are diuretic drugs that work primarily on the kidneys. They decrease sodium reabsorption which leads to increased salt excretion by the kidneys. By regulating salt (sodium) excretion, mineralocorticoid receptor antagonists lower blood pressure and reduce fluid around the heart which can be very beneficial in some cardiovascular conditions. Mineralocorticoid receptor antagonists have been used for many clinical conditions in the cardiovascular system. It has proven

beneficial for diseases like primary aldosteronism, primary and resistant hypertension, heart failure and chronic kidney disease.

[0016] Aldosterone is a mineralocorticoid which is synthesized in the adrenal glands. When aldosterone is secreted from the adrenal glands, it binds to the mineralocorticoid receptor in the renal tubule cell and forms a complex. This complex enhances transcription of specific DNA segments in the nucleus, leading to the formation of two protein transporters, Na+/K+ ATPase pump at the basolateral membrane and Na+ channel called ENaC, located at the apical membrane of the renal tubule cell. These protein transporters increase sodium reabsorption and potassium excretion in the distal tubule and the collecting duct of the kidneys. This helps the body to maintain normal volume status and electrolyte balance, increasing the blood pressure.

[0017] Mineralocorticoid receptor antagonists decrease the aldosterone effect by binding to the mineralocorticoid receptor inhibiting aldosterone activation of the receptor. This leads to increased sodium excretion, resulting in decreased body fluid and lower blood pressure.

[0018] Members of this class in clinical use include spironolactone, eplerenone, canrenone and potassium canrenoate, and finerenone. Some drugs also have antimineralocorticoid effects secondary to their main mechanism of actions. Examples include progesterone, drospirenone, gestodene, and benidipine.

[0019] Spironolactone and eplerenone competitively block the binding of aldosterone to the mineralocorticoid receptor and hindering the reabsorption of sodium and chloride ions. The activity of mineralocorticoid antagonists is dependent on the presence of a y-lactone ring on the C-17 position. The C-7 position is also important for activity as substituents there sterically hinder the interaction of C-7-unsubstituted agonists such as aldosterone.

[0020] Eplerenone is a newer drug that was developed as a spironolactone analog with reduced adverse effects. In addition to the y-lactone ring and the substituent on C-7, eplerenone has a 9α,11α-epoxy group. This group is believed to be the reason why eplerenone has a 20-40-fold lower affinity for the mineralocorticoid receptor than spironolactone.

[0021] There remains a need for pharmaceutical products that safely treat testosterone deficiency and symptoms thereof, which includes mitigating the potential for elevated blood pressure resulting from TRT. Described herein are pharmaceutical products that meet such need through reliance on the mechanistic synergy between T esters and anti-hypertensive agents such as mineralocorticoid antagonists or aldosterone antagonists or epithelial Na-channel blockers.

SUMMARY OF THE INVENTION

[0022] One aspect of the present invention is directed to a pharmaceutical product comprising one or more pharmaceutical compositions, wherein the one or more pharmaceutical compositions comprise:

anti-hypertensive agents such as mineralocorticoid antagonists or aldosterone antagonists or epithelial Na-channel blockers; and a testosterone replacement therapy.

[0023] In some embodiments, the anti-hypertensive agent described herein is a mineralocorticoid antagonist. In some embodiments, the anti-hypertensive agent is an aldosterone antagonist. In some embodiments, the aldosterone antagonist is selected from: spironolactone, eplerenone, canrenone and potassium canrenoate, and finerenone. In an embodiment, said anti-hypertensive agent is a drug also having antimineralocorticoid effects secondary to their main mechanism of actions, such as progesterone, drospirenone, gestodene, and benidipine.

[0024] In some embodiments, the anti-hypertensive agent described herein is an epithelial Na-channel blocker. In some embodiments, the epithelial Na-channel blocker is selected from: amiloride, triamterene, phenamil, benzamil, and (*N*-(3,5-diamino-6-chloropyrazine-2-carbonyl)-N'-4-[4-(2,3-dihydroxypropoxy)phenyl]butyl-guanidine methanesulfonate (552-02). In an embodiment, said anti-hypertensive agent is a drug also having K-sparing diuretic effects secondary to their main mechanism of actions, such as blocking Na-channels.

[0025] In an embodiment, said anti-hypertensive agent is administered at a dose of 200mg daily.

[0026] In an embodiment, said anti-hypertensive agent is administered at a dose of 100mg daily.

[0027] In an embodiment, said anti-hypertensive agent is administered at a dose of 50mg daily.

[0028] In an embodiment, said anti-hypertensive agent is administered at a dose of 25mg daily.

[0029] In an embodiment, said anti-hypertensive agent is administered at a dose of 10mg daily.

[0030] In an embodiment, said anti-hypertensive agent is administered at a dose of 5mg daily.

[0031] In an embodiment, said TRT comprises oral administration of testosterone or a testosterone ester. In an embodiment, said testosterone ester is chosen from testosterone undecanoate and testosterone tridecanoate. In an embodiment, said testosterone ester is testosterone undecanoate.

[0032] In an embodiment, the daily dose of said testosterone undecanoate is 474 mg.

[0033] In an embodiment, the daily dose of said testosterone undecanoate is 316 mg.

[0034] In an embodiment, the daily dose of said testosterone undecanoate is 396 mg.

[0035] In an embodiment, the daily dose of said testosterone undecanoate is 632 mg.

[0036] In an embodiment, the daily dose of said testosterone undecanoate is 792 mg.

