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(54) Title: CAPSULE-IN-CAPSULE COMPOSITIONS OF DABIGATRAN ETEXILATE

(57) Abstract: The present invention relates to capsule-in-capsule compositions comprising dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof and at least one organic acid, characterized in that one of the capsules comprises at least one coating.

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CAPSULE-IN-CAPSULE COMPOSITIONS OF DABIGATRAN ETEXILATE

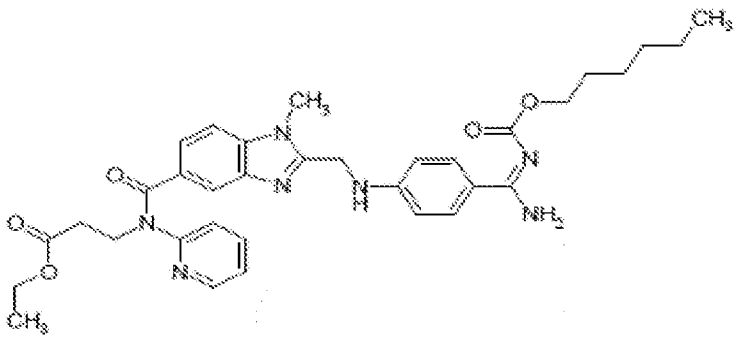
Field of the invention

The present invention relates to capsule-in-capsule compositions comprising dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof and at least one organic acid, characterized in that one of the capsules comprises at least one coating.

Background of the invention

Dabigatran is a potent, reversible, univalent direct thrombin inhibitor. Dabigatran was first disclosed in WO98/37075, which claimed compounds with a thrombin-inhibiting effect and the effect of prolonging the thrombin time, under the name 1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino) phenyl] aminomethyl] benzimidazol-5-ylcarboxylic acid-N-(2-pyridyl)-N-(2 ethoxycarbonylethyl)amides.

Dabigatran etexilate, a novel direct thrombin inhibitor, is a prodrug of dabigatran and is a non-peptide thrombin inhibitor. The structural formula is:



Formula 1: Dabigatran etexilate

Dabigatran is currently available as dabigatran etexilate mesylate, under the trade name Pradaxa from Boehringer Ingelheim is used for the reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

The solubility of dabigatran etexilate mesylate in water is 1.8 mg/mL and dependent on the pH value. To increase the solubility of dabigatran etexilate, EP1658056B1 suggests a tablet

formulation containing dabigatran etexilate and an organic acid with a solubility in water of > 1g / 250 ml at 20°C.

Dabigatran etexilate is also less stable in acidic environment. To avoid stability problem, many solutions were offered in the prior art. EP2740471B1 discloses a pharmaceutical composition contains the following main components: a core material comprising an inorganic acid layer, an active substance layer and an insulating layer between inorganic acid layer and active substance layer. EP2588090A2 discloses a process for the preparation of an oral dosage comprising a spherical core coated with tartaric acid, a isolating layer on the coated tartaric acid layer and a layer comprising dabigatran etexilate on the isolating layer. WO2015145462A1 discloses a pharmaceutical composition comprising a first component in the form of tablet comprising dabigatran and a second component in the form of capsule comprising organic acid.

There is still a need to prepare alternate compositions of dabigatran etexilate that are desired stability and improved dissolution profile. We have found an easy way to provide stability at capsule-in-capsule composition by using at least one capsule coating. It also provides improvement in dissolution profile.

Detailed description of the Invention

The main object of the present invention is to provide capsule-in-capsule compositions comprising dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof and at least one organic acid in a unit dosage form with desired stability and effective dissolution profile.

Another object of the present invention is to provide an easy and cost-effective process for the preparation of the said pharmaceutical composition.

In one embodiment, said pharmaceutical composition comprises a direct thrombin inhibitor in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof and at least one organic acid, wherein the capsule-in-capsule composition is comprising a first capsule and a second capsule which is located within the first capsule.

As used herein, the term “unit dosage form” refers to nested capsule technology which is comprising a first capsule and a second capsule, the second capsule being located within the

body of the first capsule. The first capsule comprises a first formulation which may be a direct thrombin inhibitor or an organic acid. The second capsule comprises a second formulation which may be a direct thrombin inhibitor or an organic acid.

As used herein, the term “dabigatran etexilate free base” refers to dabigatran etexilate which is free from other forms of the active moiety, especially acid addition salts.

According to this embodiment of the present invention, the first capsule is comprising a first formulation, the second capsule is comprising a second formulation.

According to these embodiments of the present invention provides stable composition in a single dosage unit. Especially, coating the second capsule with at least one coating has surprisingly provided the stability of the composition. To prepare the coating step at capsule-in-capsule composition is easier and this method eliminates both incompatibility and stability problems encountered in the prior art.

According to these embodiments of the present invention, the first formulation and the second formulation are in the form of mini tablets or granules or pellets or powder or beads or capsules or mixtures thereof.

In one embodiment of the present invention, the first formulation is comprising a direct thrombin inhibitor in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof or an organic acid.

In one embodiment of the present invention, the second formulation is comprising a direct thrombin inhibitor in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof or an organic acid.

In one embodiment, the pharmaceutical composition in a dosage unit form comprises a first capsule and a second capsule which is located within the first capsule, wherein the first capsule comprising a first formulation held between the first and second capsule and comprising a second formulation held in the second capsule, and wherein the first formulation or the second formulation comprising a direct thrombin inhibitor in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof or at least one organic acid.

According to an embodiment of the present invention, a capsule-in-capsule composition comprises,

- the first capsule comprising a first formulation held between the first and second capsule comprising a direct thrombin inhibitor in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof or at least one organic acid

- the second capsule comprising a second formulation comprising a direct thrombin inhibitor in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof or at least one organic acid
wherein the second capsule further comprising at least one coating.

According to an embodiment of the present invention, the direct thrombin inhibitor is dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof.

In one embodiment, the raw material of the capsule is hydroxypropyl methylcellulose (HPMC) or gelatin which can be alkali-treated gelatin, acid-treated gelatin, or chemically modified gelatin.

In one embodiment, the capsule material may further include agar, starch, alginic acid, guar gum, plasticizer and mixtures thereof.

HPMC based capsules has retardant effects on the rate of dissolution compared to gelatin based capsules. Gelatin based capsules can be more preferable than HPMC based capsules when using acid in the pharmaceutical composition.

In one embodiment, the capsule filled with the organic acid, or the coated organic acid, or the powder mixture containing organic acid is made of gelatin or HPMC, preferably gelatin.

In one embodiment, the capsule filled with dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof is made of gelatin or HPMC.

Hard gelatin capsules contain 13-16% water. Low humidity may cause them to become fragile. However, Dabigatran etexilate is able to maintain its stability against heat and light

under hardened conditions, while moisture is degraded. In order to protect the dabigatran etexylate in a capsule from the moisture of the other capsule comprising organic acid, the second capsule can be coated with at least one coating comprising water-soluble polymer. The weight of at least one coating is between 0.5% and 4.0% or between 0.75% and 2.0% in the composition. It is used in such a small proportion provides an advantage in terms of stability without causing any delay in resolution.

According to an embodiment of the present invention, the second capsule comprises at least one coating which having water-soluble polymer.

Suitable water-soluble polymer is selected from hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), hydroxyethylcellulose and derivatives, ethylcellulose and ethyl hydroxyethylcellulose, carboxymethylcellulose (CMC), methyl cellulose (MC), polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyethylene oxide (PEO), poly(ethylene oxide-b-propylene oxide), polyoxyethylene (POE), polyvinylpyrrolidone (PVP), polyethylenimine (PEI), poly(N-vinylpyrrolidone/vinyl acetate), polyvinylpyrollidone PVP K-90, polyacrylic acid and copolymers, poly(vinylamine) hydrochloride, poly(acrylic acid sodium salt), poly(methacrylic acid), poly(methylacrylic acid sodium salt), poly(ethylene/acrylic acid), poly(2-hydroxyethyl methacrylate/methacrylic acid), poly(2-hydroxypropyl methacrylate), polyacrylamides (PAM), poly(acrylamide/acrylic acid), polymethacrylamide, poly(N-isopropylacrylamide) (PNIPAM), poly(styrenesulfonic acid) sodium salt, poly(2-oxazoline), poly(2-ethyl-2-oxazoline), poly (3-chloro-2-hydroxypropyl-2-methacryloxyethyldimethyl-ammonium chloride), poly(2-vinyl-1-methylpyridinium bromide), poly(2-vinylpyridine), polyamines, poly(2-vinylpyridine N-oxide), poly(N-vinylpyrrolidone/2-dimethylaminoethyl methacrylate) dimethyl sulfate quaternary, poly(4-vinylpyridine N-oxide), poly(4-vinylpyridine), poly(styrenesulfonic acid/maleic acid) sodium salt, poly(N-vinyl acetamide), poly(N-vinyl acetamide-co-sodium acrylate), poly(vinylsulfonic acid) sodium salt, polyelectrolytes; agar, alginates, casein and caseinates, carrageenan, chitosan, cucurbit[n]uril hydrate, curdlan, dextran, gelatin, gellan gum, guar gum and derivatives, gum carrageenan, gum arabic and other tree and shrub exudates, locust bean gum, maltodextrins, methocel, pectin, pullulan, resin, sodium alginate, starch and starch derivatives, xanthan gum or mixture thereof.

