ABSTRACT

PHARMACEUTICAL COMBINATIONS OF DRONEDARONE

The present invention relates to a pharmaceutical combination comprising dronedarone or a pharmaceutically acceptable salt thereof in combination with rivaroxaban and at least one pharmaceutically acceptable excipient.

CLAIMS

1. A pharmaceutical combination comprising dronedarone or a pharmaceutically acceptable salt thereof in combination with rivaroxaban and at least one pharmaceutically acceptable excipient.

2. The pharmaceutical combination according to claim 1, wherein dronedarone or a pharmaceutically acceptable salt is dronedarone hydrochloride.

3. The pharmaceutical combination according to claim 1 or 2, wherein dronedarone hydrochloride is present in an amount of between 5 to 98 %, preferably between 20 to 98 % and more preferably it is 40 to 98 % by weight of total formulation.

4. The pharmaceutical combination according to claim 1 or 2, wherein dronedarone hydrochloride present in an amount of between 50 to 1000 mg, preferably 200 to 800 mg and more preferably it is 400 to 800 mg.

5. The pharmaceutical combination according to claim 1, wherein rivaroxaban is present in an amount of between 0.01 to 50 %, preferably between 0.01 to 30 % and more preferably it is 0.01 to 10 % by weight of total formulation.

6. The pharmaceutical combination according to claim 5, wherein rivaroxaban present in an amount of between 3 to 50 mg, preferably 5 to 40 mg and more preferably it is 10 to 20 mg.

7. The pharmaceutical combination according to claim 1, wherein the ratio of dronedarone HCl to rivaroxaban is between 5.0 - 80.0 (w/w), preferably 10.0 - 50.0 (w/w) and more preferably 20.0 - 40.0 (w/w).

8. The pharmaceutical combination according to claim 1, wherein said pharmaceutical combination is in the form of solid, liquid or semisolid dosage form.

9. The pharmaceutical combination according to claim 8, wherein said pharmaceutical combination is formulated as tablets comprising compressed tablets, coated or uncoated tablets, capsules, multilayer tablets, buccal tablets, sublingual tablets, tablet in tablets, in-lay tablets, effervescent combinations, effervescent tablets, immediate release tablets, modified release tablets, orally disintegrating tablet, film-

coated tablets, orally disintegrating tablets, gastric disintegrating tablets, pills, hard or soft gelatin capsules, powders, mini tablets, pellets, coated bead systems, granules, microspheres, ion exchange resin systems, sterile solutions or suspensions, sterile ocular solutions, aerosols, sprays, drops, ampoules, suppositories, ocular systems, parenteral systems, creams, gels, ointments, dragees, sachets; films, orally administrable films, solutions, solids; elixirs, tinctures, suspensions, syrups, colloidal dispersions, dispersions, emulsions.

10. The pharmaceutical combination according to claim 9, wherein said pharmaceutical combination is formulated preferably in the form of tablet or capsule or multilayer tablet.

11. The pharmaceutical combination according to claim 10, wherein said pharmaceutical combination is formulated in the form of tablet or capsule or multilayer tablet comprising rivaroxaban pellets and dronedarone HCl pellets.

12. The pharmaceutical combination according to claim 11, wherein said dronedarone HCl pellets comprising an enteric coating.

13. The pharmaceutical combination according to claim 12, wherein the enteric coating is selected from the group comprising cellulose acetate phthalate, methacrylic acid copolymers, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate and methacrylic acid co-polymer type C.

14. The pharmaceutical combination according to any preceding claims, wherein the one or more pharmaceutically acceptable excipients are selected from the group comprising buffering agents, stabilizers, binders, diluents, dispersing agents, lubricants, glidants, disintegrants, plasticizers, preservatives, sweeteners, flavoring agents, coloring agents, acids or mixtures thereof.

15. The pharmaceutical combination according to claim 1, wherein said pharmaceutical combination is in the form of tablet or capsule or multilayer tablet comprising dronedarone HCl pellets and rivaroxaban pellets which are separate pellets or bilayer or multilayer pellets.

