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(54) Title: THE COMPOSITION COMPRISING RALOXIFENE WITH AT LEAST ONE ANTIPSYCHOTIC AGENT

(57) Abstract: The present invention relates to a composition which comprises raloxifene or a pharmaceutically acceptable salt thereof and at least one antipsychotic agent or the pharmaceutically acceptable salt thereof and optionally at least one pharmaceutically acceptable excipient for simultaneous, separate or sequential use.



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THE COMPOSITION COMPRISING RALOXIFENE WITH AT LEAST ONE ANTIPSYCHOTIC AGENT

Field of the invention

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The present invention relates to a composition which comprises raloxifene or a pharmaceutically acceptable salt thereof and at least one antipsychotic agent or the pharmaceutically acceptable salt thereof and optionally at least one pharmaceutically acceptable excipient for simultaneous, separate or sequential use.

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Background of the invention

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Schizophrenia is a mental illness which affects how a person thinks, feels and acts. It's not known what causes schizophrenia, but researchers believe that a combination of genetics, brain chemistry and environment contribute to the development of the disorder.

The symptoms of schizophrenia are described as positive, negative, and cognitive.

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- Positive symptoms include hallucinations, delusions, problem of memory and attention, movement disorders.
- negative symptoms include reducing expression of emotions via facial expression or voice, reducing feelings of pleasure in everyday life, difficulty beginning and sustaining activities, reducing speaking
- cognitive symptoms include the ability to understand information and use it to make decisions, trouble focusing or paying attention, problems with the ability to use information immediately after learning it.

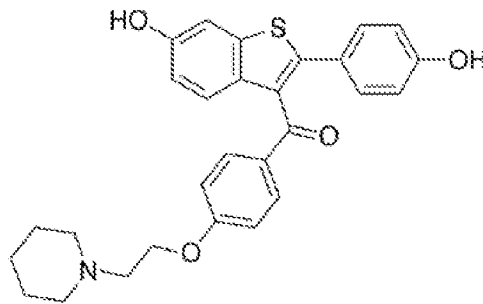
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In the prior art, it is stated that estrogen may be a beneficial treatment for women with schizophrenia. Patients with schizophrenia were treated with estrogen and conjugated estrogens modulate various neurotransmitter symptoms involved in the pathogenesis of schizophrenia. There was significant improvement in their positive symptoms. Furthermore, negative symptoms did not progress. So, estrogen is used for both men and women in the treatment of schizophrenia.

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The chemical name of raloxifene is [6-hydroxy-2-(4-hydroxyphenyl)-benzothiophen-3-yl]-[4-[2-(1-piperidyl) ethoxy] phenyl]-methanone. Its chemical structure, shown below (Formula I), has a formula of $C_{28}H_{27}NO_4S$, with the molecular weight of 473.587 g/mol.



Formula I: raloxifene

Raloxifene is a benzothiophene-derived selective estrogen receptor modulator and widely used for the treatment and prevention of osteoporosis in postmenopausal women. It is disclosed in U.S. patent number 4,418,068. In pharmaceutical formulations, it is used in the form of a hydrochloride salt and is marketed under the brand name Evista® by Eli Lilly.

It has also been found that the combination of raloxifene with at least one antipsychotic agent is more effective compared to antipsychotic agent alone because, this combination also helps to reduce positive symptoms (hallucinations, delusions, problem of memory and attention) due to the disease. Furthermore, there is no combination of raloxifene with at least one antipsychotic agent in the prior art.

At this invention, combining more than one molecule in one dosage form increases the patient's compliance. However, while this combination is increasing the patients' quality of life, combining more than one molecule in one dosage form is also reduce undesired schizophrenia symptoms which can be hallucinations, delusions, problem of memory and attention.

Detailed description of the Invention

The main object of the present invention is to provide stable dosage form with desired dissolution profiles, eliminating schizophrenia symptoms and bringing additional advantages to the relevant prior art.

Another object of the present invention is to provide improved compositions which are less irritating, stable, rapid and effective treatment.

Another object of the present invention is to provide rapid penetration of drug substances and provide high stability.

The term "composition" means that when drugs are administered together, a combined action is obtained which is higher than the individual actions of the respective drugs when they are used separately.

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The term "raloxifene" as used herein refers to raloxifene in the form the free base or in the form of pharmaceutically acceptable salts, crystalline polymorph, solvates, hydrates, esters or mixture thereof.

- 10 The term "antipsychotic agent" as used herein refers to an antipsychotic agent in the form the free base or in the form of pharmaceutically acceptable salts, crystalline polymorph, solvates, hydrates, esters or mixture thereof. Antipsychotic agents are drugs that are used to treat symptoms of psychosis such as delusions, hallucinations, paranoia, or confused thoughts.

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An embodiment of this present invention is to provide a pharmaceutical composition comprising raloxifene and at least one antipsychotic agent.

An embodiment of this present invention is to combine raloxifene and at least one antipsychotic agent in a same or stable dosage form with desired dissolution profiles.

- 20 According to the present invention, suitable antipsychotic agents are selected from the group comprising paliperidone, aripiprazole, brexpiprazole, olanzapine, amisulpride or mixtures thereof.

