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**ORALLY ADMINISTERABLE PHARMACEUTICAL FORMULATIONS**

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(57) Claim

1. An orally administrable pharmaceutical formulation comprising raloxifene hydrochloride in combination with a surfactant, polyvinylpyrrolidone, and a water-soluble diluent, wherein:

the surfactant is a sorbitan fatty acid ester or a polyoxyethylene sorbitan fatty acid ester; and

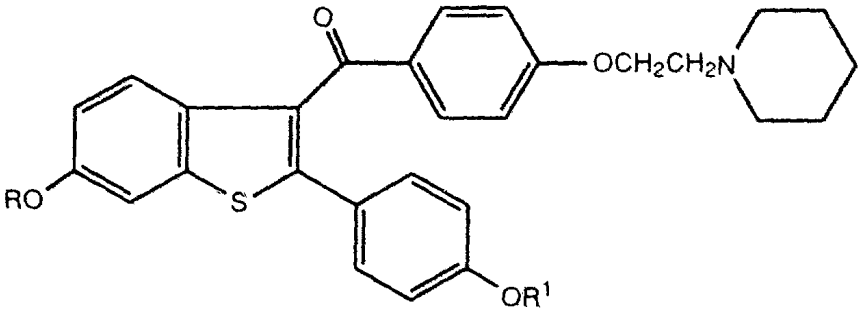
the water-soluble diluent is a polyol or sugar.

2. The formulation of claim 1, wherein the surfactant is a polyoxyethylene sorbitol fatty acid ester.

8. An orally administrable pharmaceutical formulation comprising raloxifene hydrochloride in combination with polysorbate 80, lactose, polyvinylpyrrolidone, and magnesium stearate.

# Orally Administerable Pharmaceutical Formulations

Certain benzothiophenes of the formula

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wherein R and $R^1$ are independently hydrogen, $COR^2$, or $R^3$;

$R^2$ is hydrogen, $C_1$-$C_{14}$ alkyl, $C_1$-$C_3$ chloroalkyl, $C_1$-$C_3$ fluoroalkyl, $C_5$-$C_7$ cycloalkyl, $C_1$-$C_4$ alkoxy, phenyl, or phenyl mono- or disubstituted with $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl;

$R^3$ is $C_1$-$C_4$ alkyl, $C_5$-$C_7$ cycloalkyl, or benzyl; or

a pharmaceutically-acceptable salt thereof;

are nonsteriodal antiestrogens and antiandrogens. These compounds are useful in the treatment of mammary and prostatic tumors, and in the treatment of mammary and prostatic fibrocystic disease. The formula I compounds are described in U.S. Patent No. 4,418,068 (issued November 29, 1983). This patent described the preparation of these compounds, as well as their use for antiestrogen and antiandrogen therapy. The preparation of pharmaceutical compositions for antiestrogenic and antiandrogenic therapy was also described.

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Raloxifene, which is 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, is a particulary useful compound from this series of benzothiophenes. Raloxifene competitively inhibits estrogen action in a number of *in vitro* and *in vivo* models. Black, Jones, and Falcone, *Life Sci.*, **32**, 1031-1036 (1983); Knecht, Tsai-Morris, and Catt, *Endocrinology*, **116**, 1771-1777 (1985); and Simard and Labrie, *Mol. Cell. Endocrinology*, **39**, 141-144 (1985). This compound also displays some estrogen-like actions in addition to its estrogen-antagonistic effects. Ortmann, Emons, Knuppen, and Catt, *Endocrinology*, **123**, 962-968 (1988). A recent report suggests that raloxifene is useful in the treatment of osteoporosis in postmenopausal women. Turner, Sato, and Bryant, *Journal of Clinical Investigation* (In Press).

The formula I compounds may be administered as pharmaceutically-acceptable salts. A particularly useful pharmaceutically-acceptable salt of raloxifene is the hydrochloride salt. This salt form is easily prepared by the addition of hydrogen chloride to a solution of raloxifene in an organic solvent, such as tetrahydrofuran or methanol. Aqueous solubility of raloxifene hydrochloride, however, is far below what would be expected for an organic hydrochloride salt containing two phenolic hydroxyl groups. This poor solubility has somewhat limited the bioavailability of this preferred salt form. Another significant barrier to optimum and consistent absorption of raloxifene hydrochloride is its hydrophobicity.