According to an embodiment of the present invention, the water-soluble polymer is hydroxypropyl methylcellulose (HPMC) or polyethylene glycol (PEG) or polyvinylpyrrolidone or poly(N-vinylpyrrolidone/vinyl acetate) or polyvinyl alcohol or mixtures thereof.

According to an embodiment of the present invention, a first formulation in the first capsule comprises dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof and a second formulation in the second capsule comprises at least one organic acid. The presence of dabigatran etexilate and at least one organic acid in the indicated capsules helped to achieve the desired dissolution.

According to an embodiment of the present invention, the capsule-in-capsule composition comprises;

- the first capsule comprising a first formulation comprising dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof

- the second capsule comprising a second formulation comprising at least one organic acid wherein the second capsule further comprising at least one coating which having water-soluble polymer.

According to an embodiment of the present invention, the capsule-in-capsule composition comprises;

- the first capsule comprising a first formulation comprising at least one organic acid

- the second capsule comprising a second formulation comprising dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof
wherein the second capsule further comprising at least one coating which having water-soluble polymer.

Suitable organic acid comprises at least one carboxylic group. It is selected from the group comprising citric acid, tartaric acid, gallic acid, orotic acid, p-coumaric acid, hippuric acid, ferulic acid, vanillic acid, fumaric acid, maleic acid, succinic acid, malic acid, glutamic acid, aspartic acid, oxalic acid, lactic acid, formic acid, acetic acid, propionic acid, caproic acid, benzoic acid, carbonic acid, adipic acid or mixtures thereof.

According to an embodiment of the present invention, the organic acid is citric acid or tartaric acid or mixtures thereof.

In one embodiment, the organic acid pellets or the organic acid granules are coated with an isolation solution.

In one embodiment, the isolation solution is formed of a polymeric or a non-polymeric pharmaceutically acceptable agent or any combination thereof.

The organic acid has important role in high bioavailability and solubility of dabigatran etexilate. However, use of high amount of organic acid may cause incompatibilities in the patient or can limit the amount of drug used in the pharmaceutical preparation due to their intrinsic properties. That reasons should be taken in consideration when determining the amount of the direct thrombin inhibitor and the organic acid in the pharmaceutical composition.

According to an embodiment of the present invention, the weight ratio of dabigatran etexilate to the organic acid is between 0.6 and 8.0 or between 0.75 and 3.0, between 1.0 and 5.0.

According to an embodiment of the present invention, the weight ratio of the dabigatran etexilate to the citric acid is between 0.6 and 8.0 or between 0.75 and 3.0, between 1.0 and 5.0.

According to an embodiment of the present invention, the weight ratio of the dabigatran etexilate to the tartaric acid is between 0.6 and 8.0 or between 0.75 and 3.0, between 1.0 and 5.0.

In one embodiment, the said composition comprises at least one pharmaceutically acceptable excipient selected from fillers, disintegrants, diluents, dispersing agents, binders, lubricants, glidants, plasticizers, preservatives, sweeteners, flavorings, melting components, coloring agents, solvents, or mixtures thereof.

Suitable fillers may include but not limited to lactose, sugar, starches, modified starches, mannitol, calcium sulfate, xylitol, or mixtures thereof.

Suitable disintegrants may include but not limited to cross-linked polyvinylpyrrolidone (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, polyacrylate potassium, sodium alginate, corn starch, sodium starch glycolate, alginic

acid, alginates, ion-exchange resins, magnesium aluminium silica, sodium dodecyl sulphate, poloxamer, sodium glycine carbonate, sodium lauryl sulphate or mixtures thereof.

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

Suitable binders may include but not limited to polyvinylpyrrolidone, carnauba wax, pullulan, glyceryl behenate, polycarbophil, polyvinyl acetate and its copolymers, cellulose acetate phthalate, hydroxypropyl starch, sugars, tragacanth gum, cetostearyl alcohol, acacia mucilage, polyethylene glycol, polyvinyl alcohol, starch, pregelatinized starch, glucose, glucose syrup, natural gums, sucrose, sodium alginate, cellulose derivatives such as hydroxyethyl cellulose, sodium carboxymethyl cellulose, carboxymethyl cellulose calcium, ethyl cellulose, microcrystalline cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, carboxy methyl cellulose, methyl cellulose, carrageenan, guar gum, polymethacrylates, methacrylate polymers, collagens, proteins like gelatin, agar, alginate, xanthan gum, hyaluronic acid, pectin, polysaccharides, carbomer, poloxamer, polyacrylamide, aluminium hydroxide, laponite, bentonite, polyoxyethylene-alkyl ether, polydextrose, polyethylene oxide or mixtures thereof.

Suitable lubricants may include 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 stearate, sodium stearyl fumarate, sodium lauryl sulphate or mixtures thereof.

Suitable glidants may include but not limited to colloidal silicon dioxide, talc, aluminium silicate, silica or mixtures thereof.

Suitable plasticizers may include but not limited to polyethylene glycols of different molecular weights, propylene glycol or mixtures thereof.

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

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

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

Suitable melting components are selected from gelucire (stearyl macrogolglyceride), poloxamer (polyoxyethylene-polyoxypropylene block copolymer), polyethylene glycol, povidone, soluplus, cationic methacrylate, copovidone, methacrylic acid copolymers, cellulose acetate phthalate, acetylated monoglyceride, butil pthalybutyl glycolate, dibutyl tartrate, diethyl phthalate, dimethly phthalate, ethyl phthalylethly glycolate, glycerin, propylene glycol, triacetin, triacetin citrate, tripropionin or mixtures thereof.

Suitable coloring agents may include 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.

Suitable solvents may include but not limited to ethyl alcohol, 2-propanol, water or mixtures thereof.

According to an embodiment of the present invention, the pharmaceutical composition comprises the first formulation and the second formulation wherein;

a) the first formulation comprising

- 30.0 - 80.0% by weight of dabigatran etexilate;
- 5.0 - 50.0% by weight of diluent;
- 1.0 - 30.0% by weight of binder;
- 0.1 - 3.0% by weight of glidant;
- 1.0 - 15.0% by weight of disintegrant;
- 0.1 - 5.0% by weight of lubricant, and

b) the second formulation comprising

- 10.0 - 50.0% by weight of organic acid pellets or coated (isolated) organic acid pellets or powder mixture containing organic acid;

in percentages by weight based on the total weight of the composition.

According to an embodiment of the present invention, the pharmaceutical composition comprises the first formulation and the second formulation wherein;

a) the first formulation comprising

- 30.0 - 80.0% by weight of dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof;
- 5.0 - 50.0% by weight of microcrystalline cellulose;
- 1.0 - 30.0% by weight of hydroxypropyl methyl cellulose;
- 0.1 - 3.0% by weight of colloidal silicon dioxide;
- 1.0 - 15.0% by weight of croscarmellose sodium;
- 0.1 - 5.0% by weight of magnesium stearate, and

b) the second formulation comprising

- 10.0 - 50.0% by weight of citric acid or tartaric acid pellets or coated (isolated) citric acid or tartaric acid pellets or powder mixture containing citric acid or tartaric acid;

in percentages by weight based on the total weight of the composition.

According to an embodiment of the present invention, the pharmaceutical composition comprises the first formulation and the second formulation wherein;

a) the first formulation comprising

- 10.0 - 50.0% by weight of organic acid pellets or coated (isolated) organic acid pellets or powder mixture containing organic acid, and

b) the second formulation comprising

- 30.0 - 80.0% by weight of dabigatran etexilate;
- 5.0 - 50.0% by weight of diluent;
- 1.0 - 30.0% by weight of binder;
- 0.1 - 3.0% by weight of glidant;
- 1.0 - 15.0% by weight of disintegrant;
- 0.1 - 5.0% by weight of lubricant;

in percentages by weight based on the total weight of the composition.

According to an embodiment of the present invention, the pharmaceutical composition comprises the first formulation and the second formulation wherein;

a) the first formulation comprising

- 10.0 - 50.0% by weight of citric acid or tartaric acid pellets or coated (isolated) citric acid or tartaric acid pellets or powder mixture containing citric acid or tartaric acid, and

b) the second formulation comprising

- 30.0 - 80.0% by weight of dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof;
- 5.0 - 50.0% by weight of microcrystalline cellulose;
- 1.0 - 30.0% by weight of hydroxypropyl methyl cellulose;
- 0.1 - 3.0% by weight of colloidal silicon dioxide;
- 1.0 - 15.0% by weight of croscarmellose sodium;
- 0.1 - 5.0% by weight of magnesium stearate;

in percentages by weight based on the total weight of the composition.

According to an embodiment of the present invention, coating the second capsule of the present invention may be prepared by a process comprising the following steps:

a) Mixing hydroxypropyl methyl cellulose with water,
b) Adding polyethylene glycol (PEG) and then mixing to obtain suspension solution,
c) Then, coating the second capsule with the suspension solution.