16. The pharmaceutical combination according to claim 15, wherein said dronedarone HCl pellets comprising mannitol or pregelatinized starch or polyvinyl alcohol carbomer or croscarmellose sodium or polyvinylpyrrolidone or sugar pellet or microcrystalline cellulose pellet or hydroxypropyl cellulose or coloring agent or mixtures thereof as pharmaceutically acceptable excipients.

17. The pharmaceutical combination according to claim 15, wherein said rivaroxaban pellets comprising polyvinyl alcohol or isopropyl alcohol or sodium alginate or methacrylic acid–ethyl acrylate copolymer or polyvinyl alcohol or propylene glycol or mannitol or sugar pellet or polyvinylpyrrolidone or mixtures thereof.

18. The pharmaceutical combination according to claim 1, for use in the treatment of cardiac arrhythmia and blood clotting and to prevent serious or life-threatening side effects in patients.

Description

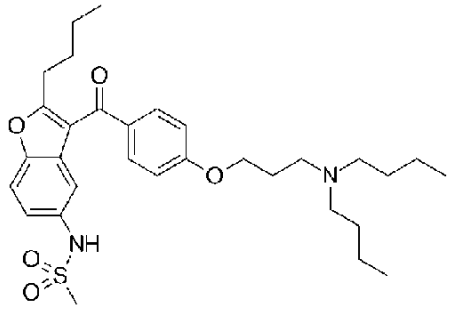
PHARMACEUTICAL COMBINATIONS OF DRONEDARONE

Field of Invention

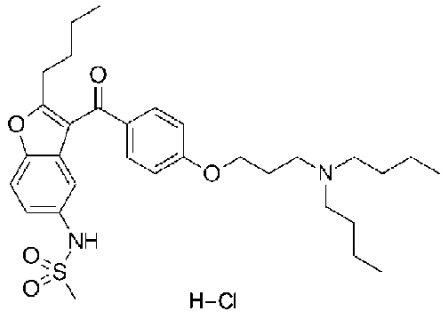
The present invention relates to a pharmaceutical combination comprising dronedarone or a pharmaceutically acceptable salt thereof in combination with rivaroxaban and at least one pharmaceutically acceptable excipient.

The background of the invention

Dronedarone is a noniodinated benzofuran derivative with antiarrhythmic properties. It is an amiodarone analog that differs structurally from amiodarone in that the iodine moiety was removed and a methane sulfonyl group was added. These modifications reduce thyroid and other adverse effects and makes dronedarone less lipophilic, with a shorter half-life. The chemical name of dronedarone is N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-1-benzofuran-5-yl]methanesulfonamide and it has the structure shown in the following formula I.



Formula I: Dronedarone



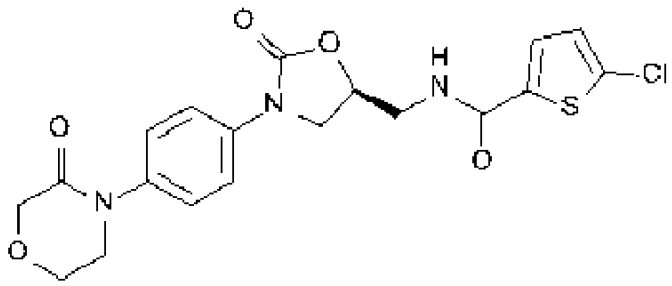
Formula II: Dronedarone hydrochloride

Dronedarone hydrochloride (shown in formula II) is an antiarrhythmic drug indicated to reduce the risk of hospitalization for atrial fibrillation (AF) in patients in sinus rhythm with a history of paroxysmal or persistent AF. Following oral administration in fed conditions, it is well absorbed from intestines to blood. It was approved by the FDA on 2009 and marketed under the brandname MULTAQ™. Recommended dose is one tablet of 400 mg twice a day with morning and evening meals.

In prior art, dronedarone and pharmaceutically acceptable salts thereof are described in EP 0 471 609 B1. US 7 323 493 B1 discloses tablet formulations of dronedarone HCl. There are also several patent applications which disclose orally administered dronedarone formulations, but none of them includes orally disintegrating tablets of dronedarone.