To overcome the limited bioavailability, the present invention provides orally administerable pharmaceutical formulations comprising raloxifene, its esters or ethers, or a pharmaceutically-acceptable salt thereof, in combination with a hydrophilic carrier composition, such

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formulations having increased solubility in aqueous media. More particularly, the present invention provides an orally administrable pharmaceutical formulation comprising raloxifene, its esters or ethers, or a pharmaceutically-acceptable salt thereof, in combination with a surfactant, a water-soluble diluent, and optionally a hydrophilic binder. The present invention also provides pharmaceutical formulations further comprising a lubricant and a disintegrant.

The present invention provides orally administrable pharmaceutical formulations comprising raloxifene, its esters or ethers, or a pharmaceutically-acceptable salt thereof, in combination with a surfactant, a water-soluble diluent, and optionally a hydrophilic binder.

According to one embodiment of the invention there is provided an orally administrable pharmaceutical formulation comprising raloxifene hydrochloride in combination with a surfactant, polyvinylpyrrolidone, and a water-soluble diluent, wherein:

the surfactant is a sorbitan fatty acid ester or a polyoxyethylene sorbitan fatty acid ester; and

the water-soluble diluent is a polyol or sugar.

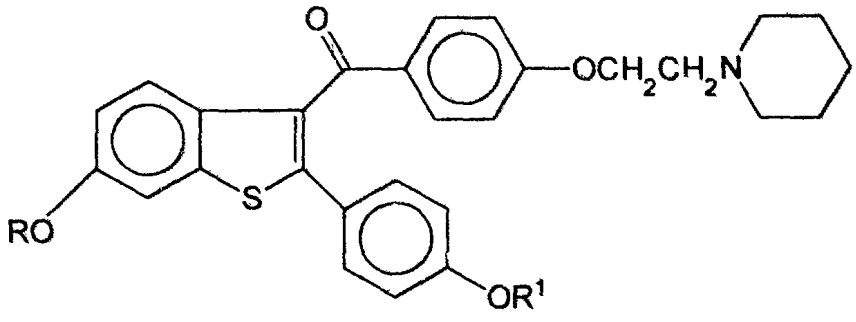
According to another embodiment of the invention there is provided an orally administrable pharmaceutical formulation consisting essentially of raloxifene, its esters or ethers, or a pharmaceutically-acceptable salt thereof, in combination with a surfactant and a water-soluble diluent, wherein:

the amount of raloxifene, its esters or ethers, or a pharmaceutically-acceptable salt thereof is about 12.5% to about 65% (w/w);

the surfactant is selected from the group consisting of sodium docusate, ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives, monoglycerides or ethoxylated derivatives thereof, and diglycerides or polyoxyethylene derivatives thereof; and

the water-soluble diluent is selected from the group consisting of sugars, polysaccharides, polyols, and cyclodextrins.

Raloxifene, its esters, and its ethers are represented by the following formula:

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wherein R and $R^1$ are independently hydrogen, $COR^2$, or $R^3$;

$R^2$ is hydrogen, $C_1$-$C_{14}$ alkyl, $C_1$-$C_3$ chloroalkyl, $C_1$-$C_3$ fluoroalkyl, $C_5$-$C_7$ cycloalkyl, $C_1$-$C_4$ alkoxy, phenyl, or phenyl mono- or disubstituted with $C_1$-$C_4$ alkyl, $C_1$-$C_4$

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alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl;

$R^3$ is $C_1$-$C_4$ alkyl, $C_5$-$C_7$ cycloalkyl, or benzyl.

Raloxifene is the compound wherein R and $R^1$ are hydrogen. The preparation of this compound is described in U.S. Patent No. 4,418,068, which is incorporated herein by reference. A pharmaceutical chemist will readily recognize that this compound can be effectively administered as an ether or ester, formed on either one or both of the phenolic hydroxyl groups. The preparation of these esters and ethers is also described in U.S. Patent No. 4,418,068.

