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(54) **NANOPARTICULATE BENZOTHIOPHENE FORMULATIONS**

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(57) **ABSTRACT**

The present invention is directed to benzothiophene compositions, preferably nanoparticulate raloxifene hydrochloride compositions having improved pharmacokinetic profiles, improved bioavailability, dissolution rates and efficacy. In one embodiment, the raloxifene hydrochloride nanoparticulate composition have an effective average particle size of less than about 2000 nm.

NANOPARTICULATE BENZOTHIOPHENE FORMULATIONS

FIELD OF THE INVENTION

[0001] This invention relates to the fields of pharmaceutical and organic chemistry and provides a benzothiophene compound, such as a raloxifene hydrochloride compound, in nanoparticulate form, which is useful for the treatment of various medical indications, including osteoporosis.

BACKGROUND OF THE INVENTION

[0002] Background Regarding Nanoparticulate Compositions

[0003] Osteoporosis describes a group of diseases which arise from diverse etiologies, but which are characterized by the net loss of bone mass per unit volume. The consequence of this loss of bone mass and resulting bone fracture is the failure of the skeleton to provide adequate structural support for the body. One of the most common types of osteoporosis is that associated with menopause. Most women lose from about 20% to about 60% of the bone mass in the trabecular compartment of the bone within 3 to 6 years after the cessation of menses. This rapid loss is generally associated with an increase of bone resorption and formation. However, the resorptive cycle is more dominant and the result is a net loss of bone mass. Osteoporosis is a common and serious disease among post-menopausal women.

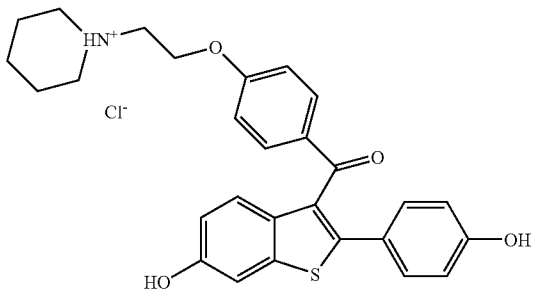
[0004] There are an estimated 25 million women in the United States, alone, who are afflicted with this disease. The results of osteoporosis are personally harmful and also account for a large economic loss due to its chronicity and the need for extensive and long term support (hospitalization and nursing home care) from the disease sequelae. This is especially true in more elderly patients. Additionally, although osteoporosis is not generally thought of as a life threatening condition, a 20% to 30% mortality rate is related with hip fractures in elderly women. A large percentage of this mortality rate can be directly associated with post-menopausal osteoporosis.

[0005] Before menopause time, most women have less incidence of cardiovascular disease than age-matched men. Following menopause, however, the rate of cardiovascular disease in women slowly increases to match the rate seen in men. This loss of protection has been linked to the loss of estrogen and, in particular, to the loss of estrogen's ability to regulated the levels of serum lipids. The nature of estrogen's ability to regulate serum lipids is not well understood, but evidence to date indicates that estrogen can up regulate the low density lipid (LDL) receptors in the liver to remove excess cholesterol. Additionally, estrogen appears to have some effect on the biosynthesis of cholesterol, and other beneficial effects on cardiovascular health.

[0006] It has been reported in the literature that post-menopausal women having estrogen replacement therapy have a return of serum lipid levels to concentrations to those of the pre-menopausal state. Thus, estrogen would appear to be a reasonable treatment for this condition. However, the side-effects of estrogen replacement therapy are not acceptable to many women, thus limiting the use of this therapy. An ideal therapy for this condition would be an agent which would regulate the serum lipid level as does estrogen, but

[0007] Preclinical findings with a structurally distinct "anti-estrogen", raloxifene hydrochloride, have demonstrated potential for improved selectivity of estrogenic effects in target tissues. Similar to tamoxifen, raloxifene hydrochloride was developed originally for treatment of breast cancer; however, the benzothiophene nucleus of raloxifene hydrochloride represented a significant structural deviation from the triphenylethylene nucleus of tamoxifen. Raloxifene hydrochloride binds with high affinity to the estrogen receptor, and inhibits estrogen-dependent proliferation in MCF-7 cells (human mammary tumor derived cell line) in cell culture. In vivo estrogen antagonist activity of raloxifene hydrochloride was furthermore demonstrated in carcinogen-induced models of mammary tumors in rodents. Significantly, in uterine tissue raloxifene hydrochloride was more effective than tamoxifen as an antagonist of the uterotrophic response to estrogen in immature rats and, in contrast to tamoxifen, raloxifene hydrochloride displayed only minimal uterotrophic response that was not dose-dependent in ovariectomized (OVX) rats. Thus, raloxifene hydrochloride is unique as an antagonist of the uterine estrogen receptor, in that it produces a nearly complete blockage of uterotrophic response of estrogen due to minimal agonist effect of raloxifene hydrochloride in this tissue. Indeed, the ability of raloxifene hydrochloride to antagonize the uterine stimulatory effect of tamoxifen was recently demonstrated in OVX rats. Raloxifene hydrochloride is more properly characterized as a Selective Estrogen Receptor Modulator (SERM), due to its unique profile. The chemical structure of raloxifene hydrochloride is:

FORMULA 1



The chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride. Raloxifene hydrochloride (CHl) has the empirical formula C 28 H 27 NO 4S.CHl, which corresponds to a molecular weight of 510.05. Raloxifene CHl is an off-white to pale-yellow solid that is very slightly soluble in water.

[0008] Raloxifene HCL is commercially available in tablet dosage form for oral administration (Eli Lilly, Indianapolis, Ind.). Each tablet is the molar equivalent of 55.71 mg free base with inactive ingredients that include anhydrous lactose, carnuba wax, crospovidone, FD&C Blue #2, aluminum lake, hypromellose, lactose monohydrate, and magnesium

[0009] Raloxifene hydrochloride and processes for its preparation are described and claimed in U.S. Pat. Nos. 5,393,763 and 5,457,117 to Black et al; U.S. Pat. No. 5,478,847 to Draper; U.S. Pat. Nos. 5,812,120 and 5,972,383 to Gibson et al., and U.S. Pat. Nos. 6,458,811 and 6,797,719 to Arbuthnat et al., all of which are incorporated herein by reference.

[0010] Nanoparticulate 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 a benzothiophene.

[0011] Methods of making nanoparticulate 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."

[0012] Nanoparticulate compositions are also described, for example, in U.S. Pat. Nos. 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 Magnetic Properties of Very Small Magnetic-Dextran Particles;" U.S. Pat. No. 5,352,459 for "Use of Purified Surface 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. 5,521,218 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 Lymphatic System Imaging;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 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

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;" and 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;" U.S. Pat. No. 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;" 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," and WO 02/098565 for "System and Method for Milling Materials," describe nanoparticulate compositions, and are specifically incorporated by reference.

[0013] Amorphous small particle compositions are described, for example, in U.S. Pat. No. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial 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."

SUMMARY OF THE INVENTION

[0014] The present invention relates to nanoparticulate compositions comprising a benzothiophene, preferably raloxifene hydrochloride. The compositions comprise a benzothiophene, preferably raloxifene hydrochloride, and at least one surface stabilizer adsorbed on or associated with the surface of the benzothiophene particles. The nanoparticulate benzothiophene, preferably raloxifene hydrochloride, particles have an effective average particle size of less than about 2000 nm. A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized.

[0015] Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate benzothiophene, preferably raloxifene hydrochloride, composition of the invention. The pharmaceutical compositions comprise a benzothiophene, preferably raloxifene hydro-

[0016] Another aspect of the invention is directed to a nanoparticulate benzothiophene, preferably raloxifene hydrochloride, composition having improved pharmacokinetic profiles as compared to conventional microcrystalline or solubilized benzothiophene formulations.

[0017] In yet another embodiment, the invention encompasses a benzothiophene, preferably raloxifene hydrochloride, composition, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

[0018] Another embodiment of the invention is directed to nanoparticulate benzothiophene, preferably raloxifene hydrochloride, compositions additionally comprising one or more compounds useful in treating osteoporosis, breast cancer, or related conditions.

[0019] This invention further discloses a method of making a nanoparticulate benzothiophene, preferably raloxifene hydrochloride, composition according to the invention. Such a method comprises contacting a benzothiophene, preferably raloxifene hydrochloride, and at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate benzothiophene composition, and preferably a raloxifene hydrochloride composition. The one or more surface stabilizers can be contacted with a benzothiophene, preferably raloxifene hydrochloride, either before, during, or after size reduction of the benzothiophene.

[0020] The present invention is also directed to methods of treatment using the nanoparticulate benzothiophene, preferably raloxifene hydrochloride, compositions of the invention for conditions such as osteoporosis, carcinomas of the breast and lymph glands, and the like.

[0021] 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

A. Introduction

[0022] The present invention is directed to nanoparticulate compositions comprising a benzothiophene, preferably raloxifene hydrochloride. The compositions comprise a benzothiophene, preferably raloxifene hydrochloride, and preferably at least one surface stabilizer adsorbed on or associated with the surface of the drug. The nanoparticulate benzothiophene, preferably raloxifene hydrochloride, particles have an effective average particle size of less than about 2000 nm.