- 25 In order to combine two different molecules in one dosage form, molecules should be compatible with each other to achieve desired stability and dissolution for the patient's compliance.

According to one embodiment of the present invention, the pharmaceutical composition is raloxifene with paliperidone.

- 30 According to one embodiment in the present invention, the pharmaceutical composition is raloxifene with aripiprazole.

According to one embodiment in the present invention, the pharmaceutical composition is raloxifene with brexpiprazole.

According to one embodiment in the present invention, the pharmaceutical composition is raloxifene with olanzapine.

According to one embodiment in the present invention, the pharmaceutical composition is raloxifene with amisulpride.

- 5 According to an embodiment of the present invention, the pharmaceutical composition comprises at least one pharmaceutically acceptable excipient is selected from fillers, binders, disintegrants, diluents, dispersing agents, surfactants, modified release agents, lubricants, glidants, plasticizers, preservatives, sweeteners, flavorings agents, melting components, inert agents, stabilizers, antioxidants, coating agents, coloring agents, pH
10 adjusters or mixtures thereof.

Suitable fillers are selected from the group comprising anhydrous lactose, lactose monohydrate, microcrystalline cellulose, ammonium alginate, calcium carbonate, calcium phosphate, calcium phosphate dehydrate, neutral pellets, calcium sulfate, cellulose,
15 cellulose acetate, compressible sugar, confectioner's sugar, dextrates, dextrin, dextrose, erythritol, ethylcellulose, fructose, glyceryl palmitostearate, hydrogenated vegetable oil type I, isomalt, kaolin, lactitol, , mannitol, magnesium carbonate, magnesium oxide, maltodextrin, maltose, medium chain triglycerides, polydextrose, polymethacrylates, polyvinylpyrrolidone, simethicone, sodium alginate, sodium chloride, sorbitol, starch,
20 sucrose, sugar sphereals, sulfobutylether beta-cyclodextrin, talc, tragacanth, trehalose, polysorbate 80, xylitol or mixtures thereof.

Suitable binders are selected from the group comprising microcrystalline cellulose and guar gum, pregelatinized starch, polyvinylpyrrolidone, sugars, glucose syrup, natural
25 gums, gelatin, collagen, agar, alginates, carbomers, carboxymethylcellulose sodium, cellulose acetate phthalate, chitosan, povidone, starch, corn starch, starch mucilage, acacia mucilage, dextrates, dextrin, dextrose, ethylcellulose, glyceryl behenate, hydrogenated vegetable oil type I, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, hydroxypropyl starch, hypromellose, liquid glucose, magnesium
30 aluminum silicate, maltodextrin, maltose, methylcellulose, pectin, poloxamer, polycarbophil, polydextrose, polyethylene oxide, polymethacrylates, alumina hydroxide, stearic acid, sucrose, bentonite, laponit, cetostearyl alcohol, polyoxyethylene-alkyl ethers, pullulan or mixtures thereof.

Suitable disintegrants are selected from the group comprising mannitol, sodium starch glycolate, polyvinylpyrrolidone, crospovidone, croscarmellose sodium, low-substituted hydroxypropyl cellulose, pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose, docusate sodium, guar gum, polyacryline potassium, sodium alginate, corn starch, alginic acid, alginates, ion-exchange resins, magnesium aluminium silica, poloxamer, sodium glycine carbonate or mixtures thereof.

Suitable diluents are selected from the group comprising microcrystalline cellulose, mannitol, spray-dried mannitol, lactose, lactose monohydrate, starch, dextrose, sucrose, fructose, maltose, sorbitol, xylitol, inositol, kaolin, inorganic salts, calcium salts, polysaccharides, dicalcium phosphate, sodium chloride, dextrates, lactitol, maltodextrin, sucrose-maltodextrin mixture, trehalose, sodium carbonate, sodium bicarbonate, calcium carbonate or mixtures thereof.

Suitable dispersing agents are selected from the group comprising calcium silicate, magnesium aluminum silicate, sorbitan esters, aluminum oxide, phospholipids, poloxamer or mixtures thereof.

Suitable surfactants are selected from the group comprising sodium lauryl sulfate, cetylpyridinium chloride, docusate sodium, lauric acid, polyoxyethylene sorbitan fatty acid esters (polysorbate), phospholipids, cetrimide or mixtures thereof.

