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(54) Title: PHARMACEUTICAL COMBINATIONS OF DRONEDARONE AND DABIGATRAN

(57) Abstract: The present invention relates to a pharmaceutical combination comprising dronedarone or a pharmaceutically acceptable salt thereof in combination with dabigatran or a pharmaceutically acceptable salt or polymorph and at least one pharmaceutically acceptable excipient.



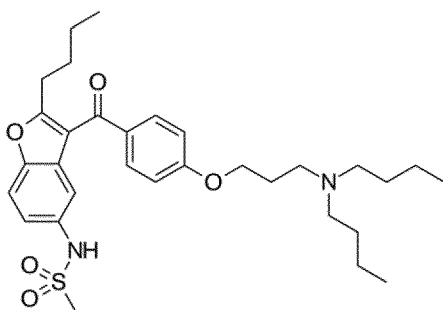
PHARMACEUTICAL COMBINATIONS OF DRONEDARONE AND DABIGATRAN

Field of Invention

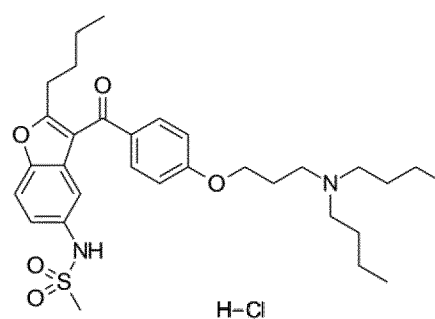
The present invention relates to a pharmaceutical combination comprising dronedarone or a pharmaceutically acceptable salt in combination with comprising dabigatran or a pharmaceutically acceptable salt or polymorph thereof and at least one pharmaceutically acceptable excipient.

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

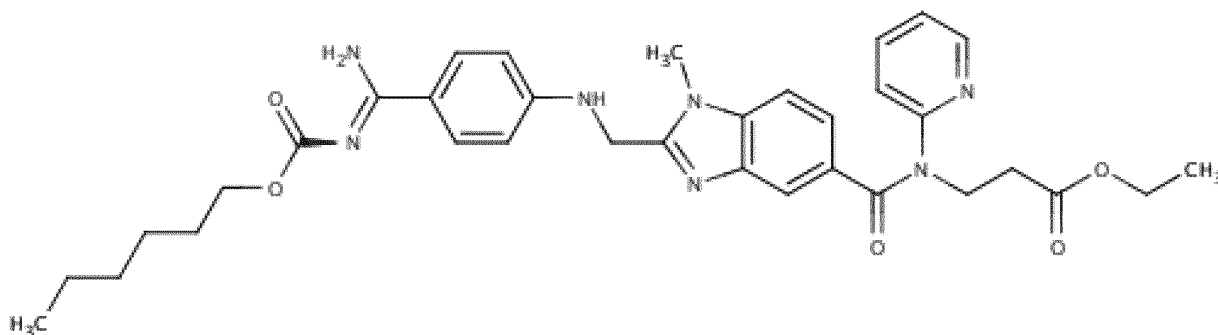
Dronedarone hydrochloride (shown in formula II) is an antiarrhythmic drug indicated to reduce the risk of hospitalization for atrial fibrillation (AF) in patients in sinus rhythm with a history of paroxysmal or persistent AF. Following oral administration in fed conditions, it is well absorbed from intestines 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.

5 Presently there are numerous antithrombotic drugs which are widely available, they also
called as Direct Thrombin Inhibitors (DTIs) which are a class of medication that act as
anticoagulants (delaying blood clotting) by directly inhibiting the enzyme thrombin. DTIs
comprise hirudin, bivalirudin (IV), lepirudin, desirudin, argatroban (IV), dabigatran,
dabigatran etexilate (oral formulation), melagatran, ximelagatran (oral formulation but
10 liver complications) and pro-drugs thereof.