The general chemical terms used in the above formula have their usual meanings. The term "$C_1$-$C_{14}$ alkyl" represents a straight or branched alkyl chain having from one to 14 carbon atoms. Typical $C_1$-$C_{14}$ alkyl groups include methyl, ethyl, n-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, *t*-butyl, *n*-pentyl, isopentyl, n-hexyl, 2-methylpentyl, *n*-octyl, decyl, 2-methyldecyl, 2,2-dimethyldecyl, undecyl, dodecyl, and the like. The term "$C_1$-$C_{14}$ alkyl" includes within it the term "$C_1$-$C_4$ alkyl". Typical $C_1$-$C_4$ alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, and *t*-butyl.

The terms "$C_1$-$C_3$ chloroalkyl" and "$C_1$-$C_3$ fluoroalkyl" represent methyl, ethyl, propyl, and isopropyl substituted to any degree with chlorine or florine atoms, from one atom to full substitution. Typical $C_1$-$C_3$ chloroalkyl groups include chloromethyl, dichloromethyl, trichloromethyl, 2-chlorethyl, 2,2-dichloroethyl, 2,2,2-trichloroethyl, 1,2-dichloroethyl, 1,1,2,2-tetrachloroethyl, 1,2,2,2-tetrachloroethyl, pentachlorethyl, 3-chloropropyl, 2-chloropropyl, 3,3-dichloropropyl, 2,3-dichloropropyl, 2,2-dichloropropyl, 3,3,3-trichloropropyl, and 2,2,3,3,3-

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pentachloropropyl. Typical $C_1$-$C_3$ fluoroalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 1,1,2,2-tetrafluoroethyl, 1,2,2,2-tetrafluoroethyl, pentafluoroethyl, 3-fluoropropyl, 2-fluoropropyl, 3,3-difluoropropyl, 2,3-difluoropropyl, 2,2-difluoropropyl, 3,3,3-trifluoropropyl, and 2,2,3,3,3-pentafluoropropyl.

The term "$C_5$-$C_7$ cycloalkyl" represents cyclic hydrocarbon groups containing from five to seven carbon atoms. The $C_5$-$C_7$ cycloalkyl groups are cyclopentyl, cyclohexyl, and cycloheptyl.

The term "$C_1$-$C_4$ alkoxy" represents groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy, and the like groups.

The term "pharmaceutically-acceptable salt" represents salt forms of raloxifene, its esters, or its ethers that are physiologically suitable for pharmaceutical use. The pharmaceutically-acceptable salts can exist in conjunction with raloxifene, its esters, or its ethers as acid addition primary, secondary, tertiary, or quaternary ammonium, alkali metal, or alkaline earth metal salts. Generally, the acid addition salts are prepared by the reaction of an acid with a compound of formula I, wherein R, $R^1$, $R^2$, and $R^3$, are as defined previously. The alkali metal and alkaline earth metal salts are generally prepared by the reaction of the metal hydroxide of the desired metal salt with a compound of formula I, wherein at least one of R and $R^1$ is hydrogen.

Acids commonly employed to form such acid addition salts include organic acids such as hydrochloric, hydrobromic, hydriodic, sulfuric, and phosphoric acid, as well as organic acids such as toluenesulfonic,

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methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic, and acetic acid, and related inorganic and organic acids. Such pharmaceutically-acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, ammonium, monohydrogen phosphate, dihydrogen phosphate, meta-phosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprolate, acrylate, formate, isobutyrate, caprate, heptanoate, propionate, oxalate, malonate, succinate, subarate, sebacate, fumarate, hippurate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, α-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, ammonium, magnesium, tetramethylammonium, potassium, trimethylammonium, sodium, methylammonium, calcium, and the like salts.