[0037] In an embodiment, said TRT comprises injection of testosterone or a testosterone ester. In an embodiment, said testosterone ester is chosen from testosterone undecanoate, testosterone cypionate, testosterone propionate, and testosterone enanthate, and combinations thereof.

[0038] In an embodiment, said TRT comprises transdermal, nasal, or buccal administration of testosterone.

[0039] In some embodiments, the testosterone ester is solubilized in a carrier comprising at least one lipophilic surfactant and at least one hydrophilic surfactant. In some embodiments, the total lipophilic surfactant to total hydrophilic surfactant ratio (w/w) in the carrier falls in the range of about 6:1 to 3.5:1.

[0040] One aspect of the present invention is directed to pharmaceutical products described herein comprising one or more pharmaceutical compositions, wherein administration of the one or more pharmaceutical compositions to the individual provides an average serum testosterone concentration at steady state in the individual falling in the range of about 300 to about 1100 ng/dL.

[0041] In some embodiments, the individual's serum testosterone C_{max} does not exceed 2500 ng/dL when the one or more pharmaceutical compositions are administered to the individual. In some embodiments, the individual's serum testosterone C_{max} does not exceed 2500 ng/dL when the one or more pharmaceutical compositions are administered to the individual with a meal. In some embodiments, the individual's serum testosterone C_{max} does not exceed 1800 ng/dL when the one or more pharmaceutical compositions are administered to the individual. In some embodiments, the individual's serum testosterone C_{max} does not exceed 1800 ng/dL when the one or more pharmaceutical compositions are administered to the individual with a meal. In some embodiments, the individual's serum testosterone C_{max} does not exceed 1500 ng/dL when the one or more pharmaceutical compositions are administered to the individual. In some embodiments, the individual's serum testosterone C_{max} does not exceed 1500 ng/dL when the one or more pharmaceutical compositions are administered to the individual with a meal.

[0042] One aspect of the present invention is directed to pharmaceutical products as described herein, wherein the at least one hydrophilic surfactant comprises Cremophor® RH 40 (polyoxyethyleneglycerol trihydroxystearate).

[0043] One aspect of the present invention is directed to pharmaceutical products as described herein, wherein the at least one lipophilic surfactant comprises oleic acid.

[0044] One aspect of the present invention is directed to pharmaceutical products as described herein, wherein the at least one lipophilic surfactant comprises Maisine 35-1 (glyceryl monolinoleate).

[0045] One aspect of the present invention is directed to pharmaceutical products comprising one or more pharmaceutical compositions as described herein, which upon oral administration of the one or more pharmaceutical compositions to the individual 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 in the

individual substantially the same as that observed upon oral administration of the one or more pharmaceutical compositions to the individual with a meal having a fat content of about 30 wt%.

[0046] One aspect of the present invention is directed to pharmaceutical products comprising one or more pharmaceutical compositions as described herein, which upon oral administration of the one or more pharmaceutical compositions to an individual suffering from testosterone deficiency or its symptoms, provides a mean serum testosterone concentration in the individual at day 30 of a daily treatment regimen with the pharmaceutical product, which is substantially the same as that observed on day 7.

[0047] One aspect of the present invention is directed to pharmaceutical products comprising one or more pharmaceutical compositions as described herein, wherein the mean serum testosterone concentration in the individual obtained at day 30 of a daily treatment regimen with the pharmaceutical product is substantially the same as that observed on day 60.

[0048] One aspect of the present invention is directed to pharmaceutical products as described herein, wherein the anti-hypertensive agent and the testosterone ester are combined in the same pharmaceutical composition. In some embodiments, the pharmaceutical composition is a liquid-filled capsule, a powder-filled capsule, or a tablet. In some embodiments, the pharmaceutical composition comprises a self-emulsifying drug delivery system, a self-microemulsifying drug delivery system, or a self-nanoemulsifying drug delivery system. In some embodiments, the pharmaceutical composition comprises a solid adsorption carrier selected from: silicon dioxide, calcium aluminometasilicate, magnesium aluminometasilicate (*e.g.*, Veegum®), and a layered 2:1 phyllosilicate. In some embodiments, the layered 2:1 phyllosilicate is selected from: montmorillonite, nontronite, beidellite, volkonskoite, hectorite, saponite, sauconite, sobockite, stevensite, and svinfordite. In some embodiments, the pharmaceutical composition comprises one or more hydrocolloid as solid adsorption carrier and thickening agent selected from: starches, cellulose esters (sodium carboxymethylcellulose, methyl cellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose and microcrystalline cellulose), gums (guar gum, xanthan gum, gum arabic), gelatin, alginates, carrageenan and pectin. In some embodiments, the testosterone ester is testosterone undecanoate. In some embodiments, the pharmaceutical composition comprises testosterone undecanoate, peppermint oil, oleic acid, and Cremophor® RH40. In some embodiments, the pharmaceutical composition comprises testosterone undecanoate, peppermint oil, oleic acid, Cremophor® RH40, Neusilin® US2, croscarmellose sodium, and magnesium stearate. In some embodiments, the pharmaceutical composition comprises testosterone undecanoate, peppermint oil, oleic acid, Cremophor® RH40, copovidone, maltodextrin, and microcrystalline cellulose.