According to an embodiment of the present invention, pharmaceutical compositions of the present invention may be prepared by a process comprising the following steps:

a. Preparing the first formulation in the form of mini tablets or granules or pellets or powder or beads or capsules or mixtures thereof;
b. Preparing the second formulation in the form of mini tablets or granules or pellets or powder or beads or capsules or mixtures thereof;
c. Filling the second formulation into the second capsule and
d. Coating the second capsule with at least one water-soluble polymer
e. Inserting the second capsule into the first capsule and subsequently filling the first formulation into the first capsule.

Table 1

Nested Capsule Technology		Example 1		Example 2		Example 3		Example 4		Example 5		Example 6	
Pharmaceutical Composition / Solid Dosage Form		Dabigatran Etexilate	Organic Acid	Dabigatran Etexilate	Organic Acid	Dabigatran Etexilate	Organic Acid	Dabigatran Etexilate	Organic Acid	Dabigatran Etexilate	Organic Acid	Dabigatran Etexilate	Organic Acid
First Capsule	Pellets	+											
	Granules			+									
	Minitablets					+							
	Beads							+					
	Powder									+			
	Capsules											+	
Second Capsule	Pellets		+		+		+		+		+		+
	Granules		+		+		+		+		+		+
	Minitablets		+		+		+		+		+		+
	Beads		+		+		+		+		+		+
	Powder		+		+		+		+		+		+
	Capsules		+		+		+		+		+		+

Table 2

Nested Capsule Technology		Example 1		Example 2		Example 3		Example 4		Example 5		Example 6	
Pharmaceutical Composition / Solid Dosage Form		Organic Acid	Dabigatran Etexilate	Organic Acid	Dabigatran Etexilate	Organic Acid	Dabigatran Etexilate	Organic Acid	Dabigatran Etexilate	Organic Acid	Dabigatran Etexilate	Organic Acid	Dabigatran Etexilate
First Capsule	Pellets	+											
	Granules			+									
	Minitablets					+							
	Beads							+					
	Powder									+			
	Capsules											+	
Second Capsule	Pellets		+		+		+		+		+		+
	Granules		+		+		+		+		+		+
	Minitablets		+		+		+		+		+		+
	Beads		+		+		+		+		+		+
	Powder		+		+		+		+		+		+
	Capsules		+		+		+		+		+		+

According to Table 1 and Table 2, all of the examples numbered from 1 to 6 are comprising a dabigatran etexilate and an organic acid. These tables show all alternative pharmaceutical formulations.

The term "granulating" or "granulation" represents a process to provide granular product consisting of particles each having almost same size and shape, from a starting material in the form of powder, melt or aqueous solution. The term "granules" as used herein refers to agglomerates of particles.

The compositions of the present invention may be prepared using wet-granulating processes in which a powder is added with a binder and a solvent then granulated, dry-granulating processes such as slugging or compaction and direct compression, or melt-granulating processes in which a powder is mixed with a heat-melting binder and then heat-granulated.

These granulating processes may be combined with various granulating processes such as agitating granulation method used with machines such as planetary mixers and screw mixers, high shear granulation method used with machines such as Henschel mixers and super mixers, extrusion granulation method used with machines such as cylindrical, rotary granulator, screw-extruding granulator and pellet-mill granulator, or other processes like, tumbling-granulation method, fluidized-bed granulation method, compression granulation method, crushing granulation method, and spray dry granulation method. The foregoing granulation processes may be used alone and no limitation in usage.

Once, the particles have been granulated, they may then be milled to achieve the desired particle size. Examples of suitable processes for milling the granules include hammer milling, ball milling, fluid-energy milling, roller milling, cutting milling, or other milling processes known in the art.

The term “pellets” refers to small particles with approximately uniform shapes and sizes produced by an extrusion process. A “small particle” refers to a particle of which diameter, length, height, and width is at most 10 mm (e.g., at most 2, 3, 4, 5, 6, 7, 8, or 9 mm).

The term “spherical pellet” refers to beads, beadlets, spherical particles, spheroids, or the like that are of round or about round in shape and are generally made by an extrusion and spheronization process.

The term “mini tablet”, as used herein, refers to small tablets with a diameter equal to or less than 4 mm that are typically filled into a capsule or further compressed into larger tablets. Thickness of this mini tablets equal to or less than 3 mm. The mini tablets have round shape and smooth surface to ease coating process.

Another embodiment of the present invention provides a method of preparing of the pharmaceutical composition, wherein the process for the first or second formulation comprising the following steps:

a. Blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof and at least one pharmaceutically acceptable excipient;

b. Granulating the blend of step (a);

c. Drying or cooling the granules obtained in step (b);

d. Optionally adding at least one pharmaceutically acceptable excipient to the granules obtained in step (c) and mixing;

e. Filling the mixture into the first capsule or the second capsule.

Another embodiment of the present invention provides a method of preparing of the pharmaceutical composition, wherein the process for the first or second formulation comprising the following steps:

a. Blending organic acid and optionally at least one pharmaceutically acceptable excipient;

b. Granulating the blend of step (a) to form organic acid granules or extruding or spheronizing the blend of step (a) to form organic acid pellets;

c. Optionally coating the organic acid granules or pellets with an isolation solution;

d. Filling the organic acid granules or pellets obtained in step (b) or step (c) into the first capsule or the second capsule.

Another embodiment of the present invention provides a method of preparing of the pharmaceutical composition, wherein the process comprising the following steps:

a. Preparing the first formulation comprising

i. Blending the direct thrombin inhibitor in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof, diluent, binder, glidant and disintegrant;

ii. Granulating the blend of step (i);

iii. Drying the granules obtained in step (ii);

iv.Optionally adding lubricant to the granules obtained in step (iii) and mixing;

b. Preparing the second formulation comprising

i. Blending organic acid and optionally at least one pharmaceutically acceptable excipient;

ii. Extruding or spheronizing the blend of step (i) to form organic acid pellets;

iii. Optionally coating the organic pellets with an isolation solution;

c. Filling the second formulation into the second capsule and;

d. Coating the second capsule with at least one water-soluble polymer

e. Inserting the second capsule into the first capsule and subsequently filling the first formulation into the first capsule.

Another embodiment of the present invention provides a method of preparing of the pharmaceutical composition, wherein the process comprising the following steps:

a. Preparing the first formulation comprising

i. Blending organic acid and optionally at least one pharmaceutically acceptable excipient;

ii. Extruding or spheronizing the blend of step (i) to form organic acid pellets;

iii. Optionally coating the organic pellets with an isolation solution;

b. Preparing the second formulation comprising

i. Blending the direct thrombin inhibitor in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof, diluent, binder, glidant and disintegrant;

ii. Granulating the blend of step (i);

iii. Drying the granules obtained in step (ii);

iv.Optionally adding lubricant to the granules obtained in step (iii) and mixing;

c. Filling the second formulation into the second capsule and;

d. Coating the second capsule with at least one water-soluble polymer

e. Inserting the second capsule into the first capsule and subsequently filling the first formulation into the first capsule.

Another embodiment of the present invention provides a method of preparing of the pharmaceutical composition, wherein the process comprising the following steps:

a. Preparing the first formulation comprising

i. Blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium;

ii. Granulating the blend of step (i) with water;

iii. Drying the granules obtained in step (ii);

iv.Optionally adding magnesium stearate to the granules obtained in step (iii) and mixing;

b. Preparing the second formulation comprising

i. Blending citric acid or tartaric acid with microcrystalline cellulose and solution of hydroxypropyl cellulose in isopropyl alcohol;

ii. Extruding or spheronizing the blend of step (i) to form citric acid pellets or tartaric acid pellets;

iii. Optionally coating the citric acid pellets or tartaric acid pellets with an isolation solution;

c. Filling the second formulation into the second capsule and;

d. Coating the second capsule with at least one water-soluble polymer

e. Inserting the second capsule into the first capsule and subsequently filling the first formulation into the first capsule.

Another embodiment of the present invention provides a method of preparing of the pharmaceutical composition, wherein the process comprising the following steps:

a. Preparing the first formulation comprising

i. Blending citric acid or tartaric acid with microcrystalline cellulose and solution of hydroxypropyl cellulose in isopropyl alcohol;

ii. Extruding or spheronizing the blend of step (i) to form citric acid pellets or tartaric acid pellets;

iii. Optionally coating the citric acid pellets or tartaric acid pellets with an isolation solution;

b. Preparing the second formulation comprising

i. Blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium;

ii. Granulating the blend of step (i) with water;

iii. Drying the granules obtained in step (ii);

iv.Optionally adding magnesium stearate to the granules obtained in step (iii) and mixing;

c. Filling the second formulation into the second capsule and;

d. Coating the second capsule with at least one water-soluble polymer

e. Inserting the second capsule into the first capsule and subsequently filling the first formulation into the first capsule.