The term "hydrophilic binder" represents binders commonly used in the formulation of pharmaceuticals, such as polyvinylpyrrolidone, polyethylene glycol, sucrose, dextrose, corn syrup, polysaccharides (including acacia, tragacanth, guar, and alginates), gelatin, and cellulose derivatives (including hydroxypropyl methylcellulose, hydroxypropyl cellulose, and sodium carboxymethylcellulose .

The term "surfactant", as used herein, represents ionic and nonionic surfactants or wetting agents commonly used in the formulation of pharmaceuticals, such as ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters,

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poloxamers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives, monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, sodium docusate, sodium laurylsulfate, cholic acid or derivatives thereof, lecithins, and phospholipids.

The term "water-soluble diluent" represents compounds typically used in the formulation of pharmaceuticals, such as sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrates and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), and cyclodextrins.

The term "disintegrant" represents compounds such as starches, clays, celluloses, alginates, gums, cross-linked polymers (such as cross-linked polyvinylpyrrolidone and cross-linked sodium carboxymethylcellulose), sodium starch glycolate, low-substituted hydroxypropyl cellulose, and soy polysaccharides. Preferably the disintegrant is a cross-linked polymer, more preferably cross-linked polyvinylpyrrolidone.

The term "lubricant" represents compounds frequently used as lubricants or glidants in the preparation of pharmaceuticals, such as talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, magnesium carbonate, magnesium oxide, calcium silicate, microcrystalline cellulose, starches, mineral oil, waxes, glyceryl behenate, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, sodium laurylsulfate, sodium stearyl fumarate, and hydrogenated vegetable oils. Preferably the lubricant is magnesium stearate or stearic acid, more preferably magnesium stearate.

While all of the formulations of the present invention have increased solubility in aqueous media and, therefore,

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greater bioavailability would be expected certain formulations are preferred. Preferably, the surfactant is an anionic or nonionic surfactant. Representative surfactants from this preferred group include sodium laurylsulfate, sodium docusate, ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives, monoglycerides or ethoxylated derivatives thereof, and diglycerides or polyoxyethylene derivatives thereof. Preferably, the water-soluble diluent is a sugar or polyol. When a hydrophilic binder is present, preferably the binder is sucrose, dextrose, corn syrup, gelatin, a cellulose derivative, or polyvinylpyrrolidone.

Certain formulations of the present invention are more preferred. More preferably, the surfactant is a nonionic surfactant, such as ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives, monoglycerides or ethoxylated derivatives thereof, and diglycerides or polyoxyethylene derivatives thereof. More preferably, the water-soluble diluent is a sugar, such as lactose, sucrose, and dextrose. More preferably, the hydrophilic binder is a cellulose derivative or polyvinylpyrrolidone.

Certain formulations of the present invention are most preferred. Most preferably, the surfactant is a polyoxyethylene sorbitan fatty acid ester, such as polysorbate 80. Most preferably, the water-soluble diluent is lactose. Most preferably the hydrophilic binder, when present, is polyvinylpyrrolidone.

The orally administerable compositions of the present invention are prepared and administered according to

methods well known in pharmaceutical chemistry. See **Remington's Pharmaceutical Sciences**, 17th ed. A. Osol ed., 1985. For example the compositions of the present invention may be adminstered by means of solid dosage forms such as tablets and capsules. Preferably, the compositions are formulated as tablets. These tablets are prepared by wet granulation, by dry granulation, or by direct compression.

Tablets for this invention are prepared utilizing conventional tabletting techniques. A general method of manufacture involves blending raloxifene, its ester, ether, or a salt thereof, the water-soluble diluent, and optionally a portion of a disintegrant. This blend is then granulated with a solution of the hydrophilic binder and surfactant in water and or organic solvent, such as methanol, ethanol, isopropanol, methylene chloride, and acetone, and milled if necessary. The granules are dried and reduced to a suitable size. Any other ingredients, such as lubricants, e.g. magnesium stearate and additional disintegrant are added to the granules and mixed. This mixture is then compressed into a suitable size and shape using conventional tabletting machines such as a rotary tablet press. The tablets may be film coated by techniques well known in the art.

