LASOFOXIFENE TABLET AND ITS COATING

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions having uniform drug distribution and potency utilizing lasofoxifene as an active ingredient and containing a silicon dioxide to reduce loss of the active ingredient during the manufacturing process. Methods for use in the manufacture of such compositions are also disclosed.

BACKGROUND

US 5,552,412 describes a class of potent and orally active selective estrogen receptor modulators (SERMS) (e.g., derivatives of tetrahydronaphthalen-2-ol) which are useful in the treatment or prevention of breast cancer, osteoporosis, obesity, cardiovascular disease, hypercholesterolemia, endometriosis and prostatic disease. These particular SERMS are of interest due to their improved oral bioavailability over current commercially available SERMS (e.g. raloxifene). The SERMS described in US 5,552,412 are very potent thus allowing for low dosage forms. However, the formulation of compositions at the lower dose range presents a challenge in maintaining consistent potency and uniformity in the drug product manufacturing process. Of particular concern is the loss of active ingredient from adherence to or absorption onto metal surfaces to which the active SERM is exposed during the blending step (e.g., contact with metal blender blades and vessel surfaces). Although one can effectively implement a manual brushing step to recover active ingredient adhered to the metal surfaces in small scale equipment, a manual brushing step is neither efficient nor desirable in a production scale environment. Liquid processes can minimize the drug loss issues during drug product manufacturing; however, compounds that are sensitive to oxidation (e.g., tetrahydronaphthalen-2-ol derivatives) make liquid processes very difficult to perform without degradation of the active ingredient. Therefore, there is a need for an improved formulation and process that would minimize adherence of active ingredients onto metal surfaces during the manufacture of medicaments, in particular, those having a low dosage content.

SUMMARY

Disclosed herein is a pharmaceutical composition having a core containing about 0.3 to about 14.0 w/w% of *cis*-6-phenyl-5-[4-(2-pyrrolidin-1 ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol; a prodrug thereof, or a pharmaceutically acceptable salt, hydrate or solvate of the compound or the prodrug, about 3.0 w/w% of a disintegrant, about 0.5 w/w% of a glidant, about 1.0 w/w% of a lubricant and about 77.0 w/w% to about 91.0 w/w% of a diluent/filler, and an aqueous coating comprising about 1.5 w/w% of a polymer, about 0.9 w/w% of an opacifier, about 0.4 w/w% of a plasticizer, about 1.5 w/w% of a pharmaceutically acceptable diluent/filler and optionally a colorant.

Also disclosed herein is an encapsulated pharmaceutical composition having as an active ingredient, about 0.3 to about 14.0 w/w% cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol; a prodrug thereof, or a pharmaceutically acceptable salt, hydrate or solvate of the compound or the prodrug, about 3.0 w/w% of a disintegrant, about 0.5 w/w% of a glidant, about 1.0 w/w% of a lubricant and about 81.0 w/w% to about 95.0 w/w% of a diluent/filler.

In one aspect, there is provided a pharmaceutical film coated tablet consisting of a tablet core, an opacifying coat and a polish coat wherein the tablet core consists of 0.341 mg lasofoxifene tartrate, 70.159 mg anhydrous lactose, 25.000 mg of microcrystalline cellulose, 3.000 mg croscarmellose sodium, 0.500 mg silicon dioxide and 1.000 mg magnesium stearate; the opacifying coat is 4.000 mg of Opadry II®, wherein the Opadry II® consists of 1.60 mg lactose monohydrate, 1.12 mg hydroxypropyl methyl cellulose 2910-15 cP, 0.94 mg titanium dioxide, 0.32 mg triacetin and 0.02 mg FD&C Yellow No. 6 Aluminum Lake 15%-18%; and the polish coat is 0.500 mg of Opadry Clear®, wherein the Opadry Clear® consists of 0.45 mg hydroxypropyl methylcellulose 2910-15cP and 0.05 mg triacetin.

In another aspect, there is provided a pharmaceutical film coated tablet consisting of a tablet core, an opacifying coat and a polish coat wherein the tablet core consists of 0.681 mg lasofoxifene tartrate, 69.819 mg anhydrous lactose, 25.000 mg of microcrystalline cellulose, 3.000 mg croscarmellose sodium, 0.500 mg silicon dioxide and 1.000 mg magnesium stearate; the opacifying coat is 4.000 mg of Opadry II®, wherein the Opadry II® consists of 1.60 mg lactose monohydrate, 1.12 mg hydroxypropyl methyl cellulose 2910-15 cP, 0.94 mg titanium dioxide, 0.32 mg

triacetin and 0.02 mg FD&C Yellow No. 6 Aluminum Lake 15%-18%; and the polish coat is 0.500 mg of Opadry Clear®, wherein the Opadry Clear® consists of 0.45 mg hydroxypropyl methylcellulose 2910-15cP and 0.05 mg triacetin.

Further, disclosed herein is a method for manufacturing a pharmaceutical composition having uniform drug distribution and potency. The method may include (in the following order) the steps of: (1) blending silicon dioxide and at least one pharmaceutically acceptable excipient, carrier or diluent in a high shear granulator for an appropriate amount of time (about 5 minutes) to produce a blended mixture; (2) adding an active ingredient to the granulator and blending for an additional period of time (about 10 to about 15 minutes) to form an active blend; (3) transferring the active blend from the granulator to a blender; (4) optionally, adding one or more additional pharmaceutically acceptable excipients, carriers or diluents to the active blend; and (5) blending for a suitable period of time (about 5 minutes) to form a pharmaceutical composition having uniform distribution of the active ingredient and uniform potency. The resultant blended composition may then be processed further into a desired unit dosage form. In a preferred dosage form, the active ingredient is present in an amount from about 0.01 to 10.0 mg per unit dose (preferably from about 0.05 to about 5.0 mg, more preferably from about 0.05 to about 4.0 mg, even more preferably from about 0.1 to about 3.5 mg, and most preferably from about 0.1 to about 2.5 mg per unit dose) and the silicon dioxide is present in an amount from about 0.1 to about 2% by weight of the unit dosage form (more preferably from about 0.15 to about 1.0% by weight of the unit dosage form

and most preferably from about 0.25 to about 0.75% by weight of the unit dosage form).

In another embodiment, there is provided a pharmaceutical composition that is prepared using the method described above. In particular, a low dosage pharmaceutical composition is provided that comprises an active ingredient (preferably lasofoxifene), a silicon dioxide, and at least one pharmaceutically acceptable excipient, carrier, or diluent wherein the active ingredient is present in an amount less than 4.0% w/w active ingredient (more preferably ≥ about 0.01% w/w active ingredient and < 4% w/w active ingredient, even more preferably ≥ about 0.01% w/w active ingredient and ≤ about 3.5% w/w active ingredient, most preferably ≥ about 0.1% w/w active ingredient and ≤ about 2.5% w/w active ingredient) and the silicon dioxide is present in an amount from about 0.1 to about 2 weight percent.

