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(54) **FORMULATIONS OF A NANOPARTICULATE FINASTERIDE, DUTASTERIDE OR TAMSULOSIN HYDROCHLORIDE, AND MIXTURES THEREOF**

(75) Inventors: **Gary Liversidge**, Westchester, PA (US); **Scott Jenkins**, Downingtown, PA (US)

Correspondence Address:
ELAN DRUG DELIVERY, INC.
C/O FOLEY & LARDNER LLP
3000 K STREET, N.W.
SUITE 500
WASHINGTON, DC 20007-5109 (US)

(73) Assignee: **Elan Pharma International Limited**

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(57) **ABSTRACT**

Described are nanoparticulate compositions of finasteride, dutasteride, tamsulosin hydrochloride, or a combination thereof. The formulations exhibit unexpectedly prolonged release and can be maintained in a depot for release to a patient for a period of up to six months.

FORMULATIONS OF A NANOPARTICULATE FINASTERIDE, DUTASTERIDE OR TAMSULOSIN HYDROCHLORIDE, AND MIXTURES THEREOF

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] The invention is directed to a nanoparticulate formulations of finasteride, dutasteride, or tamsulosin hydrochloride, or any combination thereof. The compositions of the invention, which surprisingly can be formulated into injectable depot dosage forms, are particularly useful in the treatment of benign prostatic hyperplasia. The invention also comprises methods of making and using such formulations.

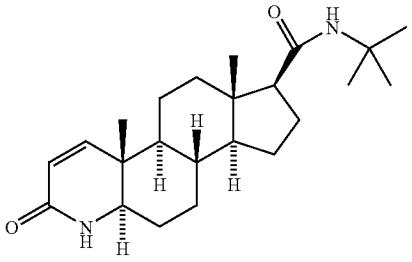
[0003] 2. Description of the Related Art

A. Background Regarding the Compounds of the Invention and Methods of Treatment

[0004] 1. Finasteride

[0005] Finasteride is a synthetic androgen inhibitor used primarily in men for the treatment of benign prostatic hyperplasia and androgenetic alopecia (hairloss). Finasteride, a synthetic, 4-azasteroid compound, is a specific inhibitor of steroid Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into 5α-dihydrotestosterone.

[0006] The compound is known chemically as (5alpha, 17beta)-N-(1,1-dimethylethyl)-3-oxo-4-azaandrost-1-ene-17-carboxamide. Finasteride is insoluble in water and soluble in chloroform and alcohol. The empirical formula of finasteride is $C_{23}H_{36}N_2O_2$ and its molecular weight is 372.55. Finasteride has the following structure:



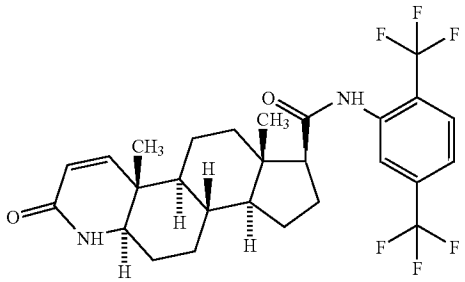
[0007] Finasteride is a white crystalline powder with a melting point near 250° C. It is freely soluble in chloroform and in lower alcohol solvents, but is practically insoluble in water. Finasteride is commercially available under the trade name PROSCAR®. PROSCAR® tablets (Merck & Co., Inc. (West Point, Pa.)) for oral administration are film-coated and contain 5 mg of finasteride and the following inactive ingredients: hydrous lactose, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, hydroxypropyl cellulose LF, hydroxypropylmethyl cellulose, titanium dioxide, magnesium stearate, talc, docusate sodium, FD&C Blue 2 aluminum lake and yellow iron oxide.

[0008] PROSCAR® is recommended for the treatment of symptomatic benign prostatic hyperplasia in men with an enlarged prostate to: improve symptoms; reduce the risk of prostatectomy. *Physician's Desk Reference* 58th Edition (Thompson PDR, Montvale, N.J., 2004) pp. 10, 325 and 2070-73.

[0009] 2. Dutasteride

[0010] Dutasteride is a synthetic 4-azasteroid compound which is an antiandrogen which inhibits the conversion of testosterone into dihydrotestosterone. Clinical studies have found it to be more effective than finasteride in doing so, as it inhibits both isoforms of steroid 5-alpha reductase (5AR), an intracellular enzyme that converts testosterone to dihydrotestosterone (DHT). Dutasteride is indicated for the treatment of symptomatic BPH in men with an enlarged prostate to: improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for BPH-related surgery. Dutasteride is currently in trial phase for the treatment of alopecia (hairloss).