Suitable modified release agents are selected from the group comprising ethyl acrylate, polymethacrylates (Eudragit), ethyl methacrylate copolymer, ethylcellulose, methylcellulose, hypromellose phthalate, polydextrose, polyvinylacetate phthalate, zein, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, hydroxymethyl cellulose, gelatin, polyethylene oxide, acacia, dextrin, starch, polyhydroxyethylmethacrylate, sodium carboxymethylcellulose, carboxymethyl cellulose, sodium alginate, alginic acid, pectin, polyglucuronic acid, polygalacturonic acid, chondroitin sulfate, carrageenan, lambda carrageenan, iota carrageenan, furcellaran, xanthan gum, a polymer of acrylic acid, Carbopol 934, 940, 941 or 974P , agar, gual gum, psyllium seed gum, gellan gum, locust bean gum, tara gum, tamarind gum, gum arabic, curdlan, galactomannan, glucomannan, glyceryl behenate, nitrocellulose, methylcellulose, proteoglycan, glycoprotein, actin, tubulin, hemoglobin, insulin, fibrin, albumin, myosin, collagen, casein, pullulan, chitosan,

glycerol, propylene glycol, macrogols, phthalate esters, dibutyl sebacate, citrate esters, triacetin, castor oil, acetylated monoglycerides, fractionated coconut oil, hydrogenated vegetable oil, hydrogenated castor oil, carnauba wax, candellia wax, beeswax, paraffin wax, stearic acid, cetyl alcohol, cetostearyl alcohol, gelucire (stearyl macrogolglyceride) or mixtures thereof.

Suitable lubricants are selected from the group comprising magnesium stearate, calcium stearate, zinc stearate, talc, waxes, boric acid, hydrogenated vegetable oil, sodium chlorate, magnesium lauryl sulfate, sodium oleate, sodium acetate, sodium benzoate, polyethylene glycol, stearic acid, fatty acid, fumaric acid, glyceryl palmito sulphate, sodium stearyl fumarate, sodium lauryl sulphate or mixtures thereof.

Suitable glidants are selected from the group comprising talc, aluminium silicate, colloidal silicon dioxide, colloidal silica, calcium silicate, magnesium silicate, magnesium oxide, starch or mixtures thereof.

Suitable plasticizers are selected from the group comprising polyethylene glycols of different molecular weights, triacetin, tributyl citrate, triethyl citrate, chlorobutanol, dibutyl phthalate, dibutyl sebacate, dimethyl phthalate, glycerin, mannitol, petrolatum and lanolin alcohols or mixtures thereof.

Suitable preservatives are selected from the group comprising methyl paraben, propyl paraben and their salts (such as sodium, potassium), sodium benzoate, benzyl alcohol, citric acid, benzoic acid, m-cresol, phenol or mixtures thereof.

Suitable sweeteners are selected from the group comprising aspartame, potassium acesulfame, sodium saccharinate, neohesperidine dihydrochalcone, sucralose, saccharin, sugars, sucrose, glucose, lactose, fructose, mannitol, sorbitol, xylitol, erythritol or mixtures thereof.

Suitable flavoring agents are selected from the group comprising menthol, peppermint, cinnamon, chocolate, vanillin, fruit essences, cherry, orange, strawberry, grape, black currant, raspberry, banana, red fruits, wild berries or mixtures thereof.

Suitable melting components are selected from the group comprising gelucire (stearyl macrogolglyceride), poloxamer (polyoxyethylene-polyoxypropylene block copolymer),

polyethylene glycol, povidone, soluplus, cationic methacrylate, copovidone, methacrylic acid copolymers, cellulose acetate phthalate, acetylated monoglyceride, butyl phthalylbutyl glycolate, dibutyl tartrate, diethyl phthalate, dimethyl phthalate, ethyl phthalylethyl glycolate, glycerin, propylene glycol, triacetin, triacetin citrate, tripropionin or mixtures thereof.

Suitable inert agents between the two molecules wherein the inert agents are selected from starch, lactose, sugar alcohol like D-mannitol, erythritol, low substituted hydroxypropyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, methylcellulose, hydroxyethyl methylcellulose or mixtures thereof.

Suitable stabilizers are selected from the group comprising citric acid, fumaric acid, tartaric acid, sodium citrate, sodium chloride, sodium benzoate, sodium dihydrogen phosphate, calcium carbonate, magnesium carbonate, arginine, lysine, meglamine, ascorbic acid, gallic acid esters or the mixtures thereof, and preferably, citric acid, fumaric acid, arginine or mixtures thereof.

Suitable antioxidants are selected from the group comprising alpha tocopherol, ascorbic acid, ascorbyl palmitate, butylhydroxyanisole (BHA), butylhydroxytoluene (BHT), erythorbic acid, monothioglycerol, potassium metabisulfite, propyl gallate, sodium ascorbate, sodium metabisulfite, sodium sulfite, thymol or mixtures thereof.

Suitable coating agents are selected from the group comprising polymethacrylates, hydroxypropyl methylcellulose, lactose monohydrate, lecithin, xanthan gum, hydroxypropyl cellulose, polyvinyl alcohol, titanium dioxide, colloidal silica, polyethylene glycol (PEG), talc, polyvinyl alcohol-polyethylene glycol copolymers, ethylcellulose dispersions (Surelease®), polyvinylpyrrolidone, polyvinylpyrrolidone-vinyl acetate copolymer (PVP-VA), all kinds of Opadry®, pigments, dyes, macrogol, coloring agents or mixtures thereof. Preferably, coating agents are Opadry® AMB and Kollicoat® IR. Opadry® AMB comprises polyvinyl alcohol, titanium dioxide, talc, lecithin, xanthan gum and coloring agents. Kollicoat® IR comprises polyvinyl alcohol, polyethylene glycol copolymers and colloidal silica.