Another embodiment of the present invention provides a method of preparing of the pharmaceutical composition, wherein the process for the first or the second formulation comprising the following steps:

a) Sieving and mixing dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof and at least one pharmaceutically acceptable excipient;

b) Passing the powder mixture through the compactor or slugging;

c) Sieving the powder which passed through the compactor or grinding the slugs and sieving;

d) Optionally adding at least one pharmaceutically acceptable excipient to the mixture and mixing for 1-2 more minutes.

e) Compressing the powder mixture into mini tablets.

f) Filling the mini tablets into the first capsule or the second capsule.

Another embodiment of the present invention provides a method of preparing of the pharmaceutical composition, wherein the process for the first or the second formulation comprising the following steps:

a. Sieving and mixing organic acid and optionally at least one pharmaceutically acceptable excipient;

b. Passing the powder mixture through the compactor or slugging

c. Sieving the powder which passed through the compactor or grinding the slugs and sieving

d. Optionally adding at least one pharmaceutically acceptable excipient to the mixture and mixing for 1-2 more minutes.

e. Compressing the powder mixture into mini tablets.

f. Filling the mini tablets into the first capsule or the second capsule.

Example 1:

First Capsule Content	**% by weight**
Dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof	30.0 - 80.0
Microcrystalline cellulose	5.0 - 50.0
Hydroxypropyl methyl cellulose	1.0 - 30.0
Colloidal Silicon dioxide	0.1 - 3.0
Croscarmellose sodium	1.0 - 15.0
Magnesium stearate	0.1 - 5.0
Second Capsule Content	
Coated (Isolated) Organic Acid Pellets / Organic Acid Pellets / Powder Mixture Containing Organic Acid	10.0 – 50.0
At least one coating	0.75 - 2.0
TOTAL	100.0

Preparation of Organic Acid Pellets:

Organic acid and microcrystalline cellulose are blended and this blend is added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass is extruded, spheronized, dried and screened to give pellets.

Preparation of Isolated Organic Acid Pellets (Coated Organic Acid Pellets) :

Preparation isolation solution:

Formula 1:

HPMC and sucrose are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 2:

HPMC and triethyl citrate are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 3:

HPMC is added to purified water and mixed in homogenisator. Talc and PEG 6000 are added to the obtained mixture and mixed in homogenisator.

Organic acid pellets are coated with isolation solution which is selected from Formula 1 to 3.

Preparation of Powder Mixture Containing Organic Acid

Organic acid, lactose spray dried, colloidal silicone dioxide and pregelatinized starch are sieved and blended. Magnesium stearate is added and mixed 1-2 more minutes.

Production method 1:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. This mixture is granulated with water. The granules are dried at 50°C and sieved. Magnesium stearate is added to the dried granules and mixed.

Preparation of Nested Capsules

Coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate granules are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 2:

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. The powder mixture is granulated with water and dried in an oven at 50°C. Magnesium stearate is added and mixed 1-2 more minutes. The powder mixture is compressed into mini tablets.

Preparation of Nested Capsules

Coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate in the form of mini tablets are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 3:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are mixed. Some of the magnesium stearate is added to the blend and mixed. The mixture is compressed by roller compaction. The compressed mixture (granules) is sieved. Remaining magnesium stearate is added to the sieved granules and mixed.

Preparation of Nested Capsules

Coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate granules are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Example 2:

First Capsule Content	**% by weight**
Coated (Isolated) Organic Acid Pellets / Organic Acid Pellets / Powder Mixture Containing Organic Acid	10.0 – 50.0
Second Capsule Content	
Dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof	30.0 - 80.0
Microcrystalline cellulose	5.0 - 50.0
Hydroxypropyl methyl cellulose	1.0 - 30.0
Colloidal Silicon dioxide	0.1 - 3.0
Croscarmellose sodium	1.0 - 15.0
Magnesium stearate	0.1 - 5.0
At least one coating	0.75 - 2.0
TOTAL	100.0

Preparation of Organic Acid Pellets:

Organic acid and microcrystalline cellulose are blended and this blend is added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass is extruded, spheronized, dried and screened to give pellets.

Preparation of Isolated Organic Acid Pellets (Coated Organic Acid Pellets) :

Preparation isolation solution:

Formula 1:

HPMC and sucrose are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 2:

HPMC and triethyl citrate are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 3:

HPMC is added to purified water and mixed in homogenisator. Talc and PEG 6000 are added to the obtained mixture and mixed in homogenisator.

Organic acid pellets are coated with isolation solution which is selected from Formula 1 to 3.

Preparation of Powder Mixture Containing Organic Acid

Organic acid, lactose spray dried, colloidal silicone dioxide and pregelatinized starch are sieved and blended. Magnesium stearate is added and mixed 1-2 more minutes.

Production method 1:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. This mixture is granulated with water. The granules are dried at 50°C and sieved. Magnesium stearate is added to the dried granules and mixed.

Preparation of Nested Capsules

Dabigatran etexilate granules are filled into the second capsule. The second capsule is inserted into the first capsule and coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 2:

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. The powder mixture is granulated with water and dried in an oven at 50°C. Magnesium stearate is added and mixed 1-2 more minutes. The powder mixture is compressed into mini tablets.

Preparation of Nested Capsules

Dabigatran etexilate in the form of mini tablets are filled into the second capsule. The second capsule is inserted into the first capsule and coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 3:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are mixed. Some of the magnesium stearate is added to the blend and mixed. The mixture is compressed by roller compaction. The compressed mixture (granules) is sieved. Remaining magnesium stearate is added to the sieved granules and mixed.

Preparation of Nested Capsules

Dabigatran etexilate granules are filled into the second capsule. The second capsule is inserted into the first capsule and coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Example 3:

First Capsule Content	**% by weight**
Dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof	30.0 - 80.0
Microcrystalline cellulose	5.0 - 50.0
Hydroxypropyl methyl cellulose	1.0 - 30.0
Colloidal Silicon dioxide	0.1 - 3.0
Croscarmellose sodium	1.0 - 15.0
Magnesium stearate	0.1 - 5.0
Second Capsule Content	
Coated (Isolated) Citric Acid Pellets/ Citric Acid Pellets / Powder Mixture Containing Citric Acid	10.0 – 50.0
At least one coating	0.75 - 2.0
TOTAL	100.0

Preparation of Citric Acid Pellets:

Citric acid and microcrystalline cellulose are blended and this blend is added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass is extruded, spheronized, dried and screened to give pellets.

Preparation of Isolated Citric Acid Pellets (Coated Citric Acid Pellets) :

Preparation isolation solution:

Formula 1:

HPMC and sucrose are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 2:

HPMC and triethyl citrate are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 3:

HPMC is added to purified water and mixed in homogenisator. Talc and PEG 6000 are added to the obtained mixture and mixed in homogenisator.

Citric acid pellets are coated with isolation solution which is selected from Formula 1 to 3.

Preparation of Powder Mixture Containing Citric Acid

Citric acid, lactose spray dried, colloidal silicone dioxide and pregelatinized starch are sieved and blended. Magnesium stearate is added and mixed 1-2 more minutes.

Production method 1:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. This mixture is granulated with water. The granules are dried at 50°C and sieved. Magnesium stearate is added to the dried granules and mixed.

Preparation of Nested Capsules

Coated citric acid pellets or citric acid pellets or powder mixture containing citric acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate granules are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 2:

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. The powder mixture is granulated with water and dried in an oven at 50°C. Magnesium stearate is added and mixed 1-2 more minutes. The powder mixture is compressed into mini tablets.

Preparation of Nested Capsules

Coated citric acid pellets or citric acid pellets or powder mixture containing citric acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate in the form of mini tablets are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 3:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are mixed. Some of the magnesium stearate is added to the blend and mixed. The mixture is compressed by roller compaction. The compressed mixture (granules) is sieved. Remaining magnesium stearate is added to the sieved granules and mixed.

Preparation of Nested Capsules

Coated citric acid pellets or citric acid pellets or powder mixture containing citric acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate granules are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Example 4:

First Capsule Content	**% by weight**
Coated (Isolated) Citric Acid Pellets/ Citric Acid Pellets / Powder Mixture Containing Citric Acid	10.0 – 50.0
Second Capsule Content	
Dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof	30.0 - 80.0
Microcrystalline cellulose	5.0 - 50.0
Hydroxypropyl methyl cellulose	1.0 - 30.0
Colloidal Silicon dioxide	0.1 - 3.0
Croscarmellose sodium	1.0 - 15.0
Magnesium stearate	0.1 - 5.0
At least one coating	0.75 - 2.0
TOTAL	100.0

Preparation of Citric Acid Pellets:

Citric acid and microcrystalline cellulose are blended and this blend is added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass is extruded, spheronized, dried and screened to give pellets.

Preparation of Isolated Citric Acid Pellets (Coated Citric Acid Pellets) :

Preparation isolation solution:

Formula 1:

HPMC and sucrose are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 2:

HPMC and triethyl citrate are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 3:

HPMC is added to purified water and mixed in homogenisator. Talc and PEG 6000 are added to the obtained mixture and mixed in homogenisator.

Citric acid pellets are coated with isolation solution which is selected from Formula 1 to 3.