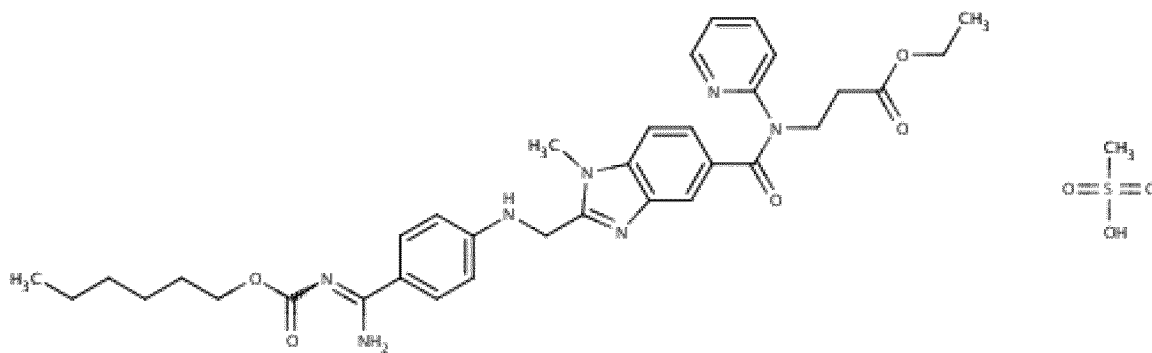
Dabigatran etexilate (Formula III), which is already known from WO 98/37075, is a competitive reversible non-peptide antagonist of thrombin. It is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-vascular atrial fibrillation. Thrombin is a multifunctional enzyme which converts fibrinogen to fibrin, cross-linking fibrin monomers via activation of factor XIII and augmenting further thrombin production via the activation of factors V and VIII. It also activates platelets, generates anticoagulant activity via activation of protein C and initiates numerous cellular processes.

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Formula III: Dabigatran etexilate

25 The methane sulphonic acid addition salt of dabigatran etexilate, which is commercially available under the trade name PRADAXA® (in the strength of 75, 110, 150mg), pellet composition of dabigatran etexilate mesylate (DEM) (Formula IV) is also disclosed in EP1870100. This composition is formulated with a core material consisting of organic acid and an active layer which covers the core.



Formula IV: Dabigatran etexilate mesylate

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 dabigatran 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 dronedarone and dabigatran etexilate as an anticoagulant 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 antiarrhythmic and dabigatran 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 **dabigatran** or a pharmaceutically acceptable salt or polymorph thereof and at least one pharmaceutically acceptable excipient.

5

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

10

According to one embodiment, dronedarone hydrochloride (HCl) is present in an amount of between 5.0 to 98.0 %, preferably between 20.0 to 98.0 % and more preferably it is 50.0 to 95.0 % by weight of total formulation.

15

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, dabigatran or a pharmaceutically acceptable salt or polymorph is the etexilate or etexilate mesylate salt of dabigatran.

20

According to one embodiment, dabigatran or a pharmaceutically acceptable salt is dabigatran etexilate mesylate.

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According to one embodiment, dabigatran etexilate mesylate is present in an amount of between 1.0 to 85.0 %, preferably between 1.0 to 60.0 % and more preferably it is 5.0 to 50.0 % by weight of total formulation.

According to this embodiment, dabigatran etexilate mesylate is present in an amount of between 30 to 350 mg, preferably 50 to 300 mg and more preferably it is 50 to 250 mg.

30

In this present invention, dronedarone HCl is used as an antiarrhythmic in combination with dabigatran etexilate mesylate 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.

35

In one embodiment, a pharmaceutical dosage form comprising dronedarone HCl in combination with dabigatran etexilate mesylate 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 dabigatran etexilate mesylate.

In this embodiment, it has been found that in specific ratio of dronedarone HCl to dabigatran etexilate mesylate which is between 0.10 - 50.0(w/w), preferably 1.0 - 35.0 (w/w) and more preferably 1.0 - 30.0 (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 dabigatran etexilate mesylate.

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 administered 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, 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.

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

10 Dronedarone is a drug molecule which is well absorbed in intestine and dabigatran 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 dabigatran etexilate mesylate pellets in stomach.

15 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.

20 The present invention provides a pharmaceutical combination comprises an enteric coating which covers dronedarone HCl layer and which separates dabigatran etexilate mesylate 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 dabigatran etexilate mesylate and dronedarone HCl molecules is also prevented at the same time. Another important reason is that the formulations of the drug molecules
25 with different release properties can be provided in the same dosage form with the enteric coating. Thus, dabigatran etexilate mesylate 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
30 diseases.

In this embodiment of this present invention, dronedarone HCl pellets comprises an enteric coating is selected from the group comprising cellulose acetate phthalate, methacrylic acid copolymers (Eudragit L types (methacrylic acid, ethyl acrylate
35 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 copolymer type C.

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

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

15

In this embodiment of the present invention said dabigatran etexilate mesylate pellets comprises polyvinyl alcohol (PVA) or isopropyl alcohol (IPA) or sodium alginate or methacrylic acid-ethyl acrylate copolymer (Eudragit EPO) or propylene glycol or lactose monohydrate or mannitol or sugar pellet or polyvinylpyrrolidone (PVP) or mixtures thereof

20 as pharmaceutically acceptable excipients.