Suitable coloring agents are selected from the group comprising ferric oxide, titanium dioxide, Food, Drug & Cosmetic (FD&C) dyes (such as; FD&C blue, FD&C green, FD&C

red, FD&C yellow, FD&C lakes), poncau, indigo Drug & Cosmetic (D&C) blue, indigotine FD&C blue, carmoisine indigotine (indigo Carmine); iron oxides (such as; iron oxide red, yellow, black), quinoline yellow, flaming red, carmine, carmoisine, sunset yellow or mixtures thereof.

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Suitable pH adjusters are selected from the group comprising alkali metal citrate, citric acid/sodium citrate, tartaric acid, fumaric acid, sorbic acid, citric acid, succinic acid, adipic acid, ascorbic acid, glutaric acid, potassium hydrogen tartrate, sodium hydrogen tartrate, potassium hydrogen phthalate, sodium hydrogen phthalate, potassium dihydrogen phosphate, sodium dihydrogen phosphate, disodium hydrogen phosphate, hydrochloric acid/sodium hydroxide or mixtures thereof, preferably pH adjusters are citric acid, fumaric acid, ascorbic acid, sodium dihydrogen phosphate, glycine, glutamic acid or mixtures thereof.

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15 According to an embodiment of this present invention, the pharmaceutical composition is administered orally.

According to an embodiment of this present invention, the pharmaceutical composition is in the form of tablets, capsules, orally disintegrating tablets, strips, syrups, powders, pastilles, sachet, effervescent compositions, pills, hard or soft gelatin capsules, coated bead systems, granules, microspheres, dragees, films, orally administrable films, solutions, solids, elixirs, tinctures, suspensions, colloidal dispersions, dispersions or emulsions.

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25 In this present invention, the pharmaceutical composition is in the form of tablets, capsules, pastilles or strips.

In this present invention, the pharmaceutical composition is in the form of tablet. Tablet may be consisted of separated compartments or layer.

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According to an embodiment of this present invention, the pharmaceutical composition is formulated as tablets comprising film-coated tablets, orally disintegrating tablets, compressed tablets, coated or uncoated tablets, multilayer tablets, mini tablets, bilayer tablets, pellet in tablet, buccal tablets, sublingual tablets, effervescent tablets, immediate release tablets, core-in-tablet, modified release tablets, tablet-in-tablet, gastric disintegrating tablets, chewable tablet, dispersing tablets or lozenges.

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Preferably, the pharmaceutical composition is formulated as film coated tablet or orally disintegrating tablets.

- 5 In this present invention, the pharmaceutical composition is formulated as tablet form. Tablet comprises at least one type of particle, for example; mini-tablets, pellets, core, agglomerates, granules, powders, liposomes, sphericals or mixtures thereof.

According to an embodiment of this present invention, each type of particle comprises at
10 least one active agent.

In this present invention, the pharmaceutical composition may further comprise a film coating if necessary.

- 15 In this present invention, the pharmaceutical composition is formulated as capsule form. Capsule comprises at least one type of particle, for example; mini-capsules, mini-tablets, pellets, core, agglomerates, granules, powders, liposomes, sphericals or mixtures thereof.

According to an embodiment of this present invention, the pharmaceutical composition is
20 formulated as mini-capsules in capsule wherein the mini-capsules comprise at least one active agent.

According to an embodiment of this present invention, the pharmaceutical composition is formulated as mini-tablets in capsule wherein a mini-tablets comprise at least one active
25 agent.

According to an embodiment of this present invention, the pharmaceutical composition is formulated as pellets in capsule wherein pellets comprise at least one active agent.

- 30 In this present invention, the pharmaceutical composition of raloxifene HCl and paliperidone comprises mini-tablets and granules.

The compositions of invention may be developed into oral dosage form comprising immediate release, extended release, sustained release, controlled release, modified
35 release and delayed release or combination thereof. At this invention, the composition may be prepared using modified release agents.

The pharmaceutical composition wherein said composition comprises at least one of the following drug compositions for combined, separate or sequential administration:

- 5 -raloxifene, paliperidone or their pharmaceutically acceptable salt, solvate or polymorph
- raloxifene, aripiprazole or their pharmaceutically acceptable salt, solvate or polymorph
- raloxifene, brexpiprazole or their pharmaceutically acceptable salt, solvate or polymorph
- raloxifene, olanzapine or their pharmaceutically acceptable salt, solvate or polymorph
- raloxifene, amisulpride or their pharmaceutically acceptable salt, solvate or polymorph

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In one embodiment of the invention, the pharmaceutical composition comprises;

- a) 4.0 - 80.0% by weight of raloxifene HCl
- b) 0.5 - 70.0% by weight of antipsychotic agents
- c) 35.0 - 60.0% by weight of filler
- 15 d) 1.0 - 20.0% by weight of binder
- e) 2.0 - 20.0% by weight of disintegrant
- f) 0.1 - 5.0% by weight of lubricant
- g) 1.0 - 15.0% by weight of surfactant
- h) 1.0 - 7.0% by weight of coating agents

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In one embodiment of the invention, the pharmaceutical composition comprises;

- i) 10.0 - 40.0% by weight of raloxifene HCl
- j) 0.5 - 17.0% by weight of aripiprazole
- k) 35.0 - 60.0% by weight of lactose monohydrate
- 25 l) 1.0 - 20.0% by weight of anhydrous lactose
- m) 1.0 - 20.0% by weight of povidone
- n) 2.0 - 20.0% by weight of sodium starch glycolate
- o) 0.1 - 5.0% by weight of magnesium stearate
- p) 1.0 - 15.0% by weight of polysorbate
- 30 q) 1.0 - 7.0% by weight of Opadry® AMB/Kollicoat® IR.