In another embodiment, there is provided a low dosage immediate release pharmaceutical composition comprising a core containing, as an active ingredient, about 0.3 to about 0.7 w/w% *cis*-6-phenyl-5- [4- (2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol; a prodrug thereof, or a pharmaceutically acceptable salt, hydrate or solvate of the compound or the prodrug, about 3.0 w/w% of a disintegrant, about 0.5 w/w% of a glidant, about 1.0 w/w% of a lubricant and about 91.0 w/w% of a diluent/filler, and an aqueous coating comprising about 1.5 w/w% of a polymer, about 0.9 w/w% of an opacifier, about 0.4 w/w% of a plastisizer, about 1.5 w/w% of a pharmaceutically acceptable diluent/filler and optionally a colorant.

In yet another embodiment, there is provided a medicament that is prepared by the method described above into a unit dosage form, in particular a low dosage form.

Definitions

As used herein, the term "uniform distribution" refers to a blended mixture, which meets the FDA criteria (Guidance for Industry ANDA's: Blend Uniformity Analysis, published August 1999) of 10 individual blend samples achieving 90-110% potency of the theoretical strength with an RSD of <5% for all blend samples.

The term "uniform potency" refers to a blended mixture that maintains a drug substance activity level greater than or equal to about 90% throughout the manufacturing process.

The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The term "active ingredient" refers to a therapeutically active compound, as well as any prodrugs thereof and pharmaceutically acceptable salts, hydrates and solvates of the compound and the prodrugs.

The term "appropriate period of time" or "suitable period of time" refers to the period of time necessary to achieve a desired effect or result. For example, a mixture may be blended until a potency distribution is reached that is within an acceptable qualitative range for a given application or use of the blended mixture.

As used herein, the term "unit dose" or "unit dosage" refers to a physically discrete unit that contains a predetermined quantity of active ingredient calculated to produce a desired therapeutic effect. The unit dose or unit dosage may be in the form of a tablet, capsule, sachet, etc. referred to herein as a "unit dosage form."

The term "immediate release" refers to pharmaceutical dosage forms that provide release immediately following drug administration.

The term "timed release" refers to pharmaceutical dosage forms that prevent drug release after drug administration until a certain amount of time has passed.

The term "sustained release" refers to pharmaceutical dosage forms that provide substantially continuous release over a predetermined time period.

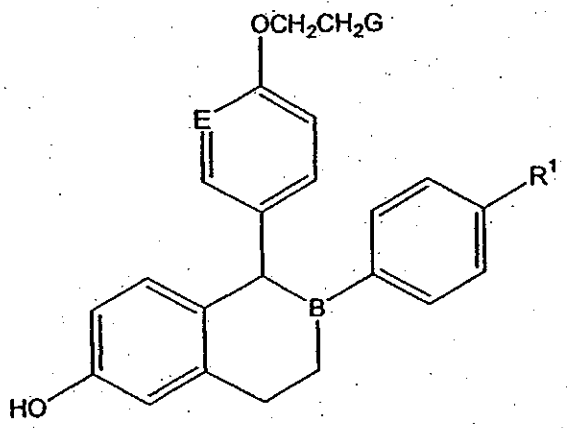
DETAILED DESCRIPTION

The present invention provides a pharmaceutical composition having a core containing about 0.3 to about 14.0 w/w% of *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol; a prodrug thereof, or a pharmaceutically acceptable salt, hydrate or solvate of the compound or the prodrug, about 3.0 w/w% of a disintegrant, about 0.5 w/w% of a glidant, about 1.0 w/w% of a lubricant and about 77.0 w/w% to about 91.0 w/w% of a diluent/filler, and an aqueous coating comprising about 1.5 w/w% of a polymer, about 0.9 w/w% of an opacifier, about 0.4 w/w% of a plasticizer, about 1.5 w/w% of a pharmaceutically acceptable diluent/filler and optionally a colorant.

The present invention also provides an encapsulated pharmaceutical composition having as an active ingredient, about 0.3 to about 14.0 w/w% *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol; a prodrug thereof, or a pharmaceutically acceptable salt, hydrate or solvate of the compound or the prodrug, about 3.0 w/w% of a disintegrant, about 0.5 w/w% of a

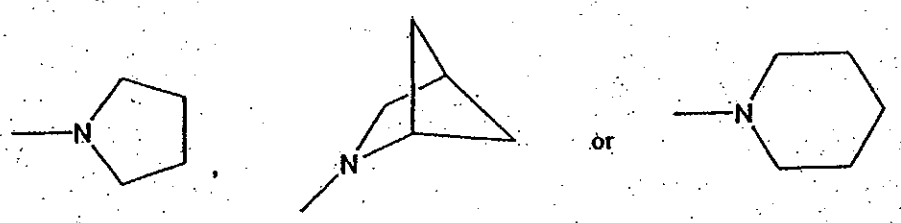
glidant, about 1.0 w/w% of a lubricant and about 81.0 w/w% to about 95.0 w/w% of a diluent/filler.

Further, the present invention provides a process for maintaining uniformity and potency during the manufacture of a pharmaceutical composition containing a highly potent active ingredient. The process includes a means for reducing the loss of active ingredients that adhere to the metal surfaces of equipment during the manufacturing process of a pharmaceutical composition or medicament. Active ingredients of particular interest are SERM compounds of Formula (I) below:



(I)

where E and B are independently selected from CH and N; R^1 is hydrogen, hydroxy, fluoro or chloro; and G is



a prodrug thereof, or a pharmaceutically acceptable salt, hydrate or solvate of the compound or the prodrug.

Preferred compounds include *cis*-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalen-2-ol; (-)-*cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalen-2-ol; *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalen-2-ol; *cis*-1-[6'-pyrrolodinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydrohaphthalen-1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; *cis*-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalen-2-ol; and 1-(4'-pyrrolidinolethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline. A more preferred compound is *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol; a prodrug

thereof, or a pharmaceutically acceptable salt, hydrate or solvate of the compound or the prodrug.

The compounds of Formula (I) are very potent compounds thus requiring special handling to reduce operator exposure during the manufacturing process. In addition, the compounds of Formula (I) may be sensitive to oxidation, which may limit or preclude the use of liquids and materials containing peroxide contaminants (e.g., polyethylene glycols) during drug product manufacture. Conventional methods for manufacturing tablets typically use a wet or dry granulation step prior to compression into a tablet.

The types of mixing processes for a dry granulation can be divided into two broad categories: (i) batch, and (ii) continuous. The most prevalent type used in the pharmaceutical industry is the batch type, which mixes a sub-lot or total lot of a formulation at one time. In a batch-type mixer, particle movement is achieved by rotation of the entire mixer shell or body. For schematics and a description of the different types of batch-type mixers, see Pharmaceutical Dosage Forms, Vol. 2, Lieberman, H.A., L. Lachman, and J.B. Schwartz (Eds.), Marcel Dekker, Inc., New York, pp 40-57 (1990).