[0049] One aspect of the present invention is directed to pharmaceutical products as described herein, comprising a first pharmaceutical composition comprising an anti-hypertensive agent that

decreases blood pressure in an individual; and a second pharmaceutical composition comprising testosterone or a testosterone ester. In some embodiments, the testosterone ester is testosterone undecanoate. In some embodiments, the second pharmaceutical composition comprises 18 to 22 percent by weight of a solubilized testosterone undecanoate. In some embodiments, the testosterone undecanoate is solubilized in a carrier substantially free of ethanol. In some embodiments, the second pharmaceutical composition comprises 15 to 17 percent by weight of the at least one hydrophilic surfactant. In some embodiments, the second pharmaceutical composition 50 to 55 percent by weight of the at least one lipophilic surfactant. In some embodiments, the second pharmaceutical composition comprises a solid adsorption carrier selected from: silicon dioxide, calcium aluminometasilicate, magnesium aluminometasilicate, and a layered 2:1 phyllosilicate. In some embodiments, the second pharmaceutical composition comprises layered 2:1 phyllosilicate is selected from: montmorillonite, nontronite, beidellite, volkonskoite, hectorite, saponite, sauconite, sobockite, stevensite, and svinfordite. In some embodiments, the second pharmaceutical composition comprises testosterone undecanoate, peppermint oil, oleic acid, and Cremophor® RH40. In some embodiments, the second pharmaceutical composition comprises testosterone undecanoate, peppermint oil, oleic acid, Cremophor® RH40, Neusilin® US2, croscarmellose sodium, and magnesium stearate. In some embodiments, the second pharmaceutical composition testosterone undecanoate, peppermint oil, oleic acid, Cremophor® RH40, copovidone, maltodextrin, and microcrystalline cellulose.

[0050] One aspect of the present invention is directed to methods of treating testosterone deficiency or its symptoms comprising orally administering to an individual suffering from testosterone deficiency or its symptoms an effective amount of one or more pharmaceutical compositions described herein. In some embodiments, the one or more pharmaceutical compositions are administered once daily. In some embodiments, the one or more pharmaceutical compositions are administered twice daily.

[0051] One aspect of the present invention is directed to methods of treating testosterone deficiency or its symptoms comprising orally administering to an individual suffering from testosterone deficiency or its symptoms an effective amount of one or more pharmaceutical compositions described herein, wherein the method gives rise to a C_{max} value in the individual falling in the range of about 900 to 1100 ng/dL.

[0052] One aspect of the present invention is directed to methods of treating testosterone deficiency or its symptoms comprising orally administering to an individual suffering from testosterone deficiency or its symptoms an effective amount of one or more pharmaceutical compositions described herein, wherein the one or more pharmaceutical compositions are administered to the individual with a meal comprising at least 20 wt% fat.

[0053] One aspect of the present invention is directed to methods of treating testosterone deficiency or its symptoms comprising orally administering to an individual suffering from testosterone deficiency or its symptoms an effective amount of one or more pharmaceutical compositions described herein.

[0054] One aspect of the present invention is directed to methods of treating testosterone deficiency or its symptoms comprising orally administering to an individual suffering from testosterone deficiency or its symptoms an effective amount of the one or more pharmaceutical compositions described herein, which gives rise to an average serum testosterone T_{max} value in the individual falling in the range of about 3 to 7 hours after oral administration. In some embodiments, the average serum T_{max} value falls in the range of about 4 to 5 hours after oral administration to the individual.

[0055] One aspect of the present invention is directed to methods of treating testosterone deficiency or its symptoms comprising orally administering to an individual suffering from testosterone deficiency or its symptoms an effective amount of the one or more pharmaceutical compositions described herein, in which substantially no significant decline in steady state serum testosterone response is observed in the individual upon repeat dosing to the individual.

[0056] One aspect of the present invention is directed to pharmaceutical products comprising one or more pharmaceutical compositions as described herein for use in a method of treatment of the human or animal body by therapy. One aspect of the present invention is directed to pharmaceutical products comprising one or more pharmaceutical compositions as described herein for use in a method of treating testosterone deficiency or its symptoms. In some embodiments, the one or more pharmaceutical compositions are administered once daily. In some embodiments, the one or more pharmaceutical compositions are administered twice daily. In some embodiments, administration of the one or more pharmaceutical compositions to an individual, gives rise to a testosterone C_{max} value in the individual falling in the range of about 900 to 1100 ng/dL. In some embodiments, the one or more pharmaceutical compositions are administered to the individual with a meal comprising at least 20 wt% fat. In some embodiments, administration of the one or more pharmaceutical compositions to an individual, gives rise to substantially no diurnal testosterone pharmacokinetic variation in the individual. In some embodiments, administration of the one or more pharmaceutical compositions to an individual, gives rise to an average serum testosterone T_{max} value in the individual falling in the range of about 3 to 7 hours after oral administration to the individual. In some embodiments, the average serum T_{max} value in the individual falls in the range of about 4 to 5 hours after oral administration. In some embodiments, substantially no significant decline in steady state serum testosterone response is observed in the individual upon repeat dosing to the individual.

[0057] In an embodiment of the present invention, pharmaceutical product is provided comprising an anti-hypertensive agent and a pharmaceutical composition 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 an individual in need thereof, gives rise to an apparent 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.

[0058] In a particularly preferred embodiment, the pharmaceutical 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 mono-/di-oleate, propylene glycol mono-/di-laurate, and glycerol mono-/di-caprylate/caprate are preferred lipophilic surfactants. Combinations of two or more lipophilic surfactants and two or more hydrophilic surfactants are also contemplated.

[0059] 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 an anti-hypertensive agent and 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_{avg}, 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) serum T_{max} 3 to 7 hours after administering the composition; and (c) substantially no decline in steady state serum testosterone response is observed upon repeat dosing.