In one embodiment of the invention, the pharmaceutical composition comprises;

- a) 10.0 - 45.0% by weight of raloxifene HCl
- b) 0.5 - 17.0% by weight of aripiprazole
- 35 c) 10.0 - 50.0% by weight of microcrystalline cellulose
- d) 1.0 - 25.0% by weight of pregelatinized starch

- e) 1.0 - 25.0% by weight of microcrystalline cellulose and guar gum
- f) 5.0 - 30.0% by weight of mannitol
- g) 5.0 - 30.0% by weight of croscarmellose sodium
- h) 0.1 - 3.0% by weight of citric acid
- 5 i) 0.1 - 5.0% by weight of sucralose
- j) 0.1 - 5.0% by weight of vanillin
- k) 0.1 - 5.0% by weight of sodium stearyl fumarate

In one embodiment of the invention, the pharmaceutical composition comprises;

- 10 a) 10.0 - 50.0% by weight of raloxifene HCl
- b) 0.5 - 20.0% by weight of brexpiprazole
- c) 50.0 - 70.0% by weight of lactose monohydrate
- d) 2.0 - 15.0% by weight of hypromellose
- e) 5.0 - 20.0% by weight of corn starch
- 15 f) 0.1 - 5.0% by weight of magnesium stearate
- g) 0.1 - 5.0% by weight of polysorbate
- h) 1.0 - 7.0% by weight of Opadry® AMB/Kollicoat® IR.

In one embodiment of the invention, the pharmaceutical composition comprises;

- 20 a) 10.0 - 50.0% by weight of raloxifene HCl
- b) 0.5 - 15.0% by weight of olanzapine
- c) 50.0 - 72.0% by weight of lactose monohydrate
- d) 2.0 - 15.0% by weight of hydroxypropyl cellulose
- e) 4.0 - 20.0% by weight of microcrystalline cellulose
- 25 f) 0.5 - 15.0% by weight of crospovidone
- g) 0.1 - 5.0% by weight of magnesium stearate
- h) 0.1 - 5.0% by weight of polysorbate
- i) 1.0 - 8.0% by weight of Opadry® AMB/Kollicoat® IR.

30 In one embodiment of the invention, the pharmaceutical composition comprises;

- a) 5.0 - 30.0% by weight of raloxifene HCl
- b) 10.0 - 70.0% by weight of amisulpride
- c) 5.0 - 60.0% by weight of lactose monohydrate
- d) 2.0 - 15.0% by weight of hydroxypropyl cellulose
- 35 e) 10.0 - 25.0% by weight of microcrystalline cellulose
- f) 0.5 - 15.0% by weight of sodium starch glycolate

- g) 0.1 - 5.0% by weight of magnesium stearate
- h) 0.1 - 5.0% by weight of polysorbate
- i) 1.0 - 8.0% by weight of Opadry® AMB/Kollicoat® IR.

- 5 In one embodiment of the invention, the pharmaceutical composition comprises;
- a) 40.0%-75.0% by weight of Raloxifene HCl
 - b) 1.0%-10.0% by weight of Paliperidone
 - c) 10.0%-55.0% by weight of lactose monohydrate
 - d) 2.0%-15.0% by weight of povidone
 - 10 e) 3.0%- 30.0% by weight of crospovidone
 - f) 20.0%-55.0% by weight of polyethylene oxide
 - g) 0.1%-5.0% by weight of magnesium stearate
 - h) 0.1%-5.0% by weight of silicon dioxide
 - i) 10.0%-55.0% by weight of sodium chloride
 - 15 j) 0.1%-5.0% by weight of polyethylene glycol
 - k) 0.1%-7.0% by weight of polysorbate 80
 - l) 8.0%-35.0% by weight of eudragit
 - m) 2.0%-12.0% by weight of Opadry® AMB/Kollicoat® IR.

- 20 The pharmaceutical composition of the present invention may be prepared, using standard techniques and manufacturing processes well known in the art, such as direct compression, wet or dry granulation, hot melt granulation, hot melt extrusion, fluidized bed granulation, extrusion/spheronization, slugging, spray drying and solvent evaporation.

- 25 Furthermore, the stable composition is obtained by using a wet granulation method or dry granulation and therefore a simple and low-cost production method was employed.

- In this present invention, a good dissolution of the pharmaceutical composition is obtained and a good content uniformity and a simple preparation process are in favor of industrial
30 production.