Preparation of Powder Mixture Containing Citric Acid

Citric acid, lactose spray dried, colloidal silicone dioxide and pregelatinized starch are sieved and blended. Magnesium stearate is added and mixed 1-2 more minutes.

Production method 1:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. This mixture is granulated with water. The granules are dried at 50°C and sieved. Magnesium stearate is added to the dried granules and mixed.

Preparation of Nested Capsules

Dabigatran etexilate granules are filled into the second capsule. The second capsule is inserted into the first capsule and coated citric acid pellets or citric acid pellets or powder mixture containing citric acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 2:

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. The powder mixture is granulated with water and dried in an oven at 50°C. Magnesium stearate is added and mixed 1-2 more minutes. The powder mixture is compressed into mini tablets.

Preparation of Nested Capsules

Dabigatran etexilate in the form of mini tablets are filled into the second capsule. The second capsule is inserted into the first capsule and coated citric acid pellets or citric acid pellets or powder mixture containing citric acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 3:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are mixed. Some of the magnesium stearate is added to the blend and mixed. The mixture is compressed by roller compaction. The compressed mixture (granules) is sieved. Remaining magnesium stearate is added to the sieved granules and mixed.

Preparation of Nested Capsules

Dabigatran etexilate granules are filled into the second capsule. The second capsule is inserted into the first capsule and coated citric acid pellets or citric acid pellets or powder mixture containing citric acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

According to another embodiment of the invention in the above given examples of 3 and 4, instead of coated citric acid pellets or citric acid pellets or powder mixture containing citric acid, we can put coated tartaric acid pellets or tartaric acid pellets or powder mixture containing tartaric acid.

Example 5:

First Capsule Content	**% by weight**
Dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof	30.0 - 80.0
Microcrystalline cellulose	10.0 - 50.0
Hydroxypropyl methyl cellulose	10.0 - 30.0
Colloidal Silicon dioxide	0.5 - 3.0
Croscarmellose sodium	1.0 - 15.0
Magnesium stearate	0.1 - 5.0
Second Capsule Content	
Coated (Isolated) Organic Acid Pellets / Organic Acid Pellets / Powder Mixture	10.0 – 50.0

Containing Organic Acid	
At least one coating	0.75 - 2.0
TOTAL	100.0

Preparation of Organic Acid Pellets:

Organic acid and microcrystalline cellulose are blended and this blend is added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass is extruded, spheronized, dried and screened to give pellets.

Preparation of Isolated Organic Acid Pellets (Coated Organic Acid Pellets) :

Preparation isolation solution:

Formula 1:

HPMC and sucrose are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 2:

HPMC and triethyl citrate are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 3:

HPMC is added to purified water and mixed in homogenisator. Talc and PEG 6000 are added to the obtained mixture and mixed in homogenisator.

Organic acid pellets are coated with isolation solution which is selected from Formula 1 to 3.

Preparation of Powder Mixture Containing Organic Acid

Organic acid, lactose spray dried, colloidal silicone dioxide and pregelatinized starch are sieved and blended. Magnesium stearate is added and mixed 1-2 more minutes.

Production method 1:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. This mixture is granulated with water. The granules are dried at 50°C and sieved. Magnesium stearate is added to the dried granules and mixed.

Preparation of Nested Capsules

Coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the second capsule. The second capsule is inserted into the first capsule and

dabigatran etexilate granules are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 2:

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. The powder mixture is granulated with water and dried in an oven at 50°C. Magnesium stearate is added and mixed 1-2 more minutes. The powder mixture is compressed into mini tablets.

Preparation of Nested Capsules

Coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate in the form of mini tablets are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 3:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are mixed. Some of the magnesium stearate is added to the blend and mixed. The mixture is compressed by roller compaction. The compressed mixture (granules) is sieved. Remaining magnesium stearate is added to the sieved granules and mixed.

Preparation of Nested Capsules

Coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate granules are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Example 6:

First Capsule Content	**% by weight**
Coated (Isolated) Organic Acid Pellets / Organic Acid Pellets / Powder Mixture Containing Organic Acid	10.0 – 50.0
Second Capsule Content	
Dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof	30.0 - 80.0
Microcrystalline cellulose	10.0 - 50.0

Hydroxypropyl methyl cellulose	10.0 - 30.0
Colloidal silicon dioxide	0.5 - 3.0
Croscarmellose sodium	1.0 - 15.0
Magnesium stearate	0.1 - 5.0
At least one coating	0.75 - 2.0
TOTAL	100.0

Preparation of Organic Acid Pellets:

Organic acid and microcrystalline cellulose are blended and this blend is added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass is extruded, spheronized, dried and screened to give pellets.

Preparation of Isolated Organic Acid Pellets (Coated Organic Acid Pellets) :

Preparation isolation solution:

Formula 1:

HPMC and sucrose are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 2:

HPMC and triethyl citrate are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 3:

HPMC is added to purified water and mixed in homogenisator. Talc and PEG 6000 are added to the obtained mixture and mixed in homogenisator.

Organic acid pellets are coated with isolation solution which is selected from Formula 1 to 3.

Preparation of Powder Mixture Containing Organic Acid

Organic acid, lactose spray dried, colloidal silicone dioxide and pregelatinized starch are sieved and blended. Magnesium stearate is added and mixed 1-2 more minutes.

Production method 1:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. This mixture is granulated with water. The granules are dried at 50°C and sieved. Magnesium stearate is added to the dried granules and mixed.

Preparation of Nested Capsules

Dabigatran etexilate granules are filled into the second capsule. The second capsule is inserted into the first capsule and coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 2:

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. The powder mixture is granulated with water and dried in an oven at 50°C. Magnesium stearate is added and mixed 1-2 more minutes. The powder mixture is compressed into mini tablets.

Preparation of Nested Capsules

Dabigatran etexilate in the form of mini tablets are filled into the second capsule. The second capsule is inserted into the first capsule and coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 3:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are mixed. Some of the magnesium stearate is added to the blend and mixed. The mixture is compressed by roller compaction. The compressed mixture (granules) is sieved. Remaining magnesium stearate is added to the sieved granules and mixed.

Preparation of Nested Capsules

Dabigatran etexilate granules are filled into the second capsule. The second capsule is inserted into the first capsule and coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Example 7:

First Capsule Content	% by weight
Dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof	30.0 - 80.0
Microcrystalline cellulose	10.0 - 50.0
Hydroxypropyl methyl cellulose	10.0 - 30.0
Colloidal Silicon dioxide	0.5 - 3.0

Croscarmellose sodium	1.0 - 15.0
Magnesium stearate	0.1 - 5.0
Second Capsule Content	
Coated (Isolated) Citric Acid Pellets/ Citric Acid Pellets / Powder Mixture Containing Citric Acid	10.0 – 50.0
At least one coating	0.75 - 2.0
TOTAL	100.0

Preparation of Citric Acid Pellets:

Citric acid and microcrystalline cellulose are blended and this blend is added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass is extruded, spheronized, dried and screened to give pellets.

Preparation of Isolated Citric Acid Pellets (Coated Citric Acid Pellets) :

Preparation isolation solution:

Formula 1:

HPMC and sucrose are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 2:

HPMC and triethyl citrate are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 3:

HPMC is added to purified water and mixed in homogenisator. Talc and PEG 6000 are added to the obtained mixture and mixed in homogenisator.

Citric acid pellets are coated with isolation solution which is selected from Formula 1 to 3.

Preparation of Powder Mixture Containing Citric Acid

Citric acid, lactose spray dried, colloidal silicone dioxide and pregelatinized starch are sieved and blended. Magnesium stearate is added and mixed 1-2 more minutes.

Production method 1:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. This mixture is granulated with water. The granules are dried at 50°C and sieved. Magnesium stearate is added to the dried granules and mixed.

Preparation of Nested Capsules

Coated citric acid pellets or citric acid pellets or powder mixture containing citric acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate granules are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 2:

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. The powder mixture is granulated with water and dried in an oven at 50°C. Magnesium stearate is added and mixed 1-2 more minutes. The powder mixture is compressed into mini tablets.

Preparation of Nested Capsules

Coated citric acid pellets or citric acid pellets or powder mixture containing citric acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate in the form of mini tablets are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 3:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are mixed. Some of the magnesium stearate is added to the blend and mixed. The mixture is compressed by roller compaction. The compressed mixture (granules) is sieved. Remaining magnesium stearate is added to the sieved granules and mixed.

Preparation of Nested Capsules

Coated citric acid pellets or citric acid pellets or powder mixture containing citric acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate granules are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Example 8:

First Capsule Content	**% by weight**
Coated (Isolated) Citric Acid Pellets/ Citric Acid Pellets / Powder Mixture Containing Citric Acid	10.0 – 50.0
Second Capsule Content	
Dabigatran etexilate in the form of the free base or in the form of pharmaceutically	30.0 - 80.0

acceptable salts, polymorphs, solvates, hydrates or esters thereof	
Microcrystalline cellulose	10.0 - 50.0
Hydroxypropyl methyl cellulose	10.0 - 30.0
Colloidal Silicon dioxide	0.5 - 3.0
Croscarmellose sodium	1.0 - 15.0
Magnesium stearate	0.1 - 5.0
At least one coating	0.75 - 2.0
TOTAL	100.0

Preparation of Citric Acid Pellets:

Citric acid and microcrystalline cellulose are blended and this blend is added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass is extruded, spheronized, dried and screened to give pellets.