In a Blend/Mill/Blend dry granulation process, the following steps are generally employed:

(1) pass an active ingredient through an appropriately sized sieve and then blend in a blender (e.g., twin shell blender) for an appropriate period of time to produce a blended mixture;

(2) filter an excipient blend through an appropriately sized sieve and add a portion of the filtered excipient blend to the blender containing the active ingredient;

(3) blend the mixture for an appropriate period of time;

(4) filter the active blend through an appropriately sized screen;

(5) charge a blender with half of the remaining filtered excipient blend followed by the filtered active blend from step (4);

(6) blend the mixture for an appropriate period of time;

(7) add the remaining filtered excipient blend to the active mixture and blend for an appropriate period of time;

(8) pass the blended mixture from step (7) through a mill;

(9) blend the active mixture from step (8) for an appropriate period of time in a blender; and

(10) add any additional excipients, carriers or diluents and blend until an acceptable distribution of materials is achieved.

The conventional blend/mill/blend dry process presents several disadvantages. For example, it is labor intensive, the dusty operation increases the operator's exposure to the active ingredient, and the increased exposure to metal surfaces increases the risk of potency loss. In addition, segregation problems are observed with mixtures having wide particle size distribution and large differences in particle densities. Tumbling-type blenders are generally not suitable for fine particulate systems because there may not be enough shear to reduce particle agglomeration and, if the powders are free flowing, serial dilution may be required for the addition of low dose active ingredients.

When the dry granulation process described above was used to blend a formulation containing a compound of Formula (I), a non-uniform distribution of potency was observed across the granulation particles. Although the potential for operator exposure to the active ingredient is greatly reduced in a conventional wet granulation process, the active ingredient is exposed to liquids and dissolved oxygen during the process, which increases the potential for oxidation of the compound. Attempts to reduce the chemical instability of the compound of Formula (I) in a wet granulation process have not been successful. However, Applicant discovered that the use of high shear wet process blending equipment adapted for use as a dry process addressed both the operator exposure to the drug and reduced degradation of the active ingredient due to oxidation observed during the conventional dry and wet granulation processes.

High-speed granulators are stationary shell mixers with a large mixer-scraper blade that mixes the ingredients, eliminates dead spots in the mixer container and presents the mixer contents to a high-speed chopper blade, which intimately mixes the ingredients. The equipment is extremely rapid and provides intimate solids/solids mixing. In a vertical type of mixer (e.g., equipment available from LÖDIGE Industries, Paderborn, Germany; NIRO Inc., Columbia, MD; and DIOSNA Dierks & Soehne GmbH, Osnabrueck, Germany), rotating mixing impellers mix the particles centrifugally at high speed causing a highly fluidized vortex of material. A chopper, rotating at a very high speed, interrupts the ascending circulation of the material and diverts the product into a vertical flow. For a more detailed description, see Record, P.C., *Manuf. Chem. Aerosol. News*, **50**, 65 (1979). Other suitable high-speed granulators include Spectrum™ and Pharma Matrix™ (both available from Niro Pharma Systems, Columbia, MD).

The present invention provides a dry process that comprises the following steps:

(1) blending at least one pharmaceutically acceptable excipient, carrier or diluent in a high shear granulator for an appropriate amount of time;

(2) adding an active ingredient to the granulator and blending for an additional period of time to form an active blend;

(3) transferring the active blend from the granulator to a blender;

(4) optionally, adding one or more additional pharmaceutically acceptable excipients, carriers or diluents to the mixture; and

(5) blending for a suitable period of time to form a final pharmaceutical composition having a uniform distribution of the active ingredient in the composition.

The final pharmaceutical composition is processed into a unit dosage form (e.g., tablet, capsule or sachet) and then packaged for distribution. The processing step will vary depending upon the particular unit dosage form. For example, a tablet is generally compressed under pressure into a desired shape and a capsule or sachet employs a simple fill operation. Those skilled in the art are well aware of the procedures used for manufacturing the various unit dosage forms.

The active blend generally includes one or more pharmaceutically acceptable excipients, carriers or diluents. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the active ingredient is being applied. In general, a tablet formulation includes materials such as diluents, binders, lubricants, disintegrants and mixtures thereof. Suitable diluents include various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts (e.g., sodium chloride), powdered sugar, and powdered cellulose derivatives. More specifically, examples of diluents or fillers include lactose, mannitol, xylitol, dextrose, sucrose, sorbitol, compressible sugar, microcrystalline cellulose, powdered cellulose, starch, pregelatinized starch, dextrates, dextran, dextrin, dextrose, maltodextrin, calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide, poloxamers such as polyethylene oxide and hydroxypropyl methyl cellulose. To ensure content uniformity of the blend, a volume mean diameter drug substance particle size of less than or equal to about 30 microns is preferably utilized. Preferred diluents are microcrystalline cellulose (e.g., Avicel® PH102 or PH101 available from FMC Pharmaceutical, Philadelphia, PA) and lactose. The mean particle size for the microcrystalline cellulose generally ranges from about 90 μm to about 200 μm. Suitable grades of lactose include anhydrous lactose (about 152 μm mean), lactose monohydrate and spray dried lactose (e.g., Fast Flo™ lactose, about 87 μm mean, available from Foremost Corp., Baraboo, WI). Generally, the microcrystalline cellulose is present in an amount from

about 20 wt% to about 90 wt% and the lactose is present in an amount from about 65 wt% to about 85 wt%.

If desired, a binder may be added. Suitable binders include substances such as celluloses (e.g., cellulose, methylcellulose, ethylcellulose, and hydroxymethylcellulose), polypropylpyrrolidone, polyvinylprrolidone, gelatin, gum arabic, polyethylene glycol, starch, sugars (e.g., lactose, sucrose, fructose, and glucose), natural and synthetic gums (e.g., acacia, alginates, and gum arabic) and waxes.

A lubricant is typically used in a tablet formulation to prevent the tablet and punches from sticking in the die. Suitable lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate. A preferred lubricant is magnesium stearate. The magnesium stearate is generally present in an amount from about 0.25 wt% to about 5.0% wt%.

Disintegrants may also be added to the composition to break up the dosage form and release the compound. Suitable disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, powdered cellulose, lower alkyl-substituted hydroxypropyl cellulose, polacrilin potassium, starch, pregelatinized starch and sodium alginate. Of these, croscarmellose sodium, lower alkyl-substituted hydroxypropyl cellulose, methyl cellulose and polacrilin potassium are preferred, with croscarmellose sodium being most preferred. The croscarmellose sodium is generally present in an amount from about 0.5 wt% to about 5.0 wt%. The amount of disintegrant included in the dosage form will depend on several factors, including the properties of the dispersion, the properties of the porosigen (discussed below), and the properties of the disintegrant selected. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 3 wt% to 20 wt% of the dosage form.