[0060] 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.

[0061] 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 a T ester and the anti-hypertensive agent 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

[0062] Figure 1 shows the percent inhibition of radioligand binding to the mineralocorticoid receptor by testosterone and aldosterone.

DETAILED DESCRIPTION OF THE INVENTION

[0063] The present invention provides pharmaceutical products that include at least one anti-hypertensive agent and a testosterone ester, and methods of using them. In some embodiments, the pharmaceutical product comprises a fixed-dose combination—a single formulation combining an anti-hypertensive agent and a testosterone ester in a predetermined ratio. In some embodiments, the pharmaceutical product comprises a co-packaged product—an anti-hypertensive agent in one formulation and a testosterone ester in a separate formulation, along with labeling to support their combined use. Two formulations in a co-packaged product may be administered simultaneously or sequentially. The present invention further provides methods of adjuvant therapy comprising prescribing or administering an anti-hypertensive agent and a testosterone ester, to an individual in need thereof, in separate dosage forms in a ratio determined by a healthcare provider.

[0064] The fixed-dose combination formulations described herein comprise an anti-hypertensive agent added to a testosterone ester formulation described herein. Such testosterone ester formulations may be modified as necessary or desirable due to the presence of the anti-hypertensive agent, such as by increasing or decreasing the amount of the testosterone ester, altering the ratio of excipients, omitting one or more excipients, or including one or more additional excipients. Any mixing incompatibilities in fixed dose combinations may be overcome through the use of one or more of the following techniques well known in the art: bilayer, multilayer tablet-in-tablet, melt extruded granules, multigranule compressed tablets, particle coating, multiparticulates, and compartmentalized capsules. Such fixed-dose combinations may be prepared by methods of pharmacy well known to those skilled in the art (See, for example, Remington: The Science and Practice of Pharmacy, 21st ed., Lippincott Williams & Wilkins, Philadelphia, PA (2005)).

[0065] The co-packaged pharmaceutical products described herein comprise an anti-hypertensive agent formulated, independently of the testosterone ester, into dosage forms suitable for oral administration. Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, forming the resulting mixture into a desired shape. Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tabletting lubricants and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives and flavorings and colorants may be added to the liquid preparations. The co-packaged pharmaceutical products described herein may be prepared by methods of pharmacy well known to those skilled in the art (see, for example, Remington: The Science and Practice of Pharmacy, 21st ed., Lippincott Williams & Wilkins, Philadelphia, PA (2005)).

[0066] The pharmaceutical products of the present invention comprise a testosterone ester in an oral pharmaceutical composition, 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 (FDA) to be undesirable, if not unacceptable. For instance, FDA approval guidelines state that more than 85% of treated subjects must have a C_{max} value of 1500 ng/dL or less, 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 testosterone ester formulations described herein are designed to be self-emulsifying drug delivery systems (SEDDS) so that a testosterone ester-containing emulsion (or dispersion) is formed upon mixing with intestinal fluids in the gastrointestinal tract.

[0067] SEDDS, as well as self-microemulsifying drug delivery systems (SMEDDS) and self-nanoemulsifying drug delivery systems (SNEDDS) form fine oil-in-water dispersions (emulsion, microemulsion, and nanoemulsion, respectively) upon dilution with aqueous media or in contact with gastrointestinal fluids. SEDDS dispersions *i.e.* emulsions are thermodynamically unstable and lipid droplets are heterogeneous in size ranging from 200 nm to 5 μm in diameter. SEDDS dispersions have a turbid appearance. SMEDDS dispersions *i.e.* microemulsions are thermodynamically stable and the droplet size is < 200. nm. SMEDDS dispersions *i.e.* nanoemulsions have an optically clear to translucent appearance. SNEDDS produce kinetically stable nanoemulsion droplets < 200 nm or more commonly < 100 nm. SNEDDS dispersions have an optically clear appearance. The smaller the

droplet size of the resulting oil-in-water droplets, the larger the surface area, which is advantageous for improved drug absorption through the portal route.

[0068] In one embodiment of the present invention, testosterone and/or esters at the C-17 position of the testosterone molecule and an anti-hypertensive agent, alone or in combination with other active ingredients, may be orally delivered using the formulations described herein. For example, the combination of testosterone undecanoate and an anti-hypertensive agent with an orally active inhibitor of Type I or Type II 5α-reductase may be preferable in some embodiments.

[0069] 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 lipophilic compounds, including T, can be adapted 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 drug delivery systems and compositions therefrom described herein may be suitable for oral delivery of an anti-hypertensive agent along with 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.

[0070] According to one aspect of the present invention, each of the components of the testosterone ester delivery system (*i.e.*, the lipophilic and hydrophilic surfactants) individually have solubilizing characteristics and contribute, in part, to solubilizing the testosterone ester. Those lipophilic surfactants that contribute substantially to dissolving the testosterone ester are defined herein as "primary" solvent(s). It should be appreciated, however, that solubility can be affected by the temperature of the solvent/formulation. In the formulations described herein comprising, for example, surfactants and TU in a ratio of about 4:1, the TU remains soluble at or above 30 °C, including in the range of 30 to about 40 °C.

[0071] A hydrophilic surfactant component may be necessary to achieve desirable dispersability of the testosterone ester formulation in the GI tract and release of the testosterone ester. That is, a hydrophilic surfactant, in addition to serving as a secondary solvent, may be required to release the testosterone ester 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 testosterone ester release without compromising the solubilization of the testosterone ester.