Rivaroxaban is an anticoagulant to treat deep vein thrombosis (DVT) and pulmonary embolism (PE). It is also used to help prevent strokes or serious blood clots in people who have atrial fibrillation. Anticoagulant drugs target various procoagulant factors in the coagulation pathway. Rivaroxaban is the first orally active direct factor Xa inhibitor. Direct factor Xa inhibitors play a central role in the cascade of blood coagulation by inhibiting factor Xa directly.

Rivaroxaban molecule is a substituted oxazolidinaone disclosed in WO0147919. It has the chemical structure shown in Formula III. Its chemical name is 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]thiophene-2-carboxamide.



Formula III: Rivaroxaban

Rivaroxaban tablet formulation is commercially available under the trade name Xarelto® in the strengths of 10, 15 and 20mg. After oral administration, it achieves maximal absorption from the stomach, with a bioavailability of 80 to 100%.

Based on common general knowledge in the art, in the treatment of cardiac arrhythmia especially atrial fibrillation, antiarrhythmic drugs are commonly used in combination with anticoagulants. However, in prior art, there is no formulation which combines dronedarone and rivaroxaban in one dosage form. Instead of one per se use, combining more than one molecule in one dosage form increases the patients' quality of life and patients' compliance.

Therefore, a combination of dorenedarone and rivaroxaban in a suitable pharmaceutical dosage formulation is needed in the art.

On the other side, there are many challenges while combining two or more molecules in a dosage form such as dissolution, compatibility and stability problems. Each drug molecule has different chemical properties and dissolution properties. They may follow different absorption and distribution pathways after administration. For that reason, it is not easy to combine drug molecules in a same dosage form with desired dissolution profiles. They also may react with each other or with other used excipients and that may cause undesired instability problems. Moreover, it is well known that even drugs used in the same therapeutic area or even for treating the same indication cannot always be combined into safe and efficacious dosage forms with the expectation of at least additive therapeutic effects.

In this present invention, dronedarone as an antiarithmic and rivaroxaban as an anticoagulant are combined in one dosage form and an effective and safe treatment of cardiovascular diseases is achieved.

Detailed description of the invention

The present invention relates to a pharmaceutical combination comprising **dronedarone** or a pharmaceutically acceptable salt thereof in combination with **rivaroxaban** and at least one pharmaceutically acceptable excipients.

According to one embodiment, dronedarone or a pharmaceutically acceptable salt used in this present invention is dronedarone hydrochloride.

According to one embodiment, dronedarone hydrochloride (HCl) is present in an amount of between 5 to 98 %, preferably between 20 to 98 % and more preferably it is 40 to 98 % by weight of total formulation.

According to this embodiment, dronedarone hydrochloride present in an amount of between 50 to 1000 mg, preferably 200 to 800 mg and more preferably it is 400 to 800 mg.

According to one embodiment, rivaroxaban is present in an amount of between 0.01 to 50 %, preferably between 0.01 to 30 % and more preferably it is 0.01 to 10 % by weight of total formulation.

According to this embodiment, rivaroxaban is present in an amount of between 3 to 50 mg, preferably 5 to 40 mg and more preferably it is 10 to 20 mg.

In this present invention, dronedarone HCl is used as an antiarrithmic in combination with rivaroxaban as an anticoagulant, for use in the treatment of cardiac arrhythmia and blood clotting and to prevent serious or life-threatening side effects in patients.

In one embodiment, a pharmaceutical dosage form comprising dronedarone HCl in combination with rivaroxaban has been developed providing a stable pharmaceutical combination with safe and effective dissolution profiles for each drug molecule.

According to one embodiment, the ratios used in this present invention ensure the required effective doses for the treatment and provide stability for both dronedarone HCl and rivaroxaban.

In this embodiment, it has been found that in spesific ratio of dronedarone HCl to rivaroxaban which is between 5.0 - 80.0(w/w), preferably 10.0 - 50.0 (w/w) and more preferably 20.0 - 40.0 (w/w) helps the formulation easily processed into a dosage form, in desired weight which can easily be swallowed by the patients, while maintaining stability of the combination.