Capsules for this invention are prepared utilizing conventional encapsulating methods. A general method of manufacture involves blending raloxifene, its ester, ether, or salt thereof, the water-soluble diluent, and optionally a portion of a disintegrant. This blend is then granulated with a solution of the hydrophilic binder and surfactant in water and or organic solvent, and milled if necessary. The granules are dried and reduced to a suitable size. Any other ingredients, such as a lubricant e.g. colloidal

silicon dioxide are added to the granules and mixed. The resulting mixture is then filled into a suitable size hard-shell gelatin capsule using conventional capsule-filling machines.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way. Tablets may be prepared using the ingredients and procedures as described below:

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**Formulation 1**

| Ingredient | Weight (mg/tablet) |
|---|---|
| Raloxifene HCl | 200.00 |
| Polyvinylpyrrolidone | 15.75 |
| Polysorbate 80 | 5.25 |
| Lactose Anhydrous | 264.62 |
| Cross-linked polyvinylpyrrolidone | 31.50 |
| Stearic Acid | 5.25 |
| Magnesium Stearate | 2.63 |

The mixture of raloxifene HCl, lactose, and a portion of the cross-linked polyvinylpyrrolidone is granulated with an aqueous solution of the polyvinylpyrrolidone and polysorbate 80. The granules are dried, reduced to a suitable size, and mixed with stearic acid, magnesium stearate, and remaining cross-linked polyvinylpyrrolidone. The mixture is compressed into individual tablets yielding a tablet weight of 525 mg.

**Formulation 2**

| Ingredient | Weight (mg/tablet) |
|---|---|
| Raloxifene HCl | 200.00 |
| Polyvinylpyrrolidone | 15.75 |
| Polysorbate 80 | 5.75 |
| Lactose Anhydrous | 132.06 |
| Dextrose | 132.06 |
| Cross-linked polyvinylpyrrolidone | 31.50 |
| Stearic acid | 5.25 |
| Magnesium Stearate | 2.63 |

The mixture of raloxifene HCl, lactose anhydrous, dextrose, and a portion of the cross-linked

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polyvinylpyrrolidone is granulated with an alcoholic solution of polyvinylpyrrolidone and polysorbate 80. The granules are dried, reduced to a suitable size, and mixed with magnesium stearate, stearic acid, and remaining cross-linked polyvinylpyrrolidone. The mixture is compressed into individual tablets yielding a tablet weight of 525 mg.

**Formulation 3**

| Ingredient | Weight (mg/tablet) |
|---|---|
| Raloxifene HCl | 200.00 |
| Hydroxypropyl Cellulose | 16.00 |
| Sodium Laurylsulfate | 10.00 |
| Dextrose | 154.00 |
| Cross-linked sodium carboxymethylcellulose | 16.00 |
| Magnesium Stearate | 4.00 |

The mixture of raloxifene HCl, dextrose, and cross-linked sodium carboxymethylcellulose is granulated with an aqueous solution of hydroxypropyl cellulose and sodium laurylsulfate. The granules are dried, reduced to a suitable size, and mixed with magnesium stearate. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg.

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**Formulation 4**

| Ingredient | Weight (mg/tablet) |
|---|---|
| Raloxifene HCl | 30.00 |
| Lactose Anhydrous | 144.00 |
| Lactose, Hydrous spray Dried | 36.00 |
| Polyvinylpyrrolidone | 12.00 |
| Polysorbate 80 | 2.40 |
| Cross-linked polyvinylpyrrolidone | 14.40 |
| Magnesium Stearate | 1.20 |

The mixture of raloxifene HCl, lactose anhydrous, spray-dried hydrous lactose, and a portion of the cross-linked polyvinylpyrrolidone is granulated with an aqueous solution of polyvinylpyrrolidone and polysorbate 80. The granules are dried, reduced to a suitable size, and mixed with magnesium stearate and remaining cross-linked polyvinylpyrrolidone. The mixture is compressed into individual tablets yielding a tablet weight of 240 mg.