The aqueous coating of the present invention compises a polymer, an opacifier, a plastisizer, a pharmaceutically acceptable diluent/filler and optionally a colorant.

Examples of polymers include cellulosics such as hydroxypropyl methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylhydroxyethylcellulose, methylcellulose, and sodium carboxymethylcellulose. Further examples of polymers include vinyls such as polyvinyl pyrrolidone. Of these polymers, the most preferred is hydroxypropyl methylcellulose.

Examples of opacifiers include titanium dioxide and talc.

Examples of plasticizers include polyhydric alcohols such as glycerol and polyethylene glycols and acetate esters such as glyceryl triacetate (triacetin) and triethyl citrate.

Examples of glidants include silicon dioxide, talc and cornstarch.

Optionally, the compositions of the present invention may include a colorant. Such colorants are available from a number of commercial vendors and are well known to those skilled in the art.

Other useful additives include materials such as agents for retarding dissolution (e.g., paraffin), resorption accelerators (e.g., quaternary ammonium compounds), surface active agents (e.g., cetyl alcohol, glycerol monostearate, and sodium lauryl sulfate), adsorptive carriers (e.g., kaolin and bentonite), preservatives, sweeteners, coloring agents, flavoring agents (e.g., citric acid, menthol, glycine or orange powder), stabilizers (e.g., citric acid or sodium citrate), binders (e.g., hydroxypropylmethylcellulose), and mixtures thereof.

There is a great deal of flexibility in the order of addition of components into the high shear granulator for the initial blending step. Preferably, the drug substance is not added to the high shear bowl first. The typical blending time for the blending in the high shear granulator is from about 10 minutes to about 15 minutes. Although blending times greater than 15 minutes can be used, care should be taken not to demix the blend. The granulator impeller speed is typically run at about 55% to about 65% unit capacity and the chopper is preferably run at the slowest speed setting. Excessive impeller speeds could lead to fluidization of the blend and produce a blend potency loss.

After the high shear blending step, the active blend is blended in a twin shell "V" or bin blender. The typical blending time is about 5 minutes, although small-scale lots have been successfully blended up to about 15 minutes. The lubricant is then added to the active blend and blended for about 5 minutes in the twin shell "V" or bin blender.

The process described above provides efficient mixing and a more uniform distribution of the active ingredient without significant degradation of the active ingredient; however, the loss of active ingredient due to adherence or attraction of the compound to the metal surfaces of the equipment (e.g., blades and vessel surfaces) presented an additional challenge especially for low dosage formulations (e.g., less than 4 mg per unit dose). The addition of a glidant such as talc did not resolve the problem. Although the addition of talc to the formulation reduced the loss of active ingredient in the blending process (potency increase from 77.2% to 91.0%

of the blended composition), talc did not completely prevent adhesion to the metal surface. When a manual brushing step was implemented after blending the talc formulation, an increase in potency to 96.8% was observed which indicates that about 5% to about 6% of the active ingredient is still adhering to the metal surface. A 5-6% loss of a very potent active ingredient, such as the compounds of Formula (I), is significant. However, when silicon dioxide (e.g., Syloid™ 244FP available from W.R. Grace, Columbia, MD) was added to the formulation, an increase of potency from 77.2% to 96.3% of the blended composition was observed without the addition of a manual brushing step.

Although the addition of silicon dioxide to pharmaceutical formulations have been utilized to improve the flow of powder blends and minimize tablet weight variation, the incorporation of SiO_2 (as observed above) unexpectedly and surprisingly reduced the loss of active ingredient due to absorption or adherence to the metal surfaces of the process equipment. A variety of silicon dioxides are available from a number of commercial vendors and are well known to those skilled in the art. A particularly useful silicon dioxide is colloidal silicon dioxide which is a submicron fumed silica prepared by the vapor-phase hydrolysis of a silicon compound, such as silicon tetrachloride. Colloidal silica is an amorphous powder, which is available commercially from a number of sources, including Cabot Corporation, Boston, MA (Cab-O-Sil™); Degussa, Inc., Düsseldorf, Germany (Aerosil™); E.I. DuPont & Co., Wilmington, DE; and W.R. Grace & Co., Columbia, MD (Syloid™). Colloidal silicon dioxide is also known as colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride, and silicon dioxide fumed, among others. A variety of commercial grades of colloidal silicon dioxide are produced by varying the manufacturing process. These modifications do not affect the silica content, specific gravity, refractive index, color or amorphous form. However, these modifications are known to change the particle size, surface areas, and bulk densities of the colloidal silicon dioxide products. The mean particle size for the silicon dioxide is generally less than or equal to about 15 μm/bulk density (less than or equal to about 21.0 lbs./ft^3 (336 kg/m^3)). Preferably, the silicon dioxide is in the form of a dry powder and not a liquid suspension.

The silicon dioxide is generally present in an amount from about 0.1 to about 2% by weight of the dosage form, preferably, in an amount from about 0.15 to about 1.0% by weight and most preferably in an amount from about 0.10 to about 0.50% by weight of the dosage form.

Procedures for making compounds of Formula (I) are described in U.S. Patent No. 5,552,412, incorporated herein by reference, and the resolution of

racemic mixtures is described in WO97/16434. The active ingredient may be used *per se* or in the form of its pharmaceutically acceptable salt, solvate and/or hydrate. The term "pharmaceutically acceptable salt" refers to non-toxic acid addition salts derived from inorganic and organic acids. Suitable salt derivatives include halides, thiocyanates, sulfates, bisulfates, sulfites, bisulfites, arylsulfonates, alkylsulfates, phosphonates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphonates, alkanoates, cycloalkylalkanoates, arylalkonates, adipates, alginates, aspartates, benzoates, fumarates, glucoheptanoates, glycerophosphates, lactates, maleates, nicotinates, oxalates, palmitates, pectinates, picrates, pivalates, succinates, tartarates, citrates, camphorates, camphorsulfonates, digluconates, trifluoroacetates, and the like. A preferred salt of compounds of Formula (I) is tartrate (in particular, D-tartrate) or citrate. A preferred compound is lasofoxifene (*cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol). The active ingredient is generally present in a pharmaceutical composition in an amount less than or equal to about 14% w/w. For a low dosage application, the active ingredient is typically present in the pharmaceutical composition in an amount less than 4.0% w/w active ingredient, more preferably ≥ about 0.01% w/w active ingredient and < 4% w/w active ingredient, even more preferably ≥ about 0.01% w/w active ingredient and ≤ about 3.5% w/w active ingredient, most preferably ≥ about 0.1% w/w active ingredient and ≤ about 2.5% w/w active ingredient).