In one embodiment, in this present invention, pharmaceutical combination formulated in one dosage form provides desired dissolution profile for both dronedarone HCl and rivaroxaban.

According to one embodiment of this invention, the pharmaceutical combination is in the form of solid, liquid or semisolid dosage form.

In this embodiment, these pharmaceutical combinations are administrated oral, parenteral, intranasal, sublingual, transdermal, transmucosal, ophthalmic, intravenous, pulmonary, intramuscular or rectal administration, and preferably for oral administration.

According to one embodiment, the pharmaceutical combination is in the form of tablets comprising compressed tablets, coated or uncoated tablets, capsules, multilayer tablets, buccal tablets, sublingual tablets, tablet in tablets, in-lay tablets, effervescent combinations, effervescent tablets, immediate release tablets, modified release tablets, ODT (orally disintegrating tablet), film-coated tablets, orally disintegrating tablets, gastric disintegrating tablets, pills, hard or soft gelatin capsules, powders, mini tablets, pellets, coated bead

systems, granules, microspheres, ion exchange resin systems, sterile solutions or suspensions, sterile ocular solutions, aerosols, sprays, drops, ampoules, suppositories, ocular systems, parenteral systems, creams, gels, ointments, dragees, sachets; films, orally administrable films, solutions, solids; elixirs, tinctures, suspensions, syrups, colloidal dispersions, dispersions, emulsions and thereof.

In one embodiment said pharmaceutical combination is formulated in the form of tablet or capsule or multilayer tablet.

In one embodiment said pharmaceutical combination is formulated in the form of tablet or capsule or multilayer tablet comprising dronedarone HCl pellets and rivaroxaban pellets.

Dronedarone is a drug molecule which is well absorbed in intestine and rivaroxaban is a drug molecule which is well absorbed in stomach. In this combination of this present invention, it is provided to dissolve the dronedarone HCl pellets in intestine not in stomach and rivaroxaban pellets in stomach.

In one embodiment, said pharmaceutical combination dronedarone HCl pellets comprises an enteric coating.

According to one embodiment, enteric coating used in this present invention ensures absorption of dronedarone HCl not in stomach but in intestine.

The present invention provides a pharmaceutical combination comprises an enteric coating which covers dronedarone HCl layer and which separates rivaroxaban and dronedarone HCl layers. Enteric coating ensures the stability of dronedarone HCl in stomach and by the virtue of the enteric coating, interaction between the rivaroxaban and dronedarone HCl molecules is also prevented at the same time. Another important reason is that the formulations of the drug molecules with different release properties can be provided in the same dosage form with the enteric coating. Thus, rivaroxaban and dronedarone HCl molecules are formulated in a way not to interact, and at the same time it is provided that these molecules remain stable in their own form. Moreover, desired release profiles are achieved for each drug molecules for a safe and effective treatment of cardiovascular diseases.

In this embodiment of this present invention, dronedarone HCl pellets comprises an enteric coating is selected from the group comprises cellulose acetate phthalate, methacrylic acid copolymers (Eudragit L types (methacrylic acid, ethyl acrylate copolymers), Eudragit RL and

RS types (copolymer of ethyl acrylate, methyl methacrylate and ammonia methacrylate), Eudragit-S types (Methacrylic acid, methyl methacrylate copolymer)), hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate and methacrylic acid co-polymer type C.

In this embodiment of the present invention, said pharmaceutical combination is in the form of tablet or capsule or multilayer tablet comprising rivaroxaban pellets and dronedarone HCl pellets which are separated pellets or bilayer or multilayer pellets.

In an embodiment of the present invention said dronedarone HCl pellets comprises mannitol or pregelatinized starch or polyvinyl alcohol (PVA) carbomer or croscarmellose sodium or polyvinylpyrrolidone (PVP K30) or sugar pellet or microcrystalline cellulose (MCC) pellet or hydroxypropyl cellulose or coloring agent or mixtures thereof as pharmaceutically acceptable excipients.