[0011] Dutasteride is known chemically as (5α, 17β)-(2,5 bis-(trifluoromethyl)phenyl)-3-oxo-4-azaandrost-1-ene-17-carboxamide. The empirical formula is $C_{27}H_{30}F_6N_2O_2$, representing a molecular weight of 528.5. The compound has the following structure:



[0012] Dutasteride is a white to pale yellow powder with a melting point of 242° C. to 250° C. It is soluble in ethanol (44 mg/mL), methanol (64 mg/mL) and polyethylene glycol 400 (3 mg/mL), but it is insoluble in water.

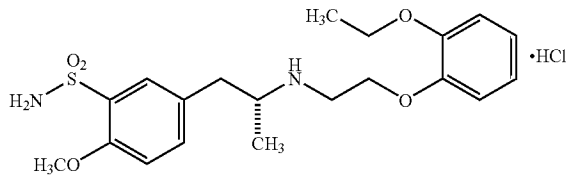
[0013] Dutasteride is commercially available under the trade name AVODART®. AVODART® Soft Gelatin Capsules (GlaxoSmithKline (Research Triangle Park, N.C.)) for oral administration contain 0.5 mg of the active ingredient dutasteride in yellow capsules with red print. Each capsule contains 0.5 mg dutasteride dissolved in a mixture of mono-di-glycerides of caprylic/capric acid and butylated hydroxytoluene. The inactive excipients in the capsule shell are gelatin (from certified BSE-free bovine sources), glycerin, and ferric oxide (yellow). The soft gelatin capsules are printed with edible red ink.

[0014] AVODART® (dutasteride) is a synthetic 4-azasteroid compound that is a selective inhibitor of both the type 1 and type 2 isoforms of steroid 5α-reductase (5AR), an intracellular enzyme that converts testosterone to 5α-dihydrotestosterone. *Physician's Desk Reference,* 58th Ed. (Thompson PDR, Montvale, N.J., 2004) pp. 316 and 1456-59.

[0015] 3. Tamsulosin Hydrochloride

clinically as an oral medication to ameliorate the dysuria associated with prostatic hypertrophy.

[0017] Tamsulosin hydrochloride is known chemically as (−)-(R)-5-[2-[[2-(0-ethoxyphenoxy) ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride. Tamsulosin hydrochloride occurs as white crystals that melt with decomposition at approximately 230° C. It is sparingly soluble in water and in methanol, slightly soluble in glacial acetic acid and in ethanol, and practically insoluble in ether. The compound has the following structure:



The empirical formula of tamsulosin hydrochloride is $C_{20}H_{28}N_2O_5S.HCl$. The molecular weight of tamsulosin hydrochloride is 444.98.

[0018] Tamsulosin hydrochloride is commercially available under the trade name FLOMAX®. FLOMAX® capsules (Boehringer Ingelheim (Ridgefield, Conn.)) for oral administration contain tamsulosin hydrochloride 0.4 mg, and the following inactive ingredients: methacrylic acid copolymer, microcrystalline cellulose, triacetin, polysorbate 80, sodium lauryl sulfate, calcium stearate, talc, FD&C blue No. 2, titanium dioxide, ferric oxide, gelatin, and trace amounts of shellac, industrial methylated spirit 74 OP, n-butyl, alcohol, isopropyl alcohol, propylene glycol, dimethylpolysiloxane, and black iron oxide E172.

[0019] Tamsulosin, an alpha$_1$ adrenoceptor blocking agent, exhibits selectivity for alpha$_1$ receptors in the human prostate. At least three discrete alpha$_1$-adrenoceptor subtypes have been identified: alpha$_{1A}$, alpha$_{1B}$ and alpha$_{1D}$; their distribution differs between human organs and tissue. Approximately 70% of the alpha$_1$-receptors in the human prostate are of the alpha$_{1A}$ subtype. *Physician's Desk Reference,* 58th Edition (Thompson PDR, Montvale, N.J., 2004) pp. 4, 310 and 1006.

[0020] 4. Treatment of Prostatic Hyperplasia

[0021] The prostate gland is located around the tube which empties urine from the bladder (urethra). As the prostate gland enlarges, usually after 50 years of age, it can obstruct or partially block the urine flow. This leads to symptoms which include dribbling of urine, narrow stream, problems starting urine flow, interruption while urinating, and a feeling of incomplete emptying. Other symptoms include wetting and staining of clothes, urinary burning, and urgency.