**Formulation 5**

| Ingredient | Weight (mg/tablet) |
|---|---|
| Raloxifene HCl | 30.00 |
| Lactose Anhydrous | 160.00 |
| Hydroxypropyl Cellulose | 11.00 |
| Poloxamer | 7.00 |
| Cross-linked sodium carboxymethylcellulose | 23.00 |
| Stearic Acid | 7.00 |
| Magnesium Stearate | 2.00 |

The mixture of raloxifene HCl, anhydrous lactose, and cross-linked sodium carboxymethylcellulose is granulated

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with an aqueous solution of poloxamer and hydroxypropyl cellulose. The granules are dried, reduced to a suitable size, and mixed with stearic acid and magnesium stearate. The mixture is then compressed into individual tablets yielding a tablet weight of 240 mg.

**Formulation 6**

| Ingredient | Weight (mg/tablet) |
|---|---|
| Raloxifene HCl | 30.00 |
| Lactose | 89.00 |
| Dextrose | 89.00 |
| Hydroxypropyl methylcellulose | 10.00 |
| Sodium Laurylsulfate | 5.00 |
| Cross-linked polyvinylpyrrolidone | 12.00 |
| Stearic Acid | 5.00 |

The mixture of raloxifene HCl, lactose, dextrose, and cross-linked polyvinylpyrrolidone is granulated with an aqueous solution of hydroxypropyl methylcellulose and sodium laurylsulfate. The granules are dried, reduced to a suitable size, and mixed with the stearic acid. The mixture is then compressed into individual tablets yielding a tablet weight of 240 mg.

**Formulation 7**

| Ingredient | Weight (mg/tablet) |
|---|---|
| Raloxifene HCl | 60.00 |
| Lactose Anhydrous | 156.00 |
| Polyvinylpyrrolidone | 7.20 |
| Polysorbate 80 | 7.20 |
| Cross-linked polyvinylpyrrolidone | 7.20 |
| Magnesium Stearate | 2.40 |

The mixture of raloxifene HCl, lactose anhydrous, and cross-linked polyvinylpyrrolidone is granulated with an aqueous solution of polyvinylpyrrolidone and polysorbate 80. The granules are dried, reduced to a suitable size, and mixed with magnesium stearate. The mixture is then compressed into individual tablets yielding a tablet weight of 240 mg.

**Formulation 8**

| Ingredient | Weight (mg/tablet) |
|---|---|
| Raloxifene HCl | 60.00 |
| Lactose Anhydrous | 120.00 |
| Lactose, hydrous spray-dried | 30.00 |
| Polyvinylpyrrolidone | 12.00 |
| Polysorbate 80 | 2.40 |
| Cross-linked polyvinylpyrrolidone | 14.40 |
| Magnesium Stearate | 1.20 |

The mixture of raloxifene HCl, lactose anhydrous, spray-dried hydrous lactose, and a portion of the cross-linked polyvinylpyrrolidone is granulated with an aqueous solution of polyvinylpyrrolidone and polysorbate 80. The granules are dried, reduced to a suitable size, and mixed with magnesium stearate and remaining cross-linked polyvinylpyrrolidone. The mixture is then compressed into individual tablets yielding a tablet weight of 240 mg.

**Formulation 9**

| Ingredient | Weight (mg tablet) |
|---|---|
| Raloxifene HCl | 60.00 |
| Mannitol | 77.00 |
| Dextrose | 73.00 |
| Hydroxypropyl methylcellulose | 7.00 |
| Polysorbate 80 | 4.00 |
| Sodium Starch Glycolate | 14.00 |
| Stearic Acid | 4.00 |
| Magnesium Stearate | 1.00 |

The mixture of raloxifene HCl, mannitol, dextrose, and sodium starch glycolate is granulated with an aqueous solution of polysorbate 80 and hydroxypropyl methylcellulose. The granules are dried, reduced to a suitable size, and mixed with stearic acid and magnesium stearate. The mixture is then compressed into individual tablets yielding a tablet weight of 240 mg.