The pharmaceutical composition can be used to produce unit dosage forms containing about 0.05 mg to about 10.0 mg active ingredient per unit dosage, preferably, about 0.1 mg to about 5.0 mg active ingredient per unit dosage. The tablet size (i.e., unit dosage form) is typically between about 100 mg and 600 mg. As used herein, "low dosage form" refers to a unit dose containing less than about 5.0 mg active ingredient. A typical low dosage form contains between about 0.01 and about 5.0 mg active ingredient, preferably between about 0.05 mg and about 4.0 mg, more preferably between about 0.1 mg and about 3.5 mg, most preferably between about 0.1 mg and 2.5 mg.

For example, the tablet formulation for a 0.25 mg, 0.1 mg and 0.05 mg tablet typically consists of a blend containing about 0.14% w/w active ingredient and the tablet size is varied to achieve the proper dosage; whereas, a 0.5 mg tablet formulation generally contains a blend having about 0.68% w/w active ingredient. The concentration of active ingredient in the final pharmaceutical composition is

generally adjusted by increasing or decreasing the amount of diluent (e.g., lactose) added to the formulation.

The tablets are generally prepared by compression in a rotary press. However, the particular method used for tablet formation is non-limiting and is well known to those skilled in the art. After formation of the tablets, the tablets are often coated with one or more coatings. The tablet may be coated with a coating to mask flavor, to act as a sealant and/or to act as a receptor for printing a logo or trademark on the tablet surface. A common coating is a sugar coating (e.g., sucrose or sorbitol coating). Alternatively, the tablet may be coated with a film-forming protecting agent(s) to modify the dissolution properties of the tablet. For example, the tablet may be coated with a film-forming coating that resists dissolution for a predictable period of time thus resulting in a delayed or prolonged release of the active ingredient. Suitable film-forming protecting agents include celluloses (e.g., hydroxypropyl-methylcellulose, hydroxypropyl cellulose, methylcellulose), polyvinyl pyrrolidone, and ethyl acrylate-methyl methacrylate copolymers. The coating formulations may also include additives such as solubilizing agents (e.g., triacetin), preservatives, sweeteners, flavoring agents, coloring agents and other known additives to provide an elegant presentation of the drug. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation.

Preferably, the aqueous coating of the present invention comprises Opadry II® (Y-30-13579-A) and Opadry Clear® (YS-2-19114-A) manufactured by Colorcon, West Point, Pennsylvania. Opadry II®, useful as an opacifying coat, contains lactose monohydrate, hydroxypropyl methyl cellulose, titanium dioxide, triacetin and FD&C Yellow No. 6 aluminum lake. Opadry Clear®, useful as a polish coat, contains hydroxypropyl methylcellulose and triacetin.

Alternatively, the active pharmaceutical blend may be filled into hard shell capsules, also referred to as the dry-filled capsule (DFC). The capsule formulation and manufacturing process is similar to the reported tablet core formulation and manufacturing process. A hard shell capsule could consist of gelatin and water or hydroxypropyl methylcellulose, water and a gelling agent (gelan gum or carageenan).

Such capsule compositions do not utilize an aqueous coating. The encapsulated pharmaceutical composition comprises about 0.3 to about 14.0 w/w% of lasofoxifene, a prodrug thereof or a pharmaceutically acceptable salt, hydrate or solvate of the compound or the prodrug, about 3.0 w/w% of a disintegrant, about 0.5 w/w% of a glidant, about 1.0 w/w% of a lubricant and about 81.0 w/w% to about 95.0 w/w% of a diluent/filler.

The pharmaceutical composition (or formulation) may be packaged in a variety of ways. Generally, an article for distribution includes a container that contains the pharmaceutical composition in an appropriate form. Suitable containers are well known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, foil blister packs, and the like. The container may also include a tamper proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container typically has deposited thereon a label that describes the contents of the container and any appropriate warnings or instructions.

The pharmaceutical compositions containing the compounds of Formula (I) described herein are useful in the treatment or prevention of *inter alia* breast cancer, osteoporosis, obesity, cardiovascular disease, hypercholesterolemia, endometriosis and prostatic disease. Accordingly, the pharmaceutical formulations and processes described herein containing the compounds of Formula (I) may be used in the manufacture of a medicament for the therapeutic applications described above.

A therapeutically effective amount of the manufactured medicament may be administered to a human in need of such treatment or prevention. As used herein, the term "therapeutically effective amount" refers to an amount of active ingredient which is capable of inhibiting or preventing the various pathological conditions or symptoms thereof and sequelae, referred to above. The terms "inhibit" or "inhibiting" refers to prohibiting, treating, alleviating, ameliorating, halting, restraining, slowing or reversing the progression, or reducing the severity of a pathological condition or symptom related to or resultant from the respective condition being treated. As such, the pharmaceutical formulations may be used for both medical therapeutic (acute or chronic) and/or prophylactic (prevention) administration as appropriate. The dose, frequency and duration will vary depending on such factors as the nature and severity of the condition being treated, the age and general health of the host and the tolerance of the host to the active ingredient. The pharmaceutical composition or medicament may be given in a single daily dose, in multiple doses during the day or even in a weekly dose. The regimen may last from about 2-3 days to several weeks or longer. Typically, the composition is administered to a human patient once a day with a unit dosage of about 0.25 mg to about 10.0 mg, but the above dosage may be properly varied depending on the age, body weight and medical condition of the patient and the type of administration.

The following Examples illustrate the preparation of compounds of Formula (I) and their use in pharmaceutical compositions and manufacturing processes of the present invention. Although a particular SERM compound (lasofoxifene) is used to illustrate the invention, it will be understood by those skilled in the art that the

inventive process can be used for any compound that would benefit from increased uniformity of potency and distribution of the active ingredient in a pharmaceutical composition by means of the present invention. The examples are not intended to be limiting to the scope of the invention in any respect, and should not be so construed.

EXAMPLES

Preparation of cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol ("lasofoxifene"):

Lasofoxifene was prepared as described in U.S. Patent No. 5,552,412 and reproduced below.

A solution of 1-[2-[4-(6-methoxy-2-phenyl-3,4 dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine hydrochloride (nafoxidene hydrochloride) (1.0 g, 2.16 mmol) in 20 mL of absolute ethanol containing 1.0 g of palladium hydroxide on carbon was hydrogenated at 60 psi (0.41 MPa) at 20°C for 19 hr. Filtration and evaporation provided 863 mg (93%) of *cis*-1-{2-[4-(6-methoxy-2-phenyl 1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy] ethyl} pyrrolidine.

^{1}H-NMR ($CDCl_3$.): δ 3.50-3.80 (m, 3H), 3.85 (s, 3H), 4.20-4.40 (m, 3H), 6.80-7.00 (m, 3H); MS 428 (P^{+1}).

To a solution of 400 mg (0.94 mmol) of *cis*-1-{2-[4-(6-methoxy-2-phenyl 1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy] ethyl} pyrrolidine in 25 mL of methylene chloride at 0°C was added, dropwise with stirring, 4.7 ml (4.7 mmol) of a 1.0 M solution of boron tribromide in methylene chloride. After 3 hours at room temperature, the reaction was poured into 100 mL of rapidly stirring saturated aqueous sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to afford 287 mg (74% yield) of lasofoxifene as the free base.