[0072] Lipophilic surfactants suitable in pharmaceutical products of the present invention include:

[0073] Fatty acids (C_6-C_{24}, preferably C_{10}-C_{24}, more preferably C_{14}-C_{24}), saturated, for example, octanoic acid, decanoic acid, undecanoic acid, lauric acid, myristic acid, palmitic acid, stearic acid, unsaturated, for example, oleic acid, linoleic acid, and linolenic acid, and mixtures thereof. Oleic acid (cis-9-octadecanoic acid) is preferred.

[0074] 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.

[0075] 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).

[0076] 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).

[0077] Polyglycerol esters of fatty acids such as Plurol® oleique (polyglyceryl oleate), Caprol® ET (polyglyceryl mixed fatty acids) and Drewpol® 10.10.10 (polyglyceryl oleate).

[0078] 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).

[0079] 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).

[0080] 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.

[0081] Alcohol ethyoxylates (HLB<10), *e.g.* Volpo™ N3 (polyoxyethylated (3) oleyl ether), Brij™ 93 (polyoxyethylated (2) oleyl ether), Marlowet® LA4 (polyoxyethylated (4) lauryl ether).

[0082] 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).

[0083] Mixtures of suitable lipophilic surfactants, such as those listed above, may be used if desired, and in some instances are found to be advantageous.

[0084] Any pharmaceutically acceptable hydrophilic surfactant (*i.e.*, having an HLB value greater than 10) may be used in the testosterone ester formulations described herein. Some non-limiting examples include:

[0085] 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.

[0086] 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.

[0087] 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.)

[0088] 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.

[0089] 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).

[0090] 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 Synperonic™ PE L44 (HLB = 16) and Synperonic™ F127 (HLB = 22), respectively.

[0091] Anionic surfactants, *e.g.* sodium lauryl sulfate, sodium oleate and sodium dioctylsulfosuccinate.

[0092] Alkylphenol surfactants (HLB>10), *e.g.* Triton™ N-101 (polyoxyethylene (9-10) nonylphenol) and Synperonic™ NP9 (polyoxyethylene (9) nonylphenol).

[0093] As mentioned, in one aspect of the present invention, each of the components of the testosterone ester delivery system (*i.e.*, the lipophilic and hydrophilic surfactants) individually has solvent characteristics and contributes, in part, to solubilizing the testosterone ester. In this way, without being bound by or limited to theory, the present invention does not require additional solvents, such as co-solvents, to solubilize the testosterone ester, but these may be optionally included in the inventive pharmaceutical products, systems and formulations.

[0094] Optional co-solvents 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 co-solvents, especially ethanol or other monoalkanols, are excluded altogether.

[0095] 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).

[0096] In other embodiments of the present invention, methods and pharmaceutical products for modulating (*i.e.*, sustaining) the rate of available serum testosterone by incorporating component(s) that may biochemically modulate (1) testosterone ester absorption, (2) testosterone ester 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 testosterone ester absorption. In this way, more testosterone esters 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 the testosterone ester. Examples of other esters or combinations thereof include botanical extracts or benign esters used as food additives (*e.g.*, propylparben, octylacetate and ethylacetate).

[0097] Other components that can modulate testosterone ester 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 a testosterone ester 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 testosterone ester metabolism. Other than within borage oil, of course, GLA could be added directly as a separate component of a testosterone ester formulation described herein. 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.

[0098] 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.

[0099] 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.*

[00100] 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 PK 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.

[00101] The following relative concentrations, by weight, are preferred (the percentages are based on the total weight of the testosterone ester formulation, not counting any anti-hypertensive agent which may be present in 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%

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

[00102] The formulations comprising a testosterone ester described herein have self-emulsifying properties, forming a fine emulsion upon dilution with aqueous media or intestinal fluids *in vivo*. In other words, these 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 testosterone ester formulations described herein 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.

[00103] The pharmaceutical compositions comprising a testosterone ester described herein 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 or magnesium aluminometasilicate, and layered 2:1 phyllosilicates, such as montmorillonite, smectite clay minerals such as montmorillonite, nontronite, beidellite, volkonskoite, hectorite, saponite, sauconite, sobockite, stevensite, and svinfordite, to obtain free-flowing powders which can be either filled into hard capsules or compressed into tablets. See, *e.g.*, US 2003/0072798, Aguzzi *et al.*, *Applied Clay Science* 36 (2007) 22-36. 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.

[00104] The pharmaceutical products described herein comprise a testosterone ester 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 testosterone ester compositions 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 delivery systems and formulations comprising a testosterone ester described herein are not limited to any one encapsulation method, specific encapsulation techniques need not be discussed further.

[00105] The drug carrier systems and pharmaceutical preparations comprising a testosterone ester described herein may be prepared by conventional techniques for lipid-based drug carrier systems. In a typical procedure for the preparation of the preferred testosterone ester carrier systems, 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 testosterone ester 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 affected 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 testosterone ester.

[00106] In a situation in which testosterone ester is weighed and added to a combined lipid mixture, mixing is continued, preferably at high temperature, until a homogenous solution is prepared. The testosterone ester 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.

[00107] Returning now to the delivery of testosterone, the pharmaceutical products 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 testosterone ester formulations described herein. Generally, "free" medicaments described herein refer to medicament that is accessible to metabolic enzymes circulating in serum.

[00108] 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 undecanoate acid ester of testosterone, in particular, can yield superior bioavailability to that found with other equivalent esters (*e.g.*, TE).

[00109] Table 2 provides composition details of various formulations of TU. For calculation purposes, 1 mg of T is equivalent to 1.58 mg T-undecanoate.