Preparation of Isolated Citric Acid Pellets (Coated Citric Acid Pellets) :

Preparation isolation solution:

Formula 1:

HPMC and sucrose are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 2:

HPMC and triethyl citrate are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 3:

HPMC is added to purified water and mixed in homogenisator. Talc and PEG 6000 are added to the obtained mixture and mixed in homogenisator.

Citric acid pellets are coated with isolation solution which is selected from Formula 1 to 3.

Preparation of Powder Mixture Containing Citric Acid

Citric acid, lactose spray dried, colloidal silicone dioxide and pregelatinized starch are sieved and blended. Magnesium stearate is added and mixed 1-2 more minutes.

Production method 1:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. This mixture is granulated with water. The granules are dried at 50°C and sieved. Magnesium stearate is added to the dried granules and mixed.

Preparation of Nested Capsules

Dabigatran etexilate granules are filled into the second capsule. The second capsule is inserted into the first capsule and coated citric acid pellets or citric acid pellets or powder mixture containing citric acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 2:

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. The powder mixture is granulated with water and dried in an oven at 50°C. Magnesium stearate is added and mixed 1-2 more minutes. The powder mixture is compressed into mini tablets.

Preparation of Nested Capsules

Dabigatran etexilate in the form of mini tablets are filled into the second capsule. The second capsule is inserted into the first capsule and coated citric acid pellets or citric acid pellets or powder mixture containing citric acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 3:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are mixed. Some of the magnesium stearate is added to the blend and mixed. The mixture is compressed by roller compaction. The compressed mixture (granules) is sieved. Remaining magnesium stearate is added to the sieved granules and mixed.

Preparation of Nested Capsules

Dabigatran etexilate granules are filled into the second capsule. The second capsule is inserted into the first capsule and coated citric acid pellets or citric acid pellets or powder mixture containing citric acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Example 9:

First Capsule Content	% by weight
Dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof	30.0 - 80.0
Microcrystalline cellulose	10.0 - 50.0
Hydroxypropyl methyl cellulose	10.0 - 30.0
Colloidal Silicon dioxide	0.5 - 3.0

Croscarmellose sodium	1.0 - 15.0
Magnesium stearate	0.1 - 5.0
Second Capsule Content	
Coated (Isolated) Tartaric Acid Pellets / Tartaric Acid Pellets / Powder Mixture Containing Tartaric Acid	10.0 – 50.0
At least one coating	0.75 - 2.0
TOTAL	100.0

Preparation of Tartaric Acid Pellets:

Tartaric acid and microcrystalline cellulose are blended and this blend is added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass is extruded, spheronized, dried and screened to give pellets.

Preparation of Isolated Tartaric Acid Pellets (Coated Tartaric Acid Pellets) :

Preparation isolation solution:

Formula 1:

HPMC and sucrose are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 2:

HPMC and triethyl citrate are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 3:

HPMC is added to purified water and mixed in homogenisator. Talc and PEG 6000 are added to the obtained mixture and mixed in homogenisator.

Tartaric acid pellets are coated with isolation solution which is selected from Formula 1 to 3.

Preparation of Powder Mixture Containing Tartaric Acid

Tartaric acid, lactose spray dried, colloidal silicone dioxide and pregelatinized starch are sieved and blended. Magnesium stearate is added and mixed 1-2 more minutes.

Production method 1:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. This mixture is granulated with water. The granules are dried at 50°C and sieved. Magnesium stearate is added to the dried granules and mixed.

Preparation of Nested Capsules

Coated tartaric acid pellets or tartaric acid pellets or powder mixture containing tartaric acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate granules are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 2:

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. The powder mixture is granulated with water and dried in an oven at 50°C. Magnesium stearate is added and mixed 1-2 more minutes. The powder mixture is compressed into mini tablets.

Preparation of Nested Capsules

Coated tartaric acid pellets or tartaric acid pellets or powder mixture containing tartaric acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate in the form of mini tablets are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 3:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are mixed. Some of the magnesium stearate is added to the blend and mixed. The mixture is compressed by roller compaction. The compressed mixture (granules) is sieved. Remaining magnesium stearate is added to the sieved granules and mixed.

Preparation of Nested Capsules

Coated tartaric acid pellets or tartaric acid pellets or powder mixture containing tartaric acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate granules are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Example 10:

First Capsule Content	**% by weight**
Coated (Isolated) Tartaric Acid Pellets/ Tartaric Acid Pellets / Powder Mixture Containing Tartaric Acid	10.0 – 50.0
Second Capsule Content	
Dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates,	30.0 - 80.0

hydrates or esters thereof	
Microcrystalline cellulose	10.0 - 50.0
Hydroxypropyl methyl cellulose	10.0 - 30.0
Colloidal Silicon dioxide	0.5 - 3.0
Croscarmellose sodium	1.0 - 15.0
Magnesium stearate	0.1 - 5.0
At least one coating	0.75 - 2.0
TOTAL	100.0

Preparation of Tartaric Acid Pellets:

Tartaric acid and microcrystalline cellulose are blended and this blend is added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass is extruded, spheronized, dried and screened to give pellets.

Preparation of Isolated Tartaric Acid Pellets (Coated Tartaric Acid Pellets) :

Preparation isolation solution:

Formula 1:

HPMC and sucrose are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 2:

HPMC and triethyl citrate are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 3:

HPMC is added to purified water and mixed in homogenisator. Talc and PEG 6000 are added to the obtained mixture and mixed in homogenisator.

Tartaric acid pellets are coated with isolation solution which is selected from Formula 1 to 3.

Preparation of Powder Mixture Containing Tartaric Acid

Tartaric acid, lactose spray dried, colloidal silicone dioxide and pregelatinized starch are sieved and blended. Magnesium stearate is added and mixed 1-2 more minutes.

Production method 1:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. This mixture is granulated with water. The granules are dried at 50°C and sieved. Magnesium stearate is added to the dried granules and mixed.

Preparation of Nested Capsules

Dabigatran etexilate granules are filled into the second capsule. The second capsule is inserted into the first capsule and coated tartaric acid pellets or tartaric acid pellets or powder mixture containing tartaric acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 2:

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed. The powder mixture is granulated with water and dried in an oven at 50°C. Magnesium stearate is added and mixed 1-2 more minutes. The powder mixture is compressed into mini tablets.

Preparation of Nested Capsules

Dabigatran etexilate in the form of mini tablets are filled into the second capsule. The second capsule is inserted into the first capsule and coated tartaric acid pellets or tartaric acid pellets or powder mixture containing tartaric acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 3:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are mixed. Some of the magnesium stearate is added to the blend and mixed. The mixture is compressed by roller compaction. The compressed mixture (granules) is sieved. Remaining magnesium stearate is added to the sieved granules and mixed.

Preparation of Nested Capsules

Dabigatran etexilate granules are filled into the second capsule. The second capsule is inserted into the first capsule and coated tartaric acid pellets or tartaric acid pellets or powder mixture containing tartaric acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

In one embodiment, the present invention provides other solutions by using cyclodextrin or polyvinylpyrrolidone (PVP) or polyethylene glycol (PEG) or mixture thereof for increasing solubility of dabigatran etexilate in these pharmaceutical compositions.

According to an embodiment of the present invention, the pharmaceutical composition comprises the first formulation and the second formulation wherein;

a) the first formulation comprising

- 30.0 - 80.0% by weight of the direct thrombin inhibitor in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof;
- 3.0 - 30.0% by weight of cylodextrin or PVP or PEG or mixtures thereof;
- 5.0 - 50.0% by weight of diluent;
- 1.0 - 30.0% by weight of binder;
- 0.1 - 3.0% by weight of glidant;
- 1.0 - 15.0% by weight of disintegrant;
- 0.1 - 5.0% by weight of lubricant, and

b) the second formulation comprising

- 10.0 - 50.0% by weight of organic acid pellets or coated (isolated) organic acid pellets or powder mixture containing organic acid;

in percentages by weight based on the total weight of the composition.

Another embodiment of the present invention provides a method of preparing of the pharmaceutical composition, wherein the process comprising the following steps:

a. Preparing the first formulation comprising

i. Suspending the direct thrombin inhibitor in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof with a solvent to obtain a first suspension;

ii. Suspending the cyclodextrin or PVP or PEG or mixture thereof with a solvent to obtain a second suspension;

iii. Adding the second suspension obtained in step (ii) to the first suspension obtained in step (i) to obtain a direct thrombin inhibitor blend;

iv. Sieving and mixing diluent, binder, glidant and disintegrant to obtain a mixture;

v. Granulating the blend of the direct thrombin inhibitor obtained in step (iii) with the mixture obtained in step (iv) to obtain granules;

vi. Drying the granules obtained in step (v) and sieving;

vii.Adding lubricant to the granules obtained in step (vi) and mixing;

b. Preparing the second formulation comprising

i. Blending organic acid and optionally at least one pharmaceutically acceptable excipient;

ii. Extruding or spheronizing the blend of step (i) to form organic acid pellets;

iii. Optionally coating the organic pellets with an isolation solution;

c. Filling the second formulation into the second capsule and;

d. Inserting the second capsule into the first capsule and subsequently filling the first formulation into the first capsule.