Example 1: Film coated tablet comprising raloxifene and antipsychotic agents

	(%) amount (w/w)
Raloxifene HCl	4.0%-80.0%
Antipsychotic agents	0.5%-70.0%
Filler	35.0%-60.0%

Binder	1.0%-20.0%
Disintegrant	2.0%- 20.0%
Lubricant	0.1%-5.0%
Surfactant	1.0%-15.0%
Coating agent	1.0%-7.0%
Total	100

Example 2: Orally disintegrating tablet comprising raloxifene and antipsychotic agents

	(%) amount (w/w)
Raloxifene HCl	4.0%-80.0%
Antipsychotic agents	0.5%-70.0%
Filler	10.0%-75.0%
Binder	1.0%-25.0%
Disintegrant	2.0%- 30.0%
Glidant	0.1%-5.0%
Lubricant	0.1%-5.0%
Ph-Adjuster	0.1%-5.0%
Sweetener	0.1%-3.0%
Flavoring	0.1%-5.0%
Total	100

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Example 3: Film coated tablet comprising aripiprazole and raloxifene

	(%) amount (w/w)
Raloxifene HCl	10.0%-40.0%
Aripiprazole	0.5%-17.0%
Filler	35.0%-60.0%
Binder	1.0%-20.0%
Disintegrant	2.0%- 20.0%
Lubricant	0.1%-5.0%
Surfactant	1.0%-15.0%
Coating agent	1.0%-7.0%
Total	100

Example 4: Film coated tablet comprising aripiprazole and raloxifene

	(%) amount (w/w)
Raloxifene HCl	10.0%-40.0%
Aripiprazole	0.5%-17.0%
Lactose monohydrate	35.0%-60.0%
Anhydrous lactose	1.0%-20.0%
Povidone	1.0%-20.0%
Sodium starch glycolate	2.0%- 20.0%
Magnesium stearate	0.1%-5.0%
Polysorbate	1.0%-15.0%
Opadry® AMB/Kollicoat® IR	1.0%-7.0%
Total	100

Process for example 4:

The process for preparation of the pharmaceutical composition comprises the following steps:

- a) Adding raloxifene HCl, aripiprazole, lactose monohydrate, sodium starch glycolate and polysorbate and mixing
- b) Mixing povidone with water on a separate tank
- c) Mixing step (a) mixture and step (b) mixture
- d) drying the mixture, then sieving the mixture
- e) Adding magnesium stearate and then mixing
- f) Then, pressing to form tablet
- g) Coating tablets with Opadry® AMB/Kollicoat® IR

Example 5: Orally disintegrating tablets comprising aripiprazole and raloxifene

	(%) amount (w/w)
Raloxifene HCl	10.0%-45.0%
Aripiprazole	0.5%-17.0%
Filler	10.0%-50.0%
Binder	1.0%-25.0%
Disintegrant	5.0%- 30.0%
Ph-Adjuster	0.1%-3.0%
Sweetener	0.1%-3.0%
Flavoring	0.1%-5.0%

Lubricant	0.1%-5.0%
Glidant	0.1%-5.0%
Total	100

Example 6: Orally disintegrating tablets comprising aripiprazole and raloxifene

	(%) amount (w/w)
Raloxifene HCl	10.0%-45.0%
Aripiprazole	0.5%-17.0%
Microcrystalline cellulose	10.0%-50.0%
Pregelatinized Starch	1.0%-25.0%
Microcrystalline cellulose and guar gum	1.0%-25.0%
Mannitol	5.0%- 30.0%
Croscarmellose sodium	5.0%- 30.0%
Citric acid	0.1%-3.0%
Sucralose	0.1%-3.0%
Vanillin	0.1%-5.0%
Sodium stearyl fumarate	0.1%-5.0%
Colloidal silicon dioxide	0.1%-5.0%
Total	100

Process for example 6:

- 5 The process for preparation of the pharmaceutical composition comprises the following steps:
 - a) Adding raloxifene HCl, aripiprazole, microcrystalline cellulose and mixing
 - b) Adding microcrystalline cellulose and guar gum, mannitol, pregelatinized starch, croscarmellose sodium, sucralose on step (a) mixture and mixing
- 10 c) Adding citric acid, colloidal silicon dioxide, sodium stearyl fumarate, vanillin and then mixing
- d) Then, pressing to form tablet

Example 7: Film coated tablet comprising brexpiprazole and raloxifene

	(%) amount (w/w)
Raloxifene HCl	10.0%-50.0%
Brexpiprazole	0.5%-20.0%
Filler	50.0%-70.0%

Binder	2.0%-15.0%
Disintegrant	5.0%- 20.0%
Lubricant	0.1%-5.0%
Surfactant	0.1%-5.0%
Coating agent	1.0%-7.0%
Total	100

Example 8: Film coated tablet comprising brexpiprazole and raloxifene

	(%) amount (w/w)
Raloxifene HCl	10.0%-50.0%
Brexpiprazole	0.5%-20.0%
Lactose monohydrate	50.0%-70.0%
Povidone	2.0%-15.0%
Corn starch	5.0%- 20.0%
Magnesium stearate	0.1%-5.0%
Polysorbate 80	0.1%-5.0%
Opadry® AMB/Kollicoat® IR	1.0%-7.0%
Total	100