In this embodiment of the present invention said rivaroxaban pellets comprises polyvinyl alcohol (PVA) or isopropyl alcohol (IPA) or sodium alginate or methacrylic acid–ethyl acrylate copolymer (Eudragit EPO) or PVA or propylene glycol or mannitol or sugar pellet or polyvinylpyrrolidone (PVP) or mixtures thereof as pharmaceutically acceptable excipients.

According to challenges mentioned above the selection of the excipients thus essential. According to this embodiment, one or more pharmaceutically acceptable excipient is selected from the group comprising buffering agents, stabilizers, binders, diluents, dispersing agents, lubricants, glidants, disintegrants, plasticizers, preservatives, sweeteners, flavoring agents, coloring agents or mixtures thereof.

Suitable buffering agents may comprise but not limited to 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, and preferably citric acid, fumaric acid, ascorbic acid, sodium dihydrogen phosphate or mixtures thereof.

Suitable stabilizers may comprise but not limited to citric acid, fumaric acid, tartaric acid, sodium citrate, sodium benzoate, sodium dihydrogen phosphate, calcium carbonate, magnesium carbonate, arginine, lysine, meglamine, tocopherol, butylhydroxyanisole (BHA),

butylhydroxytoluene (BHT), ascorbic acid, gallic acid esters or the mixtures thereof, and preferably, citric acid, fumaric acid, arginine or mixtures thereof.

Suitable binders may include but not limited to polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, starch, pregelatinized starch, glucose, glucose syrup, natural gums, sucrose, sodium alginate, cellulose derivatives such as hydroxypropyl methyl cellulose, hydroxypropyl cellulose, carboxy methyl cellulose, methyl cellulose, gelatin, carrageenan, guar gum, carbomer, polymethacrylates, methacrylate polymers, collagens, proteins like gelatin, agar, alginate, alginic acid, xanthan gum, hyaluronic acid, pectin, polysaccharides, carbomer, poloxamer, polyacrylamide, aluminium hydroxide, laponit, bentonit, polyoxyethylene-alkyl ether, polydextrose, polyethylene oxide or mixtures thereof.

Suitable diluents may comprise but not limited to mannitol, lactose, microcrystalline cellulose, spray-dried mannitol, 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 may comprise but not limited to calcium silicate, magnesium aluminum silicate or mixtures thereof.

Suitable lubricants may comprise but not limited to 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, glyseryl palmito sulphate, sodium stearyl fumarate, sodium lauryl sulphate or mixtures thereof.

Suitable glidants may comprise but not limited to talc, aluminium silicate, colloidal silica, starch or mixtures thereof.

Suitable disintegrants may comprise but not limited to cross-linked polyvinil pyrrolidone (crospovidone), povidone, cross-linked carboxymethyl cellulose (croscarmellose sodium), low-substituted hydroxypropyl cellulose, pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose, docusate sodium, guar gum, low substituted hydroxypropyl cellulose, polyacryline potassium, sodium alginate, corn starch, sodium starch glycolate, alginic acid, alginates, ion-exchange resins, magnesium

aluminium silica, sodium dodesyl sulphate, poloxamer, sodium glycine carbonate, sodium lauryl sulphate or mixtures thereof.

Suitable plasticizers may comprise but not limited to polyethylene glycols of different molecular weights, propylene glycol, glycerine, triethyl citrate (TEC), triacetin, diethyl phthalate (DEP), dibutyl phthalate (DBP), tributhyl citrate (TBC), castor oil, dibutyl sebacate (DBS), diacetylated monogglycerides or mixtures thereof.

Suitable preservatives may comprise but not limited to methyl paraben, propyl paraben and their salts (such as sodium, potassium), sodium benzoate, citric acid, benzoic acid, butylated hydroxytoluene, boric acid, sorbic acid, benzyl alcohol, benzalconium chloride, parahydroxybenzoic acids or butylated hydroxyanisole or mixtures thereof.

Suitable sweeteners may comprise but not limited to aspartame, potassium acesulfame, sodium saccharinate, neohesperidine dihydrochalcone, sucralose, saccharin, sugars such as sucrose, glucose, lactose, fructose or sugar alcohols such as mannitol, sorbitol, xylitol, erythritol or mixtures thereof.