[00110] 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, not counting any anti-hypertensive agent which may be present in the formulation. 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).

[00111] 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 2 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 3 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 (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

F.	Composition % w/w (mg/ "00" capsule)[1]							Fill Wt. (mg)[2]
	TU	Oleic Acid	Cremophor® RH40	Borage Oil	Peppermint Oil	BHT	Ascorbyl Palmitate	
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

[00112] Examples of formulations of TU filled into size "00" capsules 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**

Formulation C

Ingredients	**mg/capsule**	**%, w/w**
Testosterone Undecanoate	120	15
Cremophor RH 40	128	16
Maisine 35-1	504	63
Polyethylene Glycol 8000	48	6
TOTAL	800	100

[00113] *In vivo* and *in vitro* performance data of the testosterone ester formulations are described below. However, the scope of the invention should not be limited by following examples nor the specific formulations studied in the examples.

EXAMPLES

Example 9 – Liquid-Filled Capsule Fixed-Dose Combinations.

[00114] A liquid self-emulsifying drug delivery system (SEDDS) formulation of a testosterone ester (*e.g.*, TU) such as Formulation A or B, (or alternatively a SMEDDS or SNEDDS testosterone ester formulation) is mixed with an anti-hypertensive agent, a mineralocorticoid antagonist, or an epithelial Na-channel blocker, either alone or in combination with one or more further excipients, and the resulting mixture is then filled into "00" capsules. A SEDDS formulation of a testosterone ester (e.g., TU) which is semi-solid at room temperature but liquid at 37 °C or higher temperature can also be prepared using high melting point lipophilic surfactants, such as Precirol ATO5 (glyceryl palmitostearate), or high melting point polyethylene glycol (PEG), such as PEG with a molecular weight greater than 600 and preferably greater than 1,000 g/mol, and upon mixing with one or more

aldosterone antagonist and other excipients at high temperature is subsequently filled into "00" capsules.

Example 10 – Solid Fixed-Dose Combinations.

[00115] A liquid self-emulsifying drug delivery system (SEDDS) formulation of a testosterone ester (*e.g.*, TU) such as Formulation A or B, (or alternatively a SMEDDS or SNEDDS TU formulation) is adsorbed onto solid carrier particles, such as silicon dioxide, calcium silicate, magnesium aluminometasilicate, or 2:1 layered phyllosilicate to obtain a free-flowing powder. This powder is mixed with an anti-hypertensive agent, a mineralocorticoid antagonist, or an aldosterone antagonist, and upon mixing with other solid dose excipients, such as fillers, diluents, disintegrants and lubricants, the resulting mixture is then either filled into hard capsules or compressed into tablets.

Example 11 – Solid Fixed-Dose Combinations

[00116] A liquid SEDDS of a testosterone ester (*e.g.*, TU) is mixed with a liquid SEDDS of an anti-hypertensive agent, a mineralocorticoid antagonist, or an aldosterone antagonist, or an epithelial Na-channel blocker, at the desired ratio and the mixture is then adsorbed onto solid carrier particles. Upon mixing with other solid dose excipients, the mixture is then either filled into hard gelatin capsules or compressed into tablets.

Example 12 – Adsorption of Liquid TU Compositions onto a Carrier: Liquid Loaded Tablets (LLT)

[00117] Liquid compositions of TU (SEDDS) are adsorbed onto solid carriers to improve the flow properties of the lipids and along with other solid dose excipients such as diluents, fillers and disintegrants used to prepare free flowing powders which can then be filled into hard shell capsules or compressed into tablets. Suitable solid adsorbents include: a) porous SiO_2, 300 m^2/g, 3.2 μm (Sylysia 320) and 500 m^2/g, 3.9 μm (Sylysia 550), b) porous calcium silicate, 120 m^2/g, 26.1 μm (Florite RE) and c) magnesium aluminometasilicate, 280 m^2/g, 75 μm (Neusilin® US2) and 110 m^2/g, 100 μm (Neusilin S2). Suitable diluents and fillers include microcrystalline cellulose and lactose. Suitable disintegrants include copovidone and croscarmellose. Wetting agents such as sodium lauryl phosphate (SLS) and lubricants such as magnesium stearate may also be included. The above list of diluents, fillers, and disintegrants, as well as other pharmaceutical excipients, is not meant to be exhaustive but merely illustrative as a person of ordinary skill in the art would recognize that additional types and combination of excipients could be used to achieve the desired in vitro dissolution and in vivo pharmacokinetics.

Example 13 – Preparation of TU Liquid Loaded Tablets (LLTs)

[00118] 50 g of a SEDDS liquid formulation of TU is first prepared as described in US 8,492,369 having the following composition (%, w/w): TU (19.8), oleic acid (51.6), Cremophor® RH40 (16.1),