^{1}H-NMR ($CDCl_3$): δ 3.35 (dd, 1H), 4.00 (t, 2H), 4.21 (d, 1H), 6.35 (ABq, 4H). The corresponding hydrochloride salt was prepared by treating a solution of the base with excess 4N HCl in dioxane, followed by evaporation to dryness and ether trituration (MS: 415 [P^{+1}]).

Alternatively, lasofoxifene may be prepared using the procedures described below.

Preparation of 1-[2-[4-(6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine: A mixture of anhydrous $CeCl_3$ (138 g, 560 mmol) and THF (500 mL) was vigorously stirred for 2 h. In a separate flask, a solution of 1-[2-(4-bromophenoxy)ethyl]pyrrolidine (100 g, 370 mmol) in THF (1000 mL) was cooled to -

78°C and *n*-BuU (2.6 M in hexanes, 169 mL, 440 mmol) was slowly added over 20 min. After 15 min, the solution was added to the $CeCl_3$ slurry cooled at -78°C *via* cannula and the reaction was stirred for 2 h at -78°C. A solution of 6-methoxy-1-tetralone (65.2 g, 370 mmol) in THF (1000 mL) at -78°C was added to the arylcerium reagent *via* cannula. The reaction was allowed to warm slowly to room temperature and was stirred for a total of 16 h. The mixture was filtered through a pad of Celite™. The flitrate was concentrated *in vacuo* and 3 N HCl (500 mL) and Et_2O (500 mL) were added. After stirring for 15 min, the layers were separated. The aqueous layer was further washed with Et_2O (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to provide 6-methoxy-1-tetralone (22 g). The aqueous layer was basified to pH 12 with 5 N NaOH and 15% aqueous $(NH_4)_2CO_3$ (1000 mL) was added. The aqueous mixture was extracted with CH_2Cl_2 (2x). The organic solution was dried ($MgSO_4$), filtered, and concentrated to provide a brown oil. Impurities were distilled off (110°-140°C @0.2 mmHg) to yield the product (74 g, 57%).

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.27 (d, J=8.7 Hz, 2H), 6.92-6.99 (m, 3H), 6.78 (d, J=2.6 Hz, 1H), 6.65 (dd, J=8.6, 2.6 Hz, 1H), 5.92 (t, J =4.7 Hz, 1H), 4.15 (t Hz, 2H), 3.80 (s, 3H), 2.94 (t, J =6.0 Hz, 2H), 2.81 (t, J =7.6 Hz, 2H), 2.66 (m, 2H), 2.37 (m, 2H), 1.84 (m, 4H).

Preparation of 1-[2-[4,(2-bromo-6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine: Pyridinium bromide perbromide (21.22 g, 60.55 mmol) was added portionwise to a solution of 1-{2-[4-(6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine (23 g, 72 mmol) in THF (700 mL). The reaction was stirred for 60 h. The precipitate was filtered through a Celite pad with the aid of THF. The off-white solid was dissolved in CH_2Cl_2 and MeOH and was filtered away from the Celite. The organic solution was washed with 0.5 N aq HCl followed by saturated $NaHCO_3$ (aq). The organic solution was dried ($MgSO_4$), filtered, and concentrated to provide a brown solid (21.5 g, 83%).

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.14 (d, J=8.7 Hz, 2H), 6.97 (d, J=8.8 Hz, 2H), 6.71 (d, J=2.2 Hz, 1H), 6.55 (m, 2H), 4.17 (t, J =6.0 Hz, 2H), 3.77 (s, 3H), 2.96 m,(4H), 2.66 (m, 4 H), 1.85 (m, 4H).

Preparation of 1-{2-[4-(6-methoxy-2-phenyl-3,4-dihydronaphthalen-1 yl)phenoxy]ethyl]pyrrolidine hydrochloride (Nafoxidene hydrochloride): To a mixture of 1 [2-[4-(2-bromo-6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine (19 g, 44 mmol), phenylboronic acid (7.0 g, 57 mmol), and tetrakis(triphenylphosphonium) palladium (1.75 g, 1.51 mmol) in THF (300 mL) was

added Na_2CO_3 (13 g, 123 mmol) in H_2O (100 mL). The reaction was heated at reflux for 18 h. The layers were separated and the organic layer was washed with H_2O followed by brine. The organic solution was dried ($MgSO_4$), filtered, and concentrated to yield 17.96 g of a brown solid. The residue was dissolved in a 1:1 mixture of CH_2Cl_2 and EtOAc (250 mL) and 1 N HCl in Et_2O (100 mL) was added. After stirring for 2 h, product was allowed to crystallize from solution and 11 g of material was collected by filtration. Concentration of the mother liquor to half its volume provided an additional 7.3 g of product.

Preparation of *cis*-1-[2-[4-(6-methoxy-2-phenyl-1,2,3,4-tetrahydro-naphthalen-1yl)phenoxy]ethyl]pyrrolidine: 1-[2-[4-(6-Methoxy-2-phenyl-3,4-dihydronaphthalen 1yl)phenoxy]ethyl]pyrrolidine hydrochloride (nafoxidene hydrochloride) (75 g, 162 mmol) was dissolved in 1000 mL of EtOH and 300 mL of MeOH. Dry $Pd(OH)_2$ on carbon was added and the mixture was hydrogenated on a Parr shaker at 50°C and 50 psi (0.34 MPa) for 68 h. The catalyst was filtered off with the aid of Celite and the solvents were removed *in vacuo*. The resulting white solid was dissolved in CH_2Cl_2 and the solution was washed with saturated $NaHCO_3$ (aq). The organic solution was dried ($MgSO_4$), filtered, and concentrated to yield an off-white solid (62.6 g, 90%).

Preparation of *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol: A mixture of *cis*-1-[2-[4-(6-methoxy-2-phenyl-1,2,3,4 tetrahydronaphthalen-1-yl)phenoxy] ethyl}pyrrolidine (12 g, 28 mmol), acetic acid (75 mL), and 48% HBr (75 mL) was heated at 100°C for 15 h. The solution was cooled and the resulting white precipitate was collected by filtration. The hydrobromide salt (9.6 g, 69%) was dissolved in $CHCl_3$/MeOH and was stirred with saturated $NaHCO_3$ (aq). The layers were separated and the aqueous layer was further extracted with $CHCl_3$/MeOH. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield product as an off-white foam.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.04 (m, 3H), 6.74 (m, 2H), 6.63 (d, J =8.3 Hz, 2H), 6.50 (m, 3H), 6.28 (d, J =8.6 Hz, 2H), 4.14 (d, J=4.9 Hz, 1H), 3.94 (t, J=5.3 Hz, 2H), 3.24 (dd, J=12.5, 4.1 Hz, 1H), 2.95 (m, 4H), 4H), 2.14 (m, 1H), 1.88 (m, 4H), 1.68 (m, 1H).