Suitable flavoring agents may comprise but not limited to menthol, peppermint, cinnamon, chocolate, vanillin or fruit essences such as cherry, orange, strawberry, grape, black currant, raspberry, banana, red fruits, wild berries or mixtures thereof.

Suitable coloring agents may comprise but not limited to 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.

Example 1:

ingredients	amount (%)
Dronedarone HCl pellets	
dronedarone HCl	5.00 – 98.00
mannitol	5.00 – 90.00
pregelatinized starch	5.00 – 90.00
polyvinyl pyrrolidone	0.10 – 25.00

Enteric coating	
cellulose acetate phthalate	0.10 – 30.00
Rivaroxaban pellets	
Rivaroxaban	0.01 – 50.00
polyvinyl alcohol (PVA) or isopropyl alcohol (IPA)	0.05 – 20.00
sodium alginate	0.05 – 20.00
methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or PVA	5.00 – 40.00
propylene glycol	0.01 – 5.00
silicon dioxide	0.10 – 1.00
magnesium stearate	0.10 – 3.00

Production process of Dronedarone HCl pellets: Dronedarone HCl, mannitol and pregelatinized starch are mixed together then by spraying polyvinyl pyrrolidone solution a wet mass is formed. Pellets produced from this wet mass by extrusion/spheronization pelletizing technique. A solution/dispersion is prepared by adding cellulose acetate phthalate as enteric coating and the dronedarone HCl are coated by spraying this mixture.

Production process of Rivaroxaban pellets: Alcoholic Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or Polyvinyl alcohol (PVA) solution is sprayed onto rivaroxaban. PVA or IPA (isopropyl alcohol) and propylene glycol solution is sprayed onto this mixture and pellets produced by fluidized bed pelletizing technique. The pellets are coated with sodium alginate in fluidized bed so rivaroxaban pellets are manufactured.

The rivaroxaban and dronedarone HCl pellets first mixed with silicon dioxide and then with magnesium stearate. Finally, the pellets are pressed as tablets or filled into the capsules.

Example 2:

ingredients	**amount (%)**
Dronedarone HCl pellets	
dronedarone HCl	5.00 – 98.00

mannitol	5.00 – 90.00
pregelatinized starch	5.00 – 90.00
carbomer	0.10 – 30.00
Enteric coating	
copolymer of ethyl acrylate, methyl methacrylate and ammonia methacrylate	0.10 – 30.00
Rivaroxaban pellets	
rivaroxaban	0.01 – 50.00
methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or PVA	5.00 – 40.00
mannitol	5.0 – 90.00
magnesium stearate	0.10 – 3.00
silicon dioxide	0.10 – 1.00

Production process of Dronedarone HCl pellets: Dronedarone HCl, mannitol and pregelatinized starch are mixed together then by spraying carbomer solution a wet mass is formed. Pellets produced from this wet mass by extrusion/spheronization pelletizing technique. A solution/dispersion is prepared by adding copolymer of ethyl acrylate, methyl methacrylate and ammonia methacrylate as enteric coating and the dronedarone HCl pellets are coated by spraying this mixture in fluidized bed.

Production process of Rivaroxaban pellets: Rivaroxaban and lactose monohydrate are mixed together. Alcoholic Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or Polyvinyl alcohol (PVA) solution is sprayed onto this mixture and pellets produced by fluidized bed pelletizing technique.

The rivaroxaban and dronedarone HCl pellets first mixed with silicon dioxide and then with magnesium stearate. Finally, the pellets are pressed as tablets or filled into the capsules.