According to an embodiment of the present invention, the pharmaceutical composition comprises the first formulation and the second formulation wherein;

a) the first formulation comprising

- 30.0 - 80.0% by weight of dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof;
- 3.0 - 30.0% by weight of cylodextrin or PVP or PEG or mixtures thereof;
- 5.0 - 50.0% by weight of microcrystalline cellulose;
- 1.0 - 30.0% by weight of hydroxypropyl methyl cellulose;
- 0.1 - 3.0% by weight of colloidal silicon dioxide;
- 1.0 - 15.0% by weight of croscarmellose sodium;
- 0.1 - 5.0% by weight of magnesium stearate, and

b) the second formulation comprising

- 10.0 - 50.0% by weight of citric acid or tartaric acid pellets or coated (isolated) citric acid or tartaric acid pellets or powder mixture containing citric acid or tartaric acid;

in percentages by weight based on the total weight of the composition.

Another embodiment of the present invention provides a method of preparing of the pharmaceutical composition, wherein the process comprising the following steps:

a. Preparing the first formulation comprising

i. Suspending dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof with a solvent selected from a group comprising ethyl alcohol, 2-propanol, water or mixture thereof to obtain a first suspension;

ii. Suspending the cyclodextrin or PVP or PEG or mixture thereof with water to obtain a second suspension;

iii. Adding the second suspension obtained in step (ii) to the first suspension obtained in step (i) to obtain dabigatran etexilate blend;

iv. Sieving and mixing microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium to obtain a mixture;

v. Granulating the blend of the dabigatran etexilate obtained in step (iii) with the mixture obtained in step (iv) to obtain granules;

vi. Drying the granules obtained in step (v) and sieving;

vii.Adding magnesium stearate to the granules obtained in step (vi) and mixing;

b. Preparing the second formulation comprising

i. Blending citric acid or tartaric acid and optionally at least one pharmaceutically acceptable excipient;

ii. Extruding or spheronizing the blend of step (i) to form citric acid or tartaric acid pellets;

iii. Optionally coating the citric acid or tartaric acid pellets with an isolation solution;

c. Filling the second formulation into the second capsule and;

d. Coating the second capsule with at least one water-soluble polymer

e. Inserting the second capsule into the first capsule and subsequently filling the first formulation into the first capsule.

According to an embodiment of the present invention, the pharmaceutical composition comprises the first formulation and the second formulation wherein;

a) the first formulation comprising

- 10.0 - 50.0% by weight of organic acid pellets or coated (isolated) organic acid pellets or powder mixture containing organic acid, and

b) the second formulation comprising

- 30.0 - 80.0% by weight of the direct thrombin inhibitor in the form the free base or in the form of -pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof;
- 3.0 - 30.0% by weight of cylodextrin or PVP or PEG or mixtures thereof;
- 5.0 - 50.0% by weight of diluent;
- 1.0 - 30.0% by weight of binder;
- 0.1 - 3.0% by weight of glidant;
- 1.0 - 15.0% by weight of disintegrant;
- 0.1 - 5.0% by weight of lubricant;

in percentages by weight based on the total weight of the composition.

Another embodiment of the present invention provides a method of preparing of the pharmaceutical composition, wherein the process comprising the following steps:

a. Preparing the first formulation comprising

i. Blending organic acid and optionally at least one pharmaceutically acceptable excipient;

ii. Extruding or spheronizing the blend of step (i) to form organic acid pellets;

iii. Optionally coating the organic pellets with an isolation solution;

b. Preparing the second formulation comprising

i. Suspending the direct thrombin inhibitor in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof with a solvent to obtain a first suspension;

ii. Suspending the cyclodextrin or PVP or PEG or mixture thereof with a solvent to obtain a second suspension;

iii. Adding the second suspension obtained in step (ii) to the first suspension obtained in step (i) to obtain a direct thrombin inhibitor blend;

iv. Sieving and mixing diluent, binder, glidant and disintegrant to obtain a mixture;

v. Granulating the blend of the direct thrombin inhibitor obtained in step (iii) with the mixture obtained in step (iv) to obtain granules;

vi. Drying the granules obtained in step (v) and sieving;

vii.Adding lubricant to the granules obtained in step (vi) and mixing;

c. Filling the second formulation into the second capsule and;

d. Coating the second capsule with at least one water-soluble polymer

e. Inserting the second capsule into the first capsule and subsequently filling the first formulation into the first capsule.

According to an embodiment of the present invention, the pharmaceutical composition comprises the first formulation and the second formulation wherein;

a) the first formulation comprising

- 10.0 - 50.0% by weight of citric acid or tartaric acid pellets or coated (isolated) citric acid or tartaric acid pellets or powder mixture containing citric acid or tartaric acid, and

b) the second formulation comprising

- 30.0 - 80.0% by weight of dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof;
- 3.0 - 30.0% by weight of cylodextrin or PVP or PEG or mixtures thereof;
- 5.0 - 50.0% by weight of microcrystalline cellulose;
- 1.0 - 30.0% by weight of hydroxypropyl methyl cellulose;
- 0.1 - 3.0% by weight of colloidal silicon dioxide;
- 1.0 - 15.0% by weight of croscarmellose sodium;
- 0.1 - 5.0% by weight of magnesium stearate;

in percentages by weight based on the total weight of the composition.

Another embodiment of the present invention provides a method of preparing of the pharmaceutical composition, wherein the process comprising the following steps:

a. Preparing the first formulation comprising

i. Blending citric acid or tartaric acid and optionally at least one pharmaceutically acceptable excipient;

ii. Extruding or spheronizing the blend of step (i) to form citric acid or tartaric acid pellets;

iii. Optionally coating the citric acid or tartaric acid pellets with an isolation solution;

b. Preparing the second formulation comprising

i. Suspending dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof with a solvent selected from a group comprising ethyl alcohol, 2-propanol, water or mixture thereof to obtain a first suspension;

ii. Suspending the cyclodextrin or PVP or PEG or mixture thereof with water to obtain a second suspension;

iii. Adding the second suspension obtained in step (ii) to the first suspension obtained in step (i) to obtain dabigatran etexilate blend;

iv. Sieving and mixing microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium to obtain a mixture;

v. Granulating the blend of the dabigatran etexilate obtained in step (iii) with the mixture obtained in step (iv) to obtain granules;

vi. Drying the granules obtained in step (v) and sieving;

vii.Adding magnesium stearate to the granules obtained in step (vi) and mixing.

c. Filling the second formulation into the second capsule and;

d. Coating the second capsule with at least one water-soluble polymer

e. Inserting the second capsule into the first capsule and subsequently filling the first formulation into the first capsule.

Example 11:

First Capsule Content	**% by weight**
Dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof	30.0 - 80.0
Cylodextrin or PVP or PEG or mixtures thereof	3.0 - 30.0
Microcrystalline cellulose	5.0 - 50.0
Hydroxypropyl methyl cellulose	1.0 - 30.0

Colloidal Silicon dioxide	0.1 - 3.0
Croscarmellose sodium	1.0 - 15.0
Magnesium stearate	0.1 - 5.0
Second Capsule Content	
Coated (Isolated) Organic Acid Pellets/ Organic Acid Pellets / Powder Mixture Containing Organic Acid	10.0 – 50.0
At least one coating	0.75 - 2.0
TOTAL	100.0

Preparation of Organic Acid Pellets:

Organic acid and microcrystalline cellulose are blended and this blend is added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass is extruded, spheronized, dried and screened to give pellets.

Preparation of Isolated Organic Acid Pellets (Coated Organic Acid Pellets) :

Preparation isolation solution:

Formula 1:

HPMC and sucrose are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 2:

HPMC and triethyl citrate are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 3:

HPMC is added to purified water and mixed in homogenisator. Talc and PEG 6000 are added to the obtained mixture and mixed in homogenisator.

Organic acid pellets are coated with isolation solution which is selected from Formula 1 to 3.

Preparation of Powder Mixture Containing Organic Acid

Organic acid, lactose spray dried, colloidal silicone dioxide and pregelatinized starch are sieved and blended. Magnesium stearate is added and mixed 1-2 more minutes.

Production method 1:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate is suspended with ethyl alcohol or 2-propanol or water. Cyclodextrin or PVP or PEG is suspended with water. Suspension of cyclodextrin or PVP or PEG is added to the dabigatran etexilate suspended with ethyl alcohol or 2-propanol or water at 30-35°C.

Microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed and subsequently mixed with the blend of dabigatran etexilate and granulated. The granules are dried at 55°C and sieved. Magnesium stearate is added to the dried granules and mixed.