[0023] Advantages of a nanoparticulate benzothiophene, preferably a nanoparticulate raloxifene hydrochloride, formulation of the invention include, but are not limited to: (1) smaller tablet or other solid dosage form size, or less frequent administration of the formulation; (2) smaller doses of drug required to obtain the same pharmacological effect as compared to conventional microcrystalline or solubilized forms of a benzothiophene; (3) increased bioavailability as

profiles, such as Tmax, Cmax, and AUC profiles as compared to conventional microcrystalline or solubilized forms of a benzothiophene; (5) substantially similar pharmacokinetic profiles of the nanoparticulate benzothiophene compositions when administered in the fed versus the fasted state; (6) bioequivalent pharmacokinetic profiles of the nanoparticulate benzothiophene compositions when administered in the fed versus the fasted state; (7) an increased rate of dissolution for the nanoparticulate benzothiophene compositions as compared to conventional microcrystalline or solubilized forms of the same benzothiophene; (8) bioadhesive benzothiophene compositions; and (9) use of the nanoparticulate benzothiophene compositions in conjunction with other active agents useful in treating osteoporosis, carcinomas of the breast and lymph glands and, related conditions.

[0024] The present invention also includes nanoparticulate benzothiophene, preferably nanoparticulate raloxifene hydrochloride compositions, together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (e.g., intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

[0025] A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized. Exemplary solid dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, or granules, and the solid dosage form can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof. A solid dose tablet formulation is preferred.

B. Definitions

[0026] The present invention is described herein using several definitions, as set forth below and throughout the application.

[0027] The term "effective average particle size", as used herein means that at least 50% of the nanoparticulate benzothiophene, or preferably raloxifene hydrochloride particles, have a weight average size of less than about 2000 nm, when measured by, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, disk centrifugation, and other techniques known to those of skill in the art.

[0028] As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

[0029] As used herein with reference to a stable benzothiophene or a stable raloxifene hydrochloride particle connotes, but is not limited to one or more of the following parameters: (1), benzothiophene or raloxifene hydrochloride

increase in particle size over time; (2) that the physical structure of the benzothiophene or raloxifene hydrochloride particles is not altered over time, such as by conversion from an amorphous phase to a crystalline phase; (3) that the benzothiophene or raloxifene hydrochloride particles are chemically stable; and/or (4) where the benzothiophene or raloxifene hydrochloride has not been subject to a heating step at or above the melting point of the benzothiophene or raloxifene hydrochloride in the preparation of the nanoparticles of the present invention.

[0030] The term "conventional" or "non-nanoparticulate active agent" shall mean an active agent which is solubilized or which has an effective average particle size of greater than about 2000 nm. Nanoparticulate active agents as defined herein have an effective average particle size of less than about 2000 nm.

[0031] The phrase "poorly water soluble drugs" as used herein refers to those drugs that have a solubility in water of less than about 30 mg/ml, preferably less than about 20 mg/ml, preferably less than about 10 mg/ml, or preferably less than about 1 mg/ml.

[0032] As used herein, the phrase "therapeutically effective amount" shall mean that drug dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that a therapeutically effective amount of a drug that is administered to a particular subject in a particular instance will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

C. The Nanoparticulate Composition

[0033] There are a number of enhanced pharmacological characteristics of nanoparticulate benzothiophene compositions of the present invention.

[0034] 1. Increased Bioavailability

[0035] The benzothiophene formulations of the present invention, preferably raloxifene hydrochloride formulations of the invention, exhibit increased bioavailability at the same dose of the same benzothiophene, and require smaller doses as compared to prior conventional benzothiophene formulations, including conventional raloxifene hydrochloride formulations. Thus, a nanoparticulate raloxifene hydrochloride tablet, if administered to a patient in a fasted state is not bioequivalent to administration of a conventional microcrystalline raloxifene hydrochloride tablet in a fasted state.

[0036] The non-bioequivalence is significant because it means that the nanoparticulate raloxifene hydrochloride dosage form exhibits significantly greater drug absorption. And for the nanoparticulate raloxifene hydrochloride dosage form to be bioequivalent to the conventional microcrystalline raloxifene hydrochloride dosage form, the nanoparticulate raloxifene hydrochloride dosage form would have to contain significantly less drug. Thus, the nanoparticulate raloxifene hydrochloride dosage form significantly increases the bioavailability of the drug.

[0037] Moreover, a nanoparticulate raloxifene hydrochlo-

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