The following example compares a conventional wet granulation process and a solution wet granulation process with the present invention (dry granulation process).

Example 1

The following materials used in Example 1 may be obtained from the corresponding sources listed below:

Avicel™ PH101 (microcrystalline cellulose)	FMC Pharmaceutical (Philadelphia, PA)
Lactose Fast Flo™ 316	Foremost Corp. (Baraboo, WI)
magnesium stearate	Mallinckrodt (St. Louis, MO)
hydroxypropyl cellulose	Hercules Inc. (Hopewell, VA)
sodium croscarmellose	FMC Pharmaceutical (Philadelphia, PA)
β-cyclodextrin sulfobutyl ether	Prepared using the method described in U.S. Patent No. 6,153,746
silicon dioxide	Grace Davison (Columbia, MD)
ProSolv™ 50 (silicified microcrystalline cellulose)	Penwest, Patterson, NJ

Lasofoxifene Conventional Wet Granulation Process

(Comparative process)

The following ingredients were added to a high shear blender in the listed order.

lactose	5.000 g
microcrystalline cellulose	17.432 g
sodium croscarmellose	1.000 g
hydroxypropyl cellulose	1.250 g
silicon dioxide	0.125 g
Lasofoxifene	0.068 g

The mixture was blended for approximately 15 minutes. While blending, an appropriate amount of water (approximately 63% w/w of dry blend) was added over a 8.5 minute period and then allowed to continue blending for an additional 30 seconds to achieve the desired wet mass. The wet mass was then dried to a moisture level less than about 2% under vacuum (about 50 millibar (mB)). The dried granulation was milled through a conical mill fitted with a 0.04 inch (0.10 cm) screen and round edge impeller set at 1750 rpm speed. The mixture was blended for about 10 minutes in a 150 cc glass bottle on a Turbula mixer. Magnesium stearate (0.125 g) was added to the mixture and then blended for about 5 minutes. The active blend was

then compressed into tablets using a Kilian™ T100 tablet press (available from Kilian & Co., Inc., Horsham, PA).

Lasofoxifene Drug In Solution Wet Granulation Process

(Comparative process)

Water (100 mL) was added to a 250 mL glass beaker equipped with a mixer. While stirring, β-cyclodextrin sulfobutyl ether (0.452 g) was added followed by the lasofoxifene (0.113 g) and allowed to stir until the β-cyclodextrin sulfobutyl ether and lasofoxifene dissolved and a solution was formed. The following ingredients were then added in the order listed into a high shear blender.

lactose	5.000 g
silicified microcrystalline cellulose	17.540 g
sodium croscarmellose	1.000 g
hydroxypropyl cellulose	1.250 g

The mixture was blended for about 2 minutes. While blending, the lasofoxifene:water solution was added over a 3 minute period. The wet mass was then dried to a moisture level of less than about 1% in a 50°C forced hot air oven. The dried granulation was passed through a conical mill fitted with a 0.055 inch (0.14 cm) screen and round edge impeller set at 1750 rpm speed. Magnesium stearate (0.125 g) was added to the mixture and then blended for about 5 minutes. The active blend was then compressed into tablets using a Manesty™ F-Press tablet press (available from Thomas Engineering Inc., Hoffman Estates, IL).

Lasofoxifene Dry Granulation Process

The following ingredients were added in the order listed into a high shear blender

lactose	1052.25 g
microcrystalline cellulose	375.00 g
croscarmellose sodium	45.00 g
silicon dioxide	7.50 g
Lasofoxifene	5.25 g

The lactose, microcrystalline cellulose, croscarmellose sodium and silicon dioxide were blended for 5 minutes. The lasofoxifene was added next and blended for about 15 minutes. The active blend was then discharged from the high shear blender and blended for about 5 minutes in a twin shell "V" blender. Magnesium stearate (7.50 g) was added to the active blend and blended for about 5 minutes. The active blend was roller compacted on a Vector Freund™ roller compactor unit and milled through a rotating granulator fitted with a 0.033" (0.084 cm) screen (both available from

Vector Corp., Marion, IA). The active granulation was blended for about 5 minutes in a twin shell "V" blender. Another portion of magnesium stearate (7.50 g) was added to the granulation and blended for about 5 minutes. The final blend was compressed into tablets on a Kilian™ T100 rotary press.

The components of the lasofoxifene formulation were selected based on in-vivo and manufacturing performance and chemical stability. The drug substance has been shown to be susceptible to oxidation due to the presence of free radicals or the presence of metal impurities, which could indirectly lead to free radical formation through chelation. The disintegrant, croscarmellose sodium, was proven to be chemically more stable with the drug substance than other disintegrants such as sodium starch glycolate or polyvinylpyrrolidone. Additionally, the tablet film coating system was also designed to minimize oxidative degradation through the selection of plasticizer. Triacetin is the plasticizer of choice based on chemical stability and was proven to be more stable than other plasticizers such as polyethylene glycol.

Table 1 below summarizes the stability results by high-pressure liquid chromatography observed for the three different processes.

Table I

Comparison of Lasofoxifene Stability			
Manufacturing Process	**Dry Granulation**	**Conventional Wet Granulation (comparative)**	**Drug In Solution Wet Granulation (comparative)**
Percent Drug Load	0.14	0.28	0.068
Total Percent Initial Impurities	0.02	Not Available	0.95
Total Percent Impurities at 5°C	0.13 at 12 months	0.54 at 6 weeks	1.43 at 6 weeks
Total Percent Impurities at 30°C	0.13 at 12 months	1.21 at 6 weeks	2.03 at 6 weeks
Total Percent Impurities at 40°C/75%RH	0.41 at 6 months	4.3 at 6 weeks	3.10 at 6 weeks
Total Percent Impurities at 50°C	0.39 at 6 months	5.26 at 6 weeks	4.25 at 6 weeks

Table II below summarizes the stability results of lasofoxifene formulations with different disintegrants.

Table II

Comparison of Lasofoxifene Stability			
Binary Mixture	**Lasofoxifene: Croscarmellose Sodium 1:10 Ratio**	**Lasofoxifene: Sodium Starch Glycolate 1:10 Ratio**	**Lasofoxifene: Polyvinyl Pyrrolidone 1:10 Ratio**
Total Percent Impurities at 5°C	Not detected at 6 weeks	Not detected at 6 weeks	Not detected at 6 weeks
Total Percent Impurities at 40°C/75%RH	Not detected at 6 weeks	4.75 at 6 weeks	0.72 at 6 weeks

Table III below summarizes the stability results of film coated lasofoxifene tablet formulations.

Table III

Comparison of Lasofoxifene Film Coated Tablet Stability		
Percent Drug Load	1.42	0.34
Film Coat Plasticizer	Polyethylene Glycol	Triacetin
Total Percent Impurities at 5°C	0.06 at 12 weeks	0.08 at 6 months
Total Percent Impurities at 30°C	0.34 at 12 weeks	0.2 at 6 months
Total Percent Impurities at 40°C/75%RH	1.74 at 12 weeks	0.2 at 6 months

Immediate release low dosage formulations of the present invention were prepared as exemplified below.