borage oil (10.0), peppermint oil (2.5) and BHT (0.03). For the adsorption onto a solid carrier, 25 g of the SEDDS liquid formulation of TU is transferred into a 500 mL glass beaker equipped with a lab scale mixer using a twisted blade stirrer. Subsequently, 25 g of Neusilin® US2 adsorbent is added gradually to the beaker and the mixture is stirred at a speed of 500-700 rpm. Stirring is continued for additional 5-10 min after the addition of the adsorbent is completed in order to break down any large aggregates (lumps) of the mixture. A free flowing powder is obtained at the end of the mixing process. The free flowing powder can be passed through an 800 μm sieve to remove any not visible lumps that they be present in the formulation. Standard USP tests are used to determine the flow characteristics of the powder and include, the angle of repose, Carr's compressibility index and the Hausner ratio. The resulting free flowing powder is either filled directly into hard gelatin capsules or compressed into tablets. For the preparation of an 840 mg tablet, 748 mg of the free flowing powder is mixed with 84 mg of croscarmellose sodium, a cross-linked carboxy methyl cellulose which acts as a superdisintegrant, and 8.4 mg of magnesium stearate (lubricant) and compressed at an optimum pressure of 130-160 MPa. The tensile strength and friability of the LLT1 is measured using standard methodology. The dissolution of the LLT is determined and compared to that of free flowing powder filled into hard gelatin capsules. The composition of the free flowing powder and/or the compressed tablets as well as the various process parameters are adjusted as needed in order to optimize the *in vitro* dissolution of TU from LLTs. LLTs of TU can readily be prepared using other TU liquid compositions (SEDDS).

Example 14 – Liquid and Tablet Formulations of TU Incorporating a Eutectic Mixture of TU with Essential Oil

[00119] The formation of the eutectic mixture between TU and an essential oil at various ratios (w/w) of TU to the essential oil is monitored through a m.p. depression of TU using differential scanning calorimetry. The essential oil is selected from the group consisting of menthol, peppermint oil, spearmint oil, anise oil, and lemon oil, and mixtures thereof. The essential oil is preferably peppermint oil. The preferred ratio of TU to the essential oil is 1:1 (w/w). For the formation of a liquid or semi-solid SEDDS formulation of TU, the eutectic mixture is solubilized in a lipophilic and hydrophilic surfactant. Preferred lipophilic surfactants include oleic acid, glycerol monolein (Peceol™), glycerol monolinoleate (Maisine™ 35-1), glyceryl palmitostearate (Precirol ATO5), C_8/C_{10} mono-/diglycerides (Capmul® MCM) and mixtures thereof. Cremophor® EL and Cremophor® RH40 are the preferred hydrophilic surfactants. The resulting liquid or semi-solid formulation of TU are filled into hard or soft gelatin capsules or mixed with solid dose excipients to produce free flowing powders which can be filled into capsules or compressed into tablets. Exemplary compositions are provided in Tables 3-5 below

Table 3: Liquid SEDDS formulations of a TU-Peppermint Oil Eutectic Mixture

Component	% w/w
TU	15
Peppermint Oil	15
Oleic Acid/Maisine 35-1/Capmul® MCM	50
Cremophor EL/Cremophor RH40	20
TOTAL	100

Table 4: A liquid loaded tablet composition of TU-Peppermint Oil Eutectic Mixture

Component	% w/w
Neusilin® US2 (1:1)	89
Croscarmellose Sodium	10
Magnesium Stearate	1
TOTAL	100

Table 5: A liquid loaded tablet composition of TU without Neusilin® US2

Component	% w/w
TU	10
Peppermint oil	10
Capmul MCM/Oleic Acid/Maisine 35-1	20
Cremophor EL/Cremophor RH40	10
Copovidone	10
Maltodextrin	30
Microcrystalline Cellulose (Avicel PH112)	10

Example 15 – Radioligand Bind Assays

[00120] Testosterone and aldosterone were evaluated in radioligand binding assays to determine activity. Methods employed in this study have been adapted from the scientific literature to maximize reliability and reproducibility, see for example Farman N, Vandewalle A and Bonvalet JP (1981) Am J Physiol. 240(1): C20-27 and Wambach G and Casals-Stenzel J (1983) Biochem Pharmacol. 32(9): 1479-1485. Reference standards were run as an integral part of each assay to ensure the validity of the results obtained.

[00121] Where presented, IC50 values were determined by a non-linear, least squares regression analysis using MathIQTM (ID Business Solutions Ltd., UK). Where inhibition constants (K_I) are presented, the Ki values were calculated using the equation of Cheng and Prusoff (Cheng, Y., Prusoff,

W.H., Biochem. Pharmacol. 22:3099-3108, 1973) using the observed IC50 of the tested compound, the concentration of radioligand employed in the assay, and the historical values for the KD of the ligand (obtained experimentally at Eurofins Panlabs, Inc.). Where presented, the Hill coefficient (n_H), defining the slope of the competitive binding curve, was calculated using MathIQTM. A summary of results is shown in Table 6.

Table 6: Results of Radioligand Assay

Compound Name	IC50	K_I	n_H
Testosterone	0.53 μM	0.41 μM	0.93
D-Aldosterone	7.15 nM	5.58 nM	0.98

[00122] 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.

We claim:

1. A pharmaceutical product comprising one or more pharmaceutical compositions, wherein said one or more pharmaceutical compositions comprise:

    a. an anti-hypertensive agent chosen from an aldosterone antagonist and an epithelial Na-channel blocker; and

    b. a testosterone replacement therapy (TRT).

2. The pharmaceutical product of claim 1, wherein said aldosterone antagonist is chosen from spironolactone, eplerenone, canrenone and potassium canrenoate, and finerenone.

3. The pharmaceutical product of claim 2, wherein said aldosterone antagonist is chosen from spironolactone and eplerenone.

4. The pharmaceutical product of claim 1, wherein said aldosterone antagonist is chosen from progesterone, drospirenone, gestodene, and benidipine.

5. The pharmaceutical product of claim 1, wherein said epithelial Na-channel blocker is chosen from amiloride and triamterene.