[0022] Prostate gland enlargement (Benign Prostatic Hyperplasia or BPH), is directly dependent on DHT (a hormone converted from the male hormone testosterone). Finasteride inhibits the enzyme necessary for the conversion of testosterone to DHT in the prostate. Therefore, administration of finasteride lowers blood and tissue DHT levels and helps reduce the size of the prostate gland.

is comprised of two underlying components: static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of benign prostatic hyperplasia symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of alpha$_1$ adrenoceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of benign prostatic hyperplasia.

[0024] Treatment of benign prostatic hyperplasia is generally required over the remaining life of a patient. Current pharmaceutical compositions used in such treatment which are typically in the form of tablets or capsules taken daily, are inconvenient as they require ongoing patient compliance. The administration of such dosages may be forgotten, which lessens the efficacy of the treatment. Alternative dosage forms of drugs useful in treating BPH are therefore desirable.

B. Background Regarding Nanoparticulate Active Agent Compositions

[0025] Nanoparticulate active agent compositions, first described in U.S. Pat. No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto or associated with the surface thereof a non-crosslinked surface stabilizer. The '684 patent does not describe nanoparticulate compositions of finasteride, dutasteride, or tamsulosin hydrochloride.

[0026] Methods of making nanoparticulate active agent compositions are described in, for example, U.S. Pat. Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

[0027] Nanoparticulate active agent compositions are also described, for example, in U.S. Pat. No. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" U.S. Pat. No. 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" U.S. Pat. No. 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" U.S. Pat. No. 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" U.S. Pat. No. 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" U.S. Pat. No. 5,349,957 for "Preparation and

Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. Nos. 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" U.S. Pat. No. 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" U.S. Pat. No. 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" U.S. Pat. No. 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" U.S. Pat. No. 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,518,738 for "Nanoparticulate NSAID Formulations;" U.S. Pat. No. 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" U.S. Pat. No. 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,552,160 for "Surface Modified NSAID Nanoparticles;" U.S. Pat. No. 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" U.S. Pat. No. 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" U.S. Pat. No. 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" U.S. Pat. No. 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" U.S. Pat. No. 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" U.S. Pat. No. 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" U.S. Pat. No. 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" U.S. Pat. No. 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" U.S. Pat. No. 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" U.S. Pat. No. 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" U.S. Pat. No. 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and

stances;" U.S. Pat. No. 5,718,919 for "Nanoparticles Containing the R(−)Enantiomer of Ibuprofen;" U.S. Pat. No. 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" U.S. Pat. No. 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" U.S. Pat. No. 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" U.S. Pat. No. 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" U.S. Pat. No. 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" U.S. Pat. No. 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" U.S. Pat. No. 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" U.S. Pat. No. 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" U.S. Pat. No. 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," U.S. Pat. No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" U.S. Pat. No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" U.S. Pat. No. 6,431,478 for "Small Scale Mill;" U.S. Pat. No. 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," U.S. Pat. No. 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," U.S. Pat. No. 6,582,285 for "Apparatus for sanitary wet milling;" U.S. Pat. No. 6,656,504 for "Nanoparticulate Compositions Comprising Amorphous Cyclosporine;" U.S. Pat. No. 6,742,734 for "System and Method for Milling Materials;" 6,745,962 for "Small Scale Mill and Method Thereof;" U.S. Pat. No. 6,811,767 for "Liquid droplet aerosols of nanoparticulate drugs;" and U.S. Pat. No. 6,908,626 for "Compositions having a combination of immediate release and controlled release characteristics;" U.S. Pat. No. 6,969,529 for "Nanoparticulate compositions comprising copolymers of vinyl pyrrolidone and vinyl acetate as surface stabilizers;" U.S. Pat. No. 6,976,647 for "System and Method for Milling Materials," all of which are specifically incorporated by reference. In addition, U.S. Patent Application No. 20020012675 A1, published on Jan. 31, 2002, for "Controlled Release Nanoparticulate Compositions," describes nanoparticulate compositions, and is specifically incorporated by reference. None of these patents describe nanoparticulate formulations of dutasteride or tamsulosin hydrochloride, although U.S. Patent Application No. 20020012675 A1 refers to controlled release formulations of finasteride. Moreover, none of the patents or patent publications describe injectable depot dosage forms of nanoparticulate dutasteride, tamsulosin hydrochloride, or finasteride.