According to the challenges mentioned above the selection of the excipients thus essential. According to this embodiment, at least one pharmaceutically acceptable excipient is selected from the group comprising buffering agents, stabilizers, binders, 25 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, sorbic acid, glutaric acid, potassium hydrogen tartrate, sodium 30 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.

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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 xanthan gum, pregelatinized starch, polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, 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, 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, glyceryl 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 pregelatinized starch, cross-linked polyvinyl pyrrolidone (crospovidone), povidone, cross-linked carboxymethyl cellulose (croscarmellose sodium), low-substituted hydroxypropyl cellulose, 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.

10 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), tributyl citrate (TBC), castor oil, dibutyl sebacate (DBS), diacetylated monoglycerides or mixtures thereof.

15 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 and the like or mixtures thereof.

20 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.

25 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 (PVP)	0.10 – 25.00
Enteric coating	
cellulose acetate phthalate	0.10 – 30.00
Dabigatran etexilate mesylate pellets	
dabigatran etexilate mesylate	1.00 – 85.00
adipic acid or sorbic acid or succinic acid or glutaric acid	5.00 – 95.00
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	0.05 – 40.00
xanthan gum	0.05 – 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 processes of Organic acid pellets are coated with Dabigatran: Adipic acid or sorbic acid or succinic acid or glutaric acid and xanthan gum are mixed together.

Alcoholic polyvinyl alcohol (PVA) or IPA (isopropyl alcohol) 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 acid pellets are manufactured. DEM (dabigatran etaxylate mesylate) is dissolved in alcoholic methacrylic acid–ethyl acrylate copolymer (Eudragit EPO) or polyvinyl alcohol (PVA) solution. This solution is sprayed onto the acid pellet by fluidized bed pelletizing technique so multilayer pellets are manufactured.

The DEM 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
Dabigatran etexilate mesylate pellets	
dabigatran etexilate mesylate	1.00 – 85.00
adipic acid or sorbic acid or succinic acid or glutaric acid	5.00 – 95.00
methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or PVA	0.05 – 40.00
mannitol	5.0 – 90.00
xanthan gum	0.05 – 5.00
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 Dabigatran pellets: DEM and mannitol 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 solution is prepared by adding adipic acid or sorbic acid or succinic acid or glutaric acid and xanthan gum. This solution is sprayed onto the DEM pellets by fluidized bed pelletizing technique so multilayer pellets are manufactured.

The DEM 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
Dabigatran etexilate mesylate pellets	
dabigatran etexilate mesylate	1.00 – 85.00
sugar pellet	5.00 – 90.00
polyvinylpyrrolidone (PVP)	0.10 – 30.00
methacrylic acid–ethyl acrylate copolymer (Eudragit	0.05 – 40.00

EPO) or PVA	
Inorganic acid pellets	
nitric acid	0.05 – 10.00
microcrystalline cellulose or mannitol or lactose	5.0 – 40.00
silicon dioxide	0.1 – 0.20
methacrylic acid–ethyl acrylate copolymer (Eudragit EPO) or PVA	0.05 – 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 Dabigatran pellets: Alcoholic solution/dispersion is prepared by adding DEM 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) and then with PVP solution so DEM pellets are manufactured.

Production Process of inorganic acid pellets: Microcrystalline cellulose or mannitol or lactose and silicon dioxide are blended, then by spraying dilute nitric acid solution a wet mass is formed by high shear granulator or fluid bed granulator. The pellets are coated by methacrylic acid–ethyl acrylate copolymer (Eudragit EPO) or polyvinyl alcohol (PVA) solution in fluidized bed so inorganic acid pellets are manufactured.

Dronedarone pellets and Dabigatran etexilate mesylate pellets and inorganic acid 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 (PVP)	0.10 – 30.00
sugar pellet	5.00 – 90.00
Enteric coating	
polyvinyl acetate phthalate	0.10 – 30.00
Dabigatran etexilate mesylate pellets	
dabigatran etexilate mesylate	1.00 – 85.00
adipic acid or sorbic acid or succinic acid or glutaric acid	5.00 – 95.00
methacrylic acid–ethyl acrylate copolymer (Eudragit EPO) or polyvinyl alcohol PVA	0.05– 40.00
mannitol	5.00 – 90.00
xanthan gum	0.05 – 5.00
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
5 dronedarone and PVP. 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. DEM and mannitol are mixed with
alcoholic methacrylic acid–ethyl acrylate copolymer (Eudragit EPO) or polyvinyl alcohol
(PVA) solution. This mixture is sprayed onto dronedarone HCl pellets. The solution is
10 prepared by adding adipic acid or sorbic acid or succinic acid or glutaric acid) and xanthan
gum. This solution is sprayed onto the 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.