6. The pharmaceutical product of claim 1 said TRT comprises oral administration of a testosterone ester.

7. The pharmaceutical product of claim 6, wherein said testosterone ester is testosterone undecanoate.

8. The pharmaceutical product of claim 7, wherein said testosterone undecanoate is solubilized in a carrier comprising at least one lipophilic surfactant and at least one hydrophilic surfactant, wherein the total lipophilic surfactant to total hydrophilic surfactant ratio (w/w) in the carrier falls in the range of about 6:1 to 3.5:1.

9. The pharmaceutical product of claim 8, wherein said hydrophilic surfactant comprises Cremophor® RH 40 (polyoxyethyleneglycerol trihydroxystearate).

10. The pharmaceutical product of claim 8, wherein said lipophilic surfactant comprises oleic acid.

11. The pharmaceutical product of claim 8, wherein said lipophilic surfactant comprises Maisine 35-1 (glyceryl monolinoleate).

12. The pharmaceutical product of claim 1, wherein said TRT comprises injection of testosterone or a testosterone ester.

13. The pharmaceutical product of claim 12, wherein said testosterone ester is chosen from testosterone undecanoate, testosterone cypionate, testosterone propionate, and testosterone enanthate, and combinations thereof.

14. The pharmaceutical product of claim 1, wherein said TRT comprises transdermal, nasal, or buccal administration of testosterone.

15. A method of treating testosterone deficiency or its symptoms comprising orally administering to an individual suffering from testosterone deficiency or its symptoms an effective amount of a pharmaceutical product of any one of claims 1 to 14.

16. The method of claim 14 in which said one or more pharmaceutical compositions are administered once daily.

17. The method of claim 14 in which said one or more pharmaceutical compositions are administered twice daily.

18. The method of any one of claims 14 to 16 which gives rise to a testosterone C_{max} value in said individual falling in the range of about 900 to 1100 ng/dL.

19. The method of claim 5, in which said one or more pharmaceutical compositions are administered to said individual with a meal comprising at least 20 wt% fat.

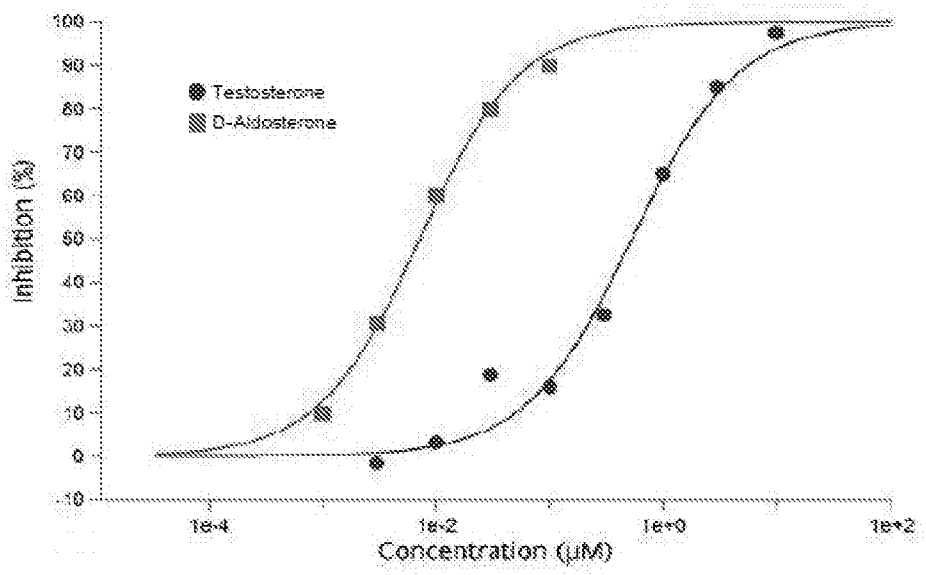
20. The method of any one of claims 14 to 18, which gives rise to substantially no diurnal testosterone pharmacokinetic variation in said individual.

21. The method of any one of claims 14 to 19, which gives rise to an average serum testosterone T_{max} value in said individual falling in the range of about 3 to 7 hours after oral administration to said individual.

22. The method of claim 20 in which the average serum T_{max} value in said individual falls in the range of about 4 to 5 hours after oral administration.

23. The method of any one of claims 14 to 21 in which substantially no significant decline in steady state serum testosterone response is observed in said individual upon repeat dosing to said individual.

Figure 1.


Testosterone
D-Aldosterone
Inhibition (%)
100
90
80
70
60
50
40
30
20
10
0
-10
1e-4
1e-2
1e+0
1e+2
Concentration (µM)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/27481

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/568; A61K 47/12; A61K 47/44 (202.01)

CPC - A61K 31/568; A61K 47/12; A61K47/44; A61K 9/0053

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 102883710 B (Clarus Therapeutics Inc.) 10 September 2014 (10.09.2014); entire document, especially abstract, pg 2 para 2, pg 2 para 5, pg 3 para 1-2, pg 3 para 4, pg 4 para 7, pg 5 para 3	1, 4, 6-14, 15/(1, 4, 6-14), 16-17 --- 19
X	US 2008/0317844 A1 (Dudley et al.) 25 December 2008 (25.12.2008); entire document, especially abstract, [0033], [0055]	1-3, 5, 15/(1-3, 5) --- 19
A	US 2005/0220825 A1 (Funke et al.) 06 October 2005 (06.10.2005); entire document	1-17, 19
A	US 2011/0142945 A1 (Chen et al.) 16 June 2011 (16.06.2011); entire document	1-17, 19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2020	01 JUL 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/27481

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 18, 20-23
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.