[0028] Amorphous small particle compositions are

Agent;" U.S. Pat. No. 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" U.S. Pat. No. 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" U.S. Pat. No. 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and U.S. Pat. No. 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

[0029] Because finasteride, dutasteride, and tamsulosin hydrochloride are poorly water soluble, and because these drugs are useful in treating chronic conditions requiring long term and periodic treatment, improved dosage forms having increased bioavailability and prolonged activity are desirable. The present invention satisfies these needs.

SUMMARY OF THE INVENTION

[0030] It is an object of the invention to provide compositions comprising nanoparticulate finesteride, nanoparticulate dutasteride, nanoparticulate tamsulosin hydrochloride, or a combination thereof, wherein the nanoparticulate finesteride, dutasteride, and/or tamsulosin hydrochloride have an effective average particle size of less than about 2000 nm. It is preferred that the active agent have adsorbed onto or associated with the surface of the active agent at least one surface stabilizer.

[0031] It is another object of the invention to provide formulations comprising a pharmaceutically effective nanoparticulate finesteride, dutasteride, and/or tamsulosin hydrochloride composition for the treatment of benign prostatic hyperplasia in mammals, in particular, in human patients.

[0032] It is a further object of the invention to provide methods of making a formulation for the treatment of benign prostatic hyperplasia.

[0033] It is a further object of the invention that the compositions of the invention be sufficiently stable so that a depot comprising one quantity or batch of the composition can provide continuous intramuscular or subcutaneous release of the composition to a patient or subject for up to about six months. In other embodiments of the invention, the release of the active agent is over alternative periods of time, such as up to about one week, up to about two weeks, up to about three weeks, up to about one month, up to about two months, up to about three months, up to about four months, or up to about five months.

[0034] In human therapy, it is important to provide a dosage form that delivers the required therapeutic amount of the active ingredient in vivo, and that renders the active ingredient bioavailable in a rapid and constant manner. The nanoparticulate formulations of the invention, which can be administered intramuscularly and subcutaneously, satisfy these needs.

[0035] The objectives are accomplished by a composition comprising at least one of finasteride, dutasteride, and tamsulosin hydrochloride which are collectively referred to in the application as the "active ingredient." The formulation of the invention comprises the active ingredient having a surface stabilizer adsorbed on or associated with the surface of the active ingredient. In one embodiment of the invention, [illegible] effective average particle size of less than about 2000 nm. In yet other embodiments of the invention, the effective average particle size of the nanoparticulate active ingredient is less than about 1000 nm, less than about 600 nm, less than about 450 nm, less than about 300 nm, less than about 250 nm, or less than about 100 nm.

[0036] The invention provides for compositions comprising concentrations of the active ingredient with rapid dissolution of the active ingredient upon administration.

[0037] In another aspect of the invention there is provided a method of preparing a nanoparticulate formulation of the active ingredient. The method comprises: (1) dispersing the active ingredient in a liquid dispersion medium; and (2) mechanically reducing the particle size of the active ingredient to an effective average particle size of less than about 2000 nm. A surface stabilizer, such as a povidone polymer with a molecular weight of less than about 40,000 daltons, can be added to the dispersion media either before, during, or after particle size reduction. Preferably, the pH of the liquid dispersion medium is maintained within the range of from about 3 to about 8 during the size reduction process.

[0038] Yet another aspect of the invention provides a method of treating a mammal, in particular, a human patient, for benign prostatic hyperplasia, comprising administering to the mammal a nanoparticulate active agent composition according to the invention. In yet another embodiment, the compositions of the invention are useful in treating alopecia.

[0039] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0040] The present invention is directed to the surprising and unexpected discovery that the pharmaceutical formulations or compositions of the invention for treatment of benign prostatic hyperplasia, or alopecia, can be intramuscularly or subcutaneously released continuously to a patient over a prolonged period of time, namely for up to about six months. The duration of release of the formulation is dependent upon the particle size of the active ingredient. The effective average particle size of the active ingredient is less than about 2000 nm, although smaller particle sizes are described herein, such less than about 600 nm, less than about 450 nm, less than about 300 nm, less than about 250 nm, or less than about 100 nm. The formulation comprises the nanoparticulate active ingredient with a surface stabilizer adsorbed onto or associated with the surface of the active ingredient particles. In one embodiment of the invention, the surface stabilizer is a povidone polymer having a molecular weight of not more than about 40,000 daltons.

[0041] The compositions comprise nanoparticles of at least one of finasteride, dutasteride and tamsulosin hydrochloride. Alternatively, the composition can be described as comprising nanoparticles of finasteride, dutasteride and tamsulosin hydrochloride, and mixtures thereof. The referenced [illegible]

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