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Process for example 8:

The process for preparation of the pharmaceutical composition comprises the following steps:

- a) Mixing lactose monohydrate and polysorbate 80 and then sieving
- 10 b) Adding raloxifene HCl, corn starch and mixing
- c) Mixing brexpiprazole and povidone with water-alcohol mixture (40:60) on a separate tank
- d) Adding step (c) mixture on step (b) mixture and mixing
- e) drying the mixture, then sieving the mixture
- 15 f) Adding magnesium stearate and then mixing
- g) Then, pressing to form tablet
- h) Coating tablets with Opadry® AMB/Kollicoat® IR

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Example 9: Film coated tablet comprising olanzapine and raloxifene

	(%) amount (w/w)
Raloxifene HCl	10.0%-50.0%
Olanzapine	0.5%-15.0%
Filler	50.0%-72.0%
Binder	2.0%-15.0%
Disintegrant	4.0%- 20.0%
Lubricant	0.1%-5.0%
Surfactant	0.1%-5.0%
Coating agent	1.0%-8.0%
Total	100

Example 10: Film coated tablet comprising olanzapine and raloxifene

	(%) amount (w/w)
Raloxifene HCl	10.0%-50.0%
Olanzapine	0.5%-15.0%
Lactose monohydrate	50.0%-72.0%
Hydroxypropyl cellulose	2.0%-15.0%
Microcrystalline cellulose	4.0%- 20.0%
Crospovidone	0.5%-15.0%
Magnesium stearate	0.1%-5.0%
Polysorbate 80	0.1%-5.0%
Opadry® Amb/Kollicoat® IR	1.0%-8.0%
Total	100

5 Process for example 10:

The process for preparation of the pharmaceutical composition comprises the following steps:

- a) Mixing lactose monohydrate and polysorbate 80 and then sieving
- b) Adding raloxifene HCl, olanzapine, microcrystalline cellulose, crospovidone,
- 10 hydroxypropyl cellulose and mixing
- c) Granulating the mixture with water on a separate tank
- d) Drying the mixture, then sieving the mixture
- e) Adding magnesium stearate and then mixing
- f) Then, pressing to form tablet
- 15 g) Coating tablets with Opadry® AMB/Kollicoat® IR

Example 11: Film coated tablet comprising amisulpride and raloxifene

	(%) amount (w/w)
Raloxifene HCl	5.0%-30.0%
Amisulpride	10.0%-70.0%
Filler	50.0%-75.0%
Binder	2.0%-15.0%
Disintegrant	8.0%- 30.0%
Lubricant	0.1%-5.0%
Surfactant	0.1%-5.0%
Coating agent	3.0%-12.0%
Total	100

Example 12: Film coated tablet comprising comprising amisulpride and raloxifene

	(%) amount (w/w)
Raloxifene HCl	5.0%-30.0%
Amisulpride	10.0%-70.0%
Lactose monohydrate	5.0%-60.0%
Hydroxypropyl cellulose	2.0%-15.0%
Microcrystalline cellulose	10.0%- 25.0%
Sodium Starch glycolate	0.5%-15.0%
Magnesium stearate	0.1%-5.0%
Polysorbate 80	0.1%-5.0%
Opadry® Amb/Kollicoat® IR	1.0%-8.0%
Total	100

5 Process for example 12:

The process for preparation of the pharmaceutical composition comprises the following steps:

- a) Mixing lactose monohydrate and polysorbate 80 and then sieving
- b) Adding raloxifene HCl, amisulpride, microcrystalline cellulose, sodium starch glycolate, hydroxypropyl cellulose and mixing
- c) Adding polysorbate 80 and granulating the mixture with water
- d) Drying the mixture, then sieving the mixture
- e) Adding magnesium stearate and then mixing
- f) Then, pressing to form tablet
- g) Coating tablets with Opadry® AMB/Kollicoat® IR

Example 13: Capsule comprising paliperidone and raloxifene

	(%) amount (w/w)
Raloxifene HCl	40.0%-75.0%
Paliperidone	1.0%-10.0%
Filler	10.0%-55.0%
Binder	2.0%-15.0%
Disintegrant	3.0%- 30.0%
Lubricant	0.1%-5.0%
Glidant	0.1%-5.0%
Stabilizer	10.0%-55.0%
Plasticizer	0.1%-5.0%
Modified release agents	8.0%-35.0%
Surfactant	0.1%-5.0%
Coating agent	2.0%-12.0%
Total	100

5 Example 14: Capsule comprising paliperidone and raloxifene

	(%) amount (w/w)
Raloxifene	40.0%-75.0%
Paliperidone	1.0%-10.0%
Lactose monohydrate	10.0%-55.0%
Povidone	2.0%-15.0%
Crospovidone	3.0%- 30.0%
Polyethylene oxide	20.0%-55.0%
Magnesium stearate	0.1%-5.0%
Silicon dioxide	0.1%-5.0%
Sodium chloride	10.0%-55.0%
Polyethylene glycol	0.1%-5.0%
Polysorbate 80	0.1%-7.0%
Eudragit	8.0%-35.0%
Opadry® AMB/Kollicoat® IR	2.0%-12.0%
Total	100

According to example 13 or 14, form of raloxifene HCl is granule and form of paliperidone is mini-tablet.