**Formulation 10**

| Ingredient | Weight (mg tablet) |
|---|---|
| Raloxifene HCl | 150.00 |
| Lactose, anhydrous | 41.00 |
| Lactose, hydrous spray dried | 10.25 |
| Polyvinylpyrrolidone | 11.50 |
| Polysorbate 80 | 2.30 |
| Cross-linked polyvinylpyrrolidone | 13.80 |
| Magnesium Stearate | 1.15 |

The mixture of raloxifene HCl, anhydrous lactose, hydrous spray-dried lactose, and a portion of the cross-linked polyvinylpyrrolidone is granulated with an aqueous

solution of polyvinylpyrrolidone and polysorbate 80. The granules are dried, reduced to a suitable size, and mixed with magnesium stearate and the remaining cross-linked polyvinylpyrrolidone. The mixture is then compressed into individual tablets yielding a tablet weight of 230 mg.

**Formulation 11**

| Ingredient | Weight (mg/tablet) |
|---|---|
| Raloxifene HCl | 150.00 |
| Lactose, hydrous spray-dried | 56.00 |
| Polyvinylpyrrolidone | 7.00 |
| Polysorbate 80 | 1.20 |
| Cross-linked polyvinylpyrrolidone | 13.80 |
| Magnesium Stearate | 2.00 |

The mixture of raloxifene HCl, hydrous spray-dried lactose, and a portion of the cross-linked polyvinylpyrrolidone is granulated with an aqueous solution of polyvinylpyrrolidone and polysorbate 80. The granules are dried, reduced to a suitable size and mixed with magnesium stearate and remaining cross-linked polyvinylpyrrolidone. The mixture is then compressed into individual tablets yielding a tablet weight of 230 mg.

**Formulation 12**

| Ingredient | Weight (mg/tablet) |
|---|---|
| Raloxifene HCl | 150.00 |
| Lactose, anhydrous | 52.40 |
| Polysorbate 80 | 4.60 |
| Polyvinylpyrrolidone | 11.50 |
| Polyethylene Glycol 8000 | 11.50 |

The mixture of raloxifene HCl and anhydrous lactose is granulated with an aqueous solution of polysorbate 80 and polyvinylpyrrolidone. The granules are dried, reduced to a suitable size, and mixed with the polyethylene glycol 8000. The mixture is then compressed into individual tablets yielding a tablet weight of 230 mg.

Capsules may be prepared using the ingredients and procedures as described below:

**Formulation 13**

| Ingredient | Weight mg capsule |
|---|---|
| Raloxifene HCl | 30.00 |
| Lactose, hydrous spray-dried | 178.30 |
| Sodium laurylsulfate | 4.60 |
| Cross-linked polyvinylpyrrolidone | 9.20 |
| Hydroxypropyl methylcellulose | 6.90 |
| Colloidal Silicon Dioxide | 1.00 |

The mixture of raloxifene HCl, hydrous spray-dried lactose, and cross-linked polyvinylpyrrolidone is granulated with an aqueous solution of sodium laurylsulfate and hydroxypropyl methylcellulose. The granules are dried, reduced to a suitable size, and mixed with colloidal silicon dioxide. This mixture is then filled into Size 3 hard-shell gelatin capsules utilizing conventional encapsulating equipment, with each capsule containing 230 mg of the final mixture.

**Formulation 14**

| Ingredient | Weight (mg capsule) |
|---|---|
| Raloxifene HCl | 60.00 |
| Lactose, hydrous spray-dried | 148.30 |
| Sodium laurylsulfate | 4.60 |
| Cross-linked polyvinylpyrrolidone | 9.20 |
| Hydroxypropyl methylcellulose | 6.90 |
| Colloidal Silicon Dioxide | 1.00 |

The mixture of raloxifene HCl, hydrous spray-dried lactose, and cross-linked polyvinylpyrrolidone is granulated with an aqueous solution of sodium laurylsulfate and hydroxypropyl methylcellulose. The granules are dried, reduced to a suitable size, and mixed with colloidal silicon dioxide. This mixture is then filled into Size 3 hard-shell gelatin capsules utilizing conventional encapsulating equipment, with each capsule containing 230 mg of the final mixture.