5 **Example 5:**

ingredients	amount (%)
Dronedarone HCl pellets	
dronedarone hcl	5.00 – 98.00
polyvinylpyrrolidone (PVP)	0.10 – 30.00
sugar pellet	5.00 – 90.00
Enteric coating	
methacrylic acid co-polymer type C	0.10 – 30.00
Dabigatran etexilate mesylate pellets	
dabigatran etexilate mesylate	1.00 – 85.00
methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or PVA	0.05 – 40.00
mannitol	5.00 – 90.00
adipic acid or sorbic acid or succinic acid or glutaric acid	5.00 – 95.00
xanthan gum	0.05 – 5.00
silicon 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. Sugar pellets are coated with this solution/dispersion.

10 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 Dabigatran pellets are coated with organic acid: DEM and mannitol monohydrate are mixed together. Alcoholic methacrylic acid–ethyl acrylate
15 copolymer (Eudragit EPO) or polyvinyl alcohol (PVA) solution is sprayed onto this mixture

and pellets produced by fluidized bed pelletizing technique. The solution is prepared by adding adipic acid or sorbic acid or succinic acid or glutaric acid and xanthan gum. This solution is sprayed onto the DEM pellets by fluidized bed pelletizing technique so multilayer pellets are manufactured.

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Dabigatran etexilate mesylate 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 tablet in tablet or inlay tablets which have dronedarone HCl pellets on the core are produced with special tablet press machine.

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CLAIMS

1. A pharmaceutical combination comprising dronedarone or a pharmaceutically acceptable salt in combination with dabigatran or a pharmaceutically acceptable salt or polymorph thereof 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 5.0 to 98.0 %, preferably between 20.0 to 98.0 % and more preferably it is 50.0 to 95.0 % by weight of total formulation.
4. The pharmaceutical combination according to claim 3, 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 dabigatran or a pharmaceutically acceptable salt or polymorph is etexilate or etexilate mesylate salt of dabigatran.
6. The pharmaceutical combination according to claim 5, dabigatran or a pharmaceutically acceptable salt is dabigatran etexilate mesylate.
7. The pharmaceutical combination according to claim 1, wherein dabigatran etexilate mesylate is present in an amount of between 1.0 to 85.0 %, preferably between 1.0 to 60.0 % and more preferably it is 5.0 to 50.0 % by weight of total formulation.
8. The pharmaceutical combination according to claim 7, wherein dabigatran etexilate mesylate is present in an amount of between 30 to 350 mg, preferably 50 to 300 mg and more preferably it is 50 to 250 mg.

9. The pharmaceutical combination according to claim 1, wherein the ratio of dronedarone HCl to dabigatran etexilate mesylate which is between 0.10 - 50.0 (w/w), preferably 1.0 - 35.0 (w/w) and more preferably 1.0 - 30.0 (w/w).
- 5 10. The pharmaceutical combination according to claim 1, wherein said pharmaceutical combination is in the form of solid, liquid or semisolid dosage form.
- 10 11. The pharmaceutical combination according to claim 10, wherein said pharmaceutical combination is formulated as 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, 15 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, 20 tinctures, suspensions, syrups, colloidal dispersions, dispersions, emulsions.
- 25 12. The pharmaceutical combination according to claim 11, wherein said pharmaceutical combination is formulated in the form of tablet or capsule or multilayer tablet.
- 30 13. The pharmaceutical combination according to claim 12, wherein said pharmaceutical combination is formulated in the form of tablet or capsule or multilayer tablet comprising dabigatran etexilate mesylate pellets and dronedarone HCl pellets.
14. The pharmaceutical combination according to claim 13, wherein said dronedarone HCl pellets comprising an enteric coating.
- 35 15. The pharmaceutical combination according to claim 14, wherein the enteric coating is selected from the group comprising cellulose acetate phthalate, methacrylic acid copolymers, methacrylic acid, ethyl acrylate copolymers,

copolymer of ethyl acrylate, methyl methacrylate and ammonia methacrylate; methacrylic acid, methyl methacrylate copolymer, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate and methacrylic acid co-polymer type C.

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16. The pharmaceutical combination according to claim 13, wherein said pharmaceutical combination is in the form of tablet or capsule or multilayer tablet comprising dronedarone HCl pellets and dabigatran etexilate mesylate pellets which are in the form of separate pellets or bilayer pellets or multilayer pellets.