Process for example 14:

5 Production mini-tablet

- a) Mixing polyethylene oxide and sodium chloride
- b) Adding magnesium stearate and then mixing
- c) Then, pressing to form mini-tablet
- d) Mixing water, hydrochloric acid, paliperidone and coating agents on a separate
- 10 tank
- e) Coating mini-tablet with coating solution in step (d)
- f) Mixing modified release agents, water, Opadry® AMB/Kollicoat® IR, polyethylene glycol on a separate tank
- g) Coating mini-tablet again with coating solution in step (f)

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Production granule

- a) Mixing lactose monohydrate, polysorbate 80 and then sieving
- b) Adding raloxifene HCl, crospovidone and mixing
- c) Adding povidone granulating the mixture with water
- 20 d) Drying the mixture, then sieving the mixture
- e) Adding silicon dioxide and mixing
- f) Adding magnesium stearate and mixing

Then, filling granules and mini-tablets in a capsule

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CLAIMS

1. A pharmaceutical composition comprising raloxifene and at least one antipsychotic agent.
- 5 2. The pharmaceutical composition according to claim 1, wherein antipsychotic agents are selected from the group comprising paliperidone, aripiprazole, brexpiprazole, olanzapine, amisulpride or mixtures thereof.
3. The pharmaceutical composition according to claim 1 or 2, wherein said composition comprising from raloxifene with paliperidone or raloxifene with
10 aripiprazole or raloxifene with brexpiprazole or raloxifene with olanzapine or raloxifene with amisulpride.
4. The pharmaceutical composition according to claim 3, wherein the composition is raloxifene with paliperidone.
5. The pharmaceutical composition according to claim 3, wherein the composition is
15 raloxifene with aripiprazole.
6. The pharmaceutical composition according to claim 3, wherein the composition is raloxifene with brexpiprazole.
7. The pharmaceutical composition according to claim 3, wherein the composition is raloxifene with olanzapine.
8. The pharmaceutical composition according to claim 3, wherein the composition is
20 raloxifene with amisulpride.
9. The pharmaceutical composition according to any preceding claims, wherein the pharmaceutical composition comprising at least one pharmaceutically acceptable excipient is selected from fillers, binders, disintegrants, diluents, dispersing agents,
25 surfactants, modified release agents, lubricants, glidants, plasticizers, preservatives, sweeteners, flavoring agents, melting components, inert agents, stabilizers, antioxidants, coating agents, coloring agents, pH adjusters or mixtures thereof.
10. The pharmaceutical composition according to any preceding claims, wherein the
30 pharmaceutical composition is administered orally.

11. The pharmaceutical composition according to claim 10, wherein the pharmaceutical composition is in the form of tablets, capsules, orally disintegrating tablets, strips, syrups, powders, pastilles, sachet, effervescent compositions, pills, hard or soft gelatin capsules, coated bead systems, granules, microspheres, dragees, films, orally administrable films, solutions, solids, elixirs, tinctures, suspensions, colloidal dispersions, dispersions or emulsions.
12. The pharmaceutical composition according to claim 11, wherein the pharmaceutical composition is in the form of tablets or capsules or pastilles or strips.
13. The pharmaceutical composition according to claim 12, wherein the pharmaceutical composition is in the form of tablet.
14. The pharmaceutical composition according to claim 13, wherein the pharmaceutical composition is formulated as tablets comprising film-coated tablets, orally disintegrating tablets, compressed tablets, coated or uncoated tablets, multilayer tablets, mini tablets, bilayer tablets, pellet in tablet, buccal tablets, sublingual tablets, effervescent tablets, immediate release tablets, core-in-tablet, modified release tablets, tablet-in-tablet, gastric disintegrating tablets, chewable tablet, dispersing tablets or lozenges.
15. The pharmaceutical composition according to claim 14, wherein the tablet comprising at least one type of particle.
16. The pharmaceutical composition according to claim 15, wherein said particle is selected from the group comprising mini-tablets, pellets, core, agglomerates, granules, powders, liposomes, sphericals or mixtures thereof.
17. The pharmaceutical composition according to claim 12, wherein the pharmaceutical composition is in the form of capsule.
18. The pharmaceutical composition according to claim 17, wherein the capsule comprising at least one type of particle.
19. The pharmaceutical composition according to claim 18, wherein said particle is selected from the group comprising mini-capsules, mini-tablets, pellets, core, agglomerates, granules, powders, liposomes, sphericals or mixtures thereof.

20. The pharmaceutical composition according to any preceding claims, wherein the pharmaceutical composition may be prepared using direct compression, wet or dry granulation, hot melt granulation, hot melt extrusion, fluidized bed granulation, extrusion/spheronization, slugging, spray drying or solvent evaporation.