**Formulation 15**

| Ingredient | Weight (mg/capsule) |
|---|---|
| Raloxifene HCl | 150.00 |
| Lactose, hydrous spray-dried | 58.30 |
| Sodium laurylsulfate | 4.60 |
| Cross-linked polyvinylpyrrolidone | 9.20 |
| Hydroxypropyl methylcellulose | 6.90 |
| Colloidal Silicon Dioxide | 1.00 |

The mixture of raloxifene HCl, hydrous spray-dried lactose, and cross-linked polyvinylpyrrolidone is

granulated with an aqueous solution of sodium laurylsulfate and hydroxypropyl methylcellulose. The granules are dried, reduced to a suitable size, and mixed with colloidal silicon dioxide. This mixture is then filled into Size 3 hard-shell gelatin capsules utilizing conventional encapsulating equipment, with each capsule containing 230 mg of the final mixture.

**The claims defining the invention are as follows:**

1. An orally administrable pharmaceutical formulation comprising raloxifene hydrochloride in combination with a surfactant, polyvinylpyrrolidone, and a water-soluble diluent, wherein:

the surfactant is a sorbitan fatty acid ester or a polyoxyethylene sorbitan fatty acid ester; and

the water-soluble diluent is a polyol or sugar.

2. The formulation of claim 1, wherein the surfactant is a polyoxyethylene sorbitol fatty acid ester.

3. The formulation of claim 1 or 2, wherein the surfactant is polysorbate 80.

4. The formulation of claims 1-3, wherein the water-soluble diluent is a sugar.

5. The formulation of claims 1-4, wherein the water-soluble diluent is lactose.

6. The formulation of claims 1-5 further comprising a lubricant and a disintegrant.

7. The formulation of claim 6, wherein the lubricant is magnesium stearate or stearic acid, and the disintegrant is cross-linked polyvinylpyrrolidone.

8. An orally administrable pharmaceutical formulation comprising raloxifene hydrochloride in combination with polysorbate 80, lactose, polyvinylpyrrolidone, and magnesium stearate.

9. The formulation of claim 8 further comprising a disintegrant.

10. The formulation of claim 9 wherein said disintegrant is cross-linked polyvinylpyrrolidine.

11. The formulation of claims 1-9 further comprising a film coating.

12. An orally administrable pharmaceutical formulation substantially as herein described with reference to the Examples.

**Dated 6 May, 1997**
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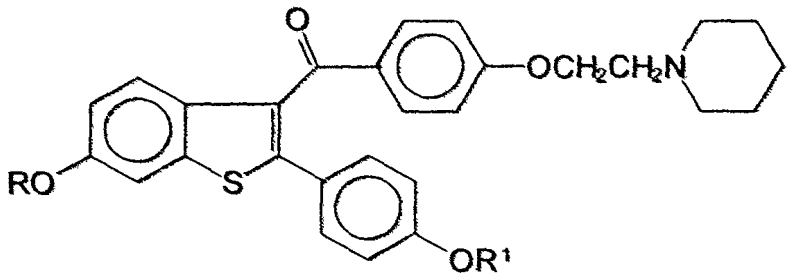
AUSTRALIAN PATENT OFFICE

# Orally Administerable Pharmaceutical Formulations


## Abstract

The invention provides an orally administerable pharmaceutical formulation comprising raloxifene, its esters or ethers, or a pharmaceutically-acceptable salt thereof,

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wherein R and $R^1$ are independently hydrogen, $COR^2$, or $R^3$;

$R^2$ is hydrogen, $C_1$-$C_{14}$ alkyl, $C_1$-$C_3$ chloroalkyl, $C_1$-$C_3$ fluoroalkyl, $C_5$-$C_7$ cycloalkyl, $C_1$-$C_4$ alkoxy, phenyl, or phenyl mono- or disubstituted with $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl;

$R^3$ is $C_1$-$C_4$ alkyl, $C_5$-$C_7$ cycloalkyl, or benzyl in combination with a surfactant and a water-soluble diluent.