Example 3:

ingredients	amount (%)
Dronedarone HCl pellets	
dronedarone HCl	5.00 – 98.00
mannitol	5.00 – 90.00
croscarmellose sodium	5.00 – 40.00
carbomer	0.10 – 30.00
Enteric coating	
methacrylic acid, methyl methacrylate copolymer	0.10 – 30.00
Rivaroxaban pellets	
rivaroxaban	0.01 – 50.00
sugar pellet	5.00 – 90.00
polyvinylpyrrolidone (PVP)	0.10 – 30.00
methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or PVA	5.00 – 40.00
silicon dioxide	0.10 – 1.00
magnesium stearate	0.10 – 3.00

Production process of Dronedarone HCl pellets: Dronedarone HCl, mannitol and croscarmellose sodium are mixed together then by spraying carbomer solution a wet mass is formed. Pellets produced from this wet mass by extrusion/spheronization pelletizing technique. A solution/dispersion is prepared by adding methacrylic acid, methyl methacrylate copolymer as enteric coating and the dronedarone HCl pellets which were coated with the enteric coating by spraying this mixture.

Production process of Rivaroxaban pellets: Alcoholic solution/dispersion is prepared by adding rivaroxaban and PVP. Sugar pellets are coated with this solution/dispersion. The sugar pellets which were coated with the active ingredient are coated with methacrylic acid–ethyl acrylate copolymer (Eudragit EPO or Polyvinyl alcohol (PVA)) so rivaroxaban pellets are manufactured.

Dronedarone HCl pellets and rivaroxaban pellets are mixed. The pellets are first mixed with silicon dioxide and then with magnesium stearate. Finally, the pellets are pressed as tablets or filled into the capsules.

Example 4:

ingredients	amount (%)
Dronedarone HCl pellets	
dronedarone HCl	5.00 – 98.00
polyvinylpyrrolidone K30 (PVP K30)	0.10 – 30.00
sugar pellet	5.00 – 90.00
Enteric coating	
polyvinyl acetate phthalate	0.10 – 30.00
Rivaroxaban pellets	
rivaroxaban	0.01 – 50.00
methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or PVA	5.00 – 40.00
mannitol	5.00 – 90.00
polyvinyl alcohol (PVA)	0.05 – 20.00
silicon dioxide	0.10 – 1.00
magnesium stearate	0.10 – 3.00

Production process multilayer pellets: A solution/dispersion is prepared by adding dronedarone HCl and PVP K30. Sugar pellets are coated with this solution/dispersion. The sugar pellets which were coated with the dronedarone HCl are coated with polyvinyl acetate phthalate so dronedarone HCl pellets are manufactured. Rivaroxaban and lactose monohydrate are mixed with alcoholic methacrylic acid–ethyl acrylate copolymer (Eudragit EPO) or polyvinyl alcohol (PVA) solution. This mixture is sprayed onto dronedarone HCl pellets so multilayer pellets are manufactured.

Finally the multilayer pellets are coated by PVA. The multilayer pellets first mixed with silicon dioxide and then with magnesium stearate. The pellets are pressed as tablets or filled into the capsules.

Example 5:

ingredients	amount (%)
Dronedarone HCl pellets	
dronedarone HCl	5.00 – 98.00
polyvinylpyrrolidone K30 (PVP K30)	0.10 – 30.00
Sugar pellet	5.00 – 90.00
Enteric coating	
methacrylic acid co-polymer type C	0.10 – 30.00
Rivaroxaban pellets	
rivaroxaban	0.01 – 50.00
methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or PVA	5.00 – 40.00
mannitol	5.00 – 90.00
polyvinyl alcohol (PVA)	0.05 – 20.00
Ssilicon dioxide	0.10 – 1.00
magnesium stearate	0.10 – 3.00

Production process of Dronedarone HCl pellets: A solution/dispersion is prepared by adding Dronedarone HCl and PVP K30. Sugar pellets are coated with this solution/dispersion. The sugar pellets which were coated with the active ingredient are coated with methacrylic acid co-polymer type C so Dronedarone HCl pellets are manufactured.

Production process of Rivaroxaban pellets: Rivaroxaban and lactose monohydrate are mixed together. Alcoholic Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or Polyvinyl alcohol (PVA) solution is sprayed onto this mixture and pellets produced by fluidized bed pelletizing technique.

Rivaroxaban and dronedarone HCl pellets first mixed with silicon dioxide and then with magnesium stearate. Finally, the pellets are pressed by multilayer rotary tablet press machine or dry coating–intertwined tablets which have dronedarone HCl pellets on the core are produced with special tablet press machine.