1. To an appropriate sized high shear blender was added, in order: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, silicon dioxide and blended for 5 minutes at appropriate impeller and granulator speeds.

2. Lasofoxifene tartrate was introduced and blended for 15 minutes at appropriate impeller and granulator speeds.

3. Active blend was discharged from the high shear blender.

4. Active blend was charged into an appropriate size twin shell or bin blender and blended for 5 minutes.

5. One-half of the magnesium stearate was added to the active blend and blended for 5 minutes.

6. The active blend was compacted on an appropriate roller compactor unit at the appropriate roller pressure, roller speed and feed rate.

7. The active compacts were milled through an appropriate mill fitted with a 20 mesh (0.033") screen or equivalent.

8. The milled active blend was charged into an appropriate size twin shell or bin blender and blended for 5 minutes.

9. The second half of the magnesium stearate was added to the milled active blend and blended for 5 minutes.

10. The final blend was compressed on a rotary tablet press fitted with the appropriate size tooling at a weight of 100 mg.

11. Tablet cores were film coated in an appropriate size film-coating unit. The appropriate amount of opacifying and polishing film coats was applied to the tablets.

Example No. 1

Lasofoxifene 0.25 mg Film Coated Tablet Composition:

Component	Grade	Mg/Tablet	Function
Lasofoxifene Tartrate[1]	Pfizer	0.341	Active Compound
Lactose, Anhydrous[2]	NF/USP/Eu/JP	70.159	Diluent/Filler
Microcrystalline Cellulose	NF/Eu/JP	25.000	Diluent/Filler
Croscarmellose Sodium	NF/Eu/JP	3.000	Disintegrant
Silicon Dioxide	NF/Eu	0.500	Glidant
Magnesium Stearate	NF/Eu/JP	1.000	Lubricant
Opadry II® (Y-30-13579-A) (Lactose Monohydrate) (Hydroxypropyl Methyl Cellulose 2910-15 cP) (Titanium Dioxide) (Triacetin) (FD&C Yellow No. 6 Aluminum Lake 15%-18%)	Pfizer (NF/Eu/JP) (USP/Eu/JP) (USP/Eu/JP) (USP/Eu/JPE) (21 CFR, E110)	4.000 (1.60) (1.12) (0.94) (0.32) (0.02)	Opacifying Coat (Diluent/Filler) (Polymer) (Opacifier) (Plastisizer) (Colorant)
Opadry Clear® (YS-2-19114-A) (Hydroxypropyl Methlycellulose 2910-15cP) (Triacetin)	Pfizer (NF/Eu/JP) (USP/Eu/JPE)	0.500 (0.45) (0.05)	Polish Coat (Polymer) (Plastisizer)
Total		**104.500**	

1. Based on a theoretical potency of 73.4%
2. Weight adjusted for slight potency changes in the lasofoxifene tartrate

Example No. 2

Lasofoxifene 0.5 mg Film Coated Tablet Composition:

Component	Grade	Mg/Tablet	Function
Lasofoxifene Tartrate[1]	Pfizer	0.681	Active Compound
Lactose, Anhydrous[2]	NF/USP/Eu/JP	69.819	Diluent/Filler
Microcrystalline Cellulose	NF/Eu/JP	25.000	Diluent/Filler
Croscarmellose Sodium	NF/Eu/JP	3.000	Disintegrant
Silicon Dioxide	NF/Eu	0.500	Glidant
Magnesium Stearate	NF/Eu/JP	1.000	Lubricant
Opadry II® (Y-30-13579-A) (Lactose Monohydrate) (Hydroxypropyl Methyl Cellulose 2910-15 cP) (Titanium Dioxide) (Triacetin) (FD&C Yellow No. 6 Aluminum Lake 15%-18%)	Pfizer (NF/Eu/JP) (USP/Eu/JP) (USP/Eu/JP) (USP/Eu/JPE) (21 CFR, E110)	4.000 (1.60) (1.12) (0.94) (0.32) (0.02)	Opacifying Coat (Diluent/Filler) (Polymer) (Opacifier) (Plastisizer) (Colorant)
Opadry Clear® (YS-2-19114-A) (Hydroxypropyl Methlycellulose 2910-15cP) (Triacetin)	Pfizer (NF/Eu/JP) (USP/Eu/JPE)	0.500 (0.45) (0.05)	Polish Coat (Polymer) (Plastisizer)
Total		**104.500**	

1. Based on a theoretical potency of 73.4%
2. Weight adjusted for slight potency changes in the lasofoxifene tartrate

For comparison to the tablets described in Examples 14-17, Control 1 tablets were formed using conventional immediate release dosage form tableting excipients.

The terms and expressions which have been employed in the foregoing specification are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding equivalents of the features shown and described or portions thereof, it being recognized that the scope of the invention is defined and limited only by the claims which follow:

CLAIMS:

1. A pharmaceutical film coated tablet consisting of a tablet core, an opacifying coat and a polish coat wherein the tablet core consists of 0.341 mg lasofoxifene tartrate, 70.159 mg anhydrous lactose, 25.000 mg of microcrystalline cellulose, 3.000 mg croscarmellose sodium, 0.500 mg silicon dioxide and 1.000 mg magnesium stearate; the opacifying coat is 4.000 mg of Opadry II®, wherein the Opadry II® consists of 1.60 mg lactose monohydrate, 1.12 mg hydroxypropyl methyl cellulose 2910-15 cP, 0.94 mg titanium dioxide, 0.32 mg triacetin and 0.02 mg FD&C Yellow No. 6 Aluminum Lake 15%-18%; and the polish coat is 0.500 mg of Opadry Clear®, wherein the Opadry Clear® consists of 0.45 mg hydroxypropyl methylcellulose 2910-15cP and 0.05 mg triacetin.

2. A pharmaceutical film coated tablet consisting of a tablet core, an opacifying coat and a polish coat wherein the tablet core consists of 0.681 mg lasofoxifene tartrate, 69.819 mg anhydrous lactose, 25.000 mg of microcrystalline cellulose, 3.000 mg croscarmellose sodium, 0.500 mg silicon dioxide and 1.000 mg magnesium stearate; the opacifying coat is 4.000 mg of Opadry II®, wherein the Opadry II® consists of 1.60 mg lactose monohydrate, 1.12 mg hydroxypropyl methyl cellulose 2910-15 cP, 0.94 mg titanium dioxide, 0.32 mg triacetin and 0.02 mg FD&C Yellow No. 6 Aluminum Lake 15%-18%; and the polish coat is 0.500 mg of Opadry Clear®, wherein the Opadry Clear® consists of 0.45 mg hydroxypropyl methylcellulose 2910-15cP and 0.05 mg triacetin.