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17. The pharmaceutical combination according to claim 1, wherein at least one 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, acids or mixtures thereof.

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

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19. The pharmaceutical combination according to claim 16, wherein said dabigatran etexilate mesylate pellets comprising polyvinyl alcohol or isopropyl alcohol or sodium alginate or methacrylic acid-ethyl acrylate copolymer or propylene glycol or lactose monohydrate or mannitol or sugar pellet or polyvinylpyrrolidone or mixtures thereof

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20. 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.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/053819

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/22 A61K9/52 A61K31/343 A61K31/4439 A61P7/02
A61P9/06

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, PASCAL, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/136779 A1 (MILNER PETER G [US] ET AL) 9 June 2011 (2011-06-09)	1,5, 10-12, 17,20
Y	paragraph [0050] paragraph [0223] paragraph [0307] paragraph [0488] - paragraph [0492] claim 31	2-4,6-9, 13-16, 18,19
Y	----- WO 2012/023024 A2 (LUPIN LTD [IN]; DESHMUKH ASHISH ASHOKRAO [IN]; BHUTADA PRAVIN MEGHRAJJ) 23 February 2012 (2012-02-23) the whole document, in particular page 3, paragraph 2; page 15, lines 14-24 and example 14 ----- -/-	2-4,9, 13-16, 18,19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/053819

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 870 100 A1 (BOEHRINGER INGELHEIM PHARMA [DE]) 26 December 2007 (2007-12-26) cited in the application the whole document	6-9, 13-16, 18,19
Y	----- A. G VISHWAKARMA ET AL: "Bi-Layer Tablet -A New Ways in Oral Drug Delivery System", INTERNATIONAL JOURNAL OF PHARMTECH RESEARCH CODEN (USA), vol. 6, no. 5, October 2014 (2014-10), pages 1416-1428, XP055206478, the whole document -----	13-16, 18,19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/053819

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011136779	A1	09-06-2011	NONE
WO 2012023024	A2	23-02-2012	EP 2605758 A2 26-06-2013
		JP 2013535516 A 12-09-2013	
		US 2013142849 A1 06-06-2013	
		WO 2012023024 A2 23-02-2012	
EP 1870100	A1	26-12-2007	AR 042861 A1 06-07-2005
		AR 072385 A2 25-08-2010	
		AT 540943 T 15-01-2012	
		AU 2003210400 A1 16-09-2003	
		BR 0306559 A 30-11-2004	
		CA 2476054 A1 12-09-2003	
		CN 1638771 A 13-07-2005	
		CO 5611149 A2 28-02-2006	
		CY 1112796 T1 05-08-2015	
		CY 1113158 T1 05-08-2015	
		DE 122012000047 I1 13-09-2012	
		DK 1485094 T3 15-10-2012	
		DK 1870100 T3 14-05-2012	
		EC SP045331 A 19-04-2006	
		EP 1485094 A1 15-12-2004	
		EP 1870100 A1 26-12-2007	
		ES 2380704 T3 17-05-2012	
		ES 2390661 T3 15-11-2012	
		HK 1078792 A1 31-12-2009	
		HR P20040807 A2 28-02-2005	
		IL 163863 A 28-02-2013	
		IL 209368 A 31-10-2012	
		JP 3866715 B2 10-01-2007	
		JP 4953727 B2 13-06-2012	
		JP 2005519099 A 30-06-2005	
		JP 2006328081 A 07-12-2006	
		JP 2007056018 A 08-03-2007	
		KR 20040099298 A 26-11-2004	
		LU 92025 I2 20-08-2012	
		LU 92117 I2 19-02-2013	
		ME P50708 A 10-02-2011	
		MX PA04008542 A 06-12-2004	
		MY 143734 A 15-07-2011	
		NO 326918 B1 16-03-2009	
		NO 332209 B1 30-07-2012	
		NO 2013001 I1 11-02-2013	
		NZ 535663 A 30-06-2006	
		NZ 546367 A 29-08-2008	
		PE 08892003 A1 10-12-2003	
		PL 210862 B1 30-03-2012	
		PL 212566 B1 31-10-2012	
		PT 1485094 E 09-10-2012	
		PT 1870100 E 17-04-2012	
		RS 79204 A 05-02-2007	
		SG 146435 A1 30-10-2008	
		SI 1485094 T1 30-10-2012	
		SI 1870100 T1 31-05-2012	
		TW I293879 B 01-03-2008	
		WO 03074056 A1 12-09-2003	