Preparation of Nested Capsules

Coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate granules are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 2:

Dabigatran etexilate is suspended with ethyl alcohol or 2-propanol or water. Cyclodextrin or PVP or PEG is suspended with water. Suspension of cyclodextrin or PVP or PEG is added to the dabigatran etexilate suspended with ethyl alcohol or 2-propanol or water at 30-35°C. Microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed and subsequently mixed with the blend of dabigatran etexilate and granulated. The granules are dried at 55°C and sieved. Magnesium stearate is added and mixed 1-2 more minutes. The powder mixture is compressed into mini tablets.

Preparation of Nested Capsules

Coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate in the form of mini tablets are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 3:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, Cyclodextrin or PVP or PEG, Microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide, croscarmellose sodium and half of magnesium stearate are sieved and mixed. The mixture is compressed by roller compaction. The compressed mixture (granules) is sieved. Remaining magnesium stearate is added to the sieved granules and mixed.

Preparation of Nested Capsules

Coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the second capsule. The second capsule is inserted into the first capsule and dabigatran etexilate granules are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Example 12:

First Capsule Content	**% by weight**
Coated (Isolated) Organic Acid Pellets/ Organic Acid Pellets / Powder Mixture Containing Organic Acid	10.0 – 50.0
Second Capsule Content	
Dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof	30.0 - 80.0
Cylodextrin or PVP or PEG or mixtures thereof	3.0 - 30.0
Microcrystalline cellulose	5.0 - 50.0
Hydroxypropyl methyl cellulose	1.0 - 30.0
Colloidal Silicon dioxide	0.1 - 3.0
Croscarmellose sodium	1.0 - 15.0
Magnesium stearate	0.1 - 5.0
At least one coating	0.75 - 2.0
TOTAL	100.0

Preparation of Organic Acid Pellets:

Organic acid and microcrystalline cellulose are blended and this blend is added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass is extruded, spheronized, dried and screened to give pellets.

Preparation of Isolated Organic Acid Pellets (Coated Organic Acid Pellets) :

Preparation isolation solution:

Formula 1:

HPMC and sucrose are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 2:

HPMC and triethyl citrate are added to purified water and mixed. Talc is added to the obtained mixture and mixed.

Formula 3:

HPMC is added to purified water and mixed in homogenisator. Talc and PEG 6000 are added to the obtained mixture and mixed in homogenisator.

Organic acid pellets are coated with isolation solution which is selected from Formula 1 to 3.

Preparation of Powder Mixture Containing Organic Acid

Organic acid, lactose spray dried, colloidal silicone dioxide and pregelatinized starch are sieved and blended. Magnesium stearate is added and mixed 1-2 more minutes.

Production method 1:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate is suspended with ethyl alcohol or 2-propanol or water. Cyclodextrin or PVP or PEG is suspended with water. Suspension of cyclodextrin or PVP or PEG is added to the dabigatran etexilate suspended with ethyl alcohol or 2-propanol or water at 30-35°C. Microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed and subsequently mixed with the blend of dabigatran etexilate and granulated. The granules are dried at 55°C and sieved. Magnesium stearate is added to the dried granules and mixed.

Preparation of Nested Capsules

Dabigatran etexilate granules are filled into the second capsule. The second capsule is inserted into the first capsule and coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 2:

Dabigatran etexilate is suspended with ethyl alcohol or 2-propanol or water. Cyclodextrin or PVP or PEG is suspended with water. Suspension of cyclodextrin or PVP or PEG is added to the dabigatran etexilate suspended with ethyl alcohol or 2-propanol or water at 30-35°C. Microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide and croscarmellose sodium are sieved and mixed and subsequently mixed with the blend of dabigatran etexilate and granulated. The granules are dried at 55°C and sieved. Magnesium stearate is added and mixed 1-2 more minutes. The powder mixture is compressed into mini tablets.

Preparation of Nested Capsules

Dabigatran etexilate in the form of mini tablets are filled into the second capsule. The second capsule is inserted into the first capsule and coated organic acid pellets or organic acid

pellets or powder mixture containing organic acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

Production method 3:

Preparation of Dabigatran Etexilate Granules

Dabigatran etexilate, Cyclodextrin or PVP or PEG, Microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide, croscarmellose sodium and half of magnesium stearate are sieved and mixed. The mixture is compressed by roller compaction. The compressed mixture (granules) is sieved. Remaining magnesium stearate is added to the sieved granules and mixed.

Preparation of Nested Capsules

Dabigatran etexilate granules are filled into the second capsule. The second capsule is inserted into the first capsule and coated organic acid pellets or organic acid pellets or powder mixture containing organic acid are filled into the first capsule and coating the second capsule with at least one water-soluble polymer.

According to another embodiment of the invention in the above given examples of 11 and 12, organic acid is selected from a group comprising citric acid, tartaric acid, gallic acid, orotic acid, p-coumaric acid, hippuric acid, ferulic acid, vanillic acid, fumaric acid, maleic acid, succinic acid, malic acid, glutamic acid, aspartic acid, oxalic acid, lactic acid, formic acid, acetic acid, propionic acid, caproic acid, benzoic acid, carbonic acid, adipic acid or mixtures thereof. Preferably organic acid is citric acid or tartaric acid or mixture thereof.

CLAIMS

1. A capsule-in-capsule composition comprising;

- the first capsule comprising a first formulation held between the first and second capsule comprising a direct thrombin inhibitor in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof or at least one organic acid

- the second capsule comprising a second formulation comprising a direct thrombin inhibitor in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof or at least one organic acid

wherein the second capsule further comprising at least one coating.

2. The pharmaceutical composition according to claim 1, wherein the weight of at least one coating is between 0.5% and 4.0% in the composition.

3. The pharmaceutical composition according to claim 1, wherein the second capsule comprises at least one coating which having water-soluble polymer.

4. The pharmaceutical composition according to claim 3, wherein the water-soluble polymer is selected from hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), hydroxyethylcellulose and derivatives, ethylcellulose and ethyl hydroxyethylcellulose, carboxymethylcellulose (CMC), methyl cellulose (MC), polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyethylene oxide (PEO), poly(ethylene oxide-b-propylene oxide), polyoxyethylene (POE), poly vinyl pyrrolidone (PVP), polyethylenimine (PEI), poly(N-vinylpyrrolidone/vinyl acetate), polyvinylpyrollidone PVP K-90, polyacrylic acid and copolymers, poly(vinylamine) hydrochloride, poly(acrylic acid sodium salt), poly(methacrylic acid), poly(methylacrylic acid sodium salt), poly(ethylene/acrylic acid), poly(2-hydroxyethyl methacrylate/methacrylic acid), poly(2-hydroxypropyl methacrylate), polyacrylamides (PAM), poly(acrylamide/acrylic acid), polymethacrylamide, poly(N-isopropylacrylamide) (PNIPAM), poly(styrenesulfonic acid) sodium salt, poly(2-oxazoline), poly(2-ethyl-2-oxazoline), poly(3-chloro-2-hydroxypropyl-2-methacryloxyethyldimethylammonium chloride), poly(2-vinyl-1-methylpyridinium bromide), poly(2-vinylpyridine), polyamines, poly(2-vinylpyridine N-oxide), poly(N-vinylpyrrolidone/2-dimethylaminoethyl methacrylate) dimethyl sulfate quaternary, poly(4-vinylpyridine N-oxide), poly(4-vinylpyridine), poly(styrenesulfonic acid/maleic

acid) sodium salt, poly(N-vinyl acetamide), poly(N-vinyl acetamide-co-sodium acrylate), poly(vinylsulfonic acid) sodium salt, polyelectrolytes; agar, alginates, casein and caseinates, carrageenan, chitosan, cucurbit[n]uril hydrate, curdlan, dextran, gelatin, gellan gum, guar gum and derivatives, gum carrageenan, gum arabic and other tree and shrub exudates, locust bean gum, maltodextrins, methocel, pectin, pullulan, resin, sodium alginate, starch and starch derivatives, xanthan gum or mixture thereof.

5. The pharmaceutical composition according to claim 4, wherein the water-soluble polymer is hydroxypropyl methylcellulose (HPMC) or polyethylene glycol (PEG) or polyvinylpyrrolidone or poly(N-vinylpyrrolidone/vinyl acetate) or polyvinyl alcohol or mixtures thereof.

6. The pharmaceutical composition according to claim 3, wherein

- the first capsule comprising a first formulation which having dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof
- the second capsule comprising a second formulation which having at least one organic acid and at least one coating which having water-soluble polymer.

7. The pharmaceutical composition according to claim 3, wherein

- the first capsule comprising a first formulation comprising at least one organic acid

- the second capsule comprising a second formulation comprising dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof

wherein the second capsule further comprising at least one coating which having water-soluble polymer.

8. The pharmaceutical composition according to claim 1, wherein the first capsule is made of gelatin or HPMC.

9. The pharmaceutical composition according to claim 1, wherein the second capsule is made of gelatin or HPMC.

10. The pharmaceutical composition according to claim 1, wherein the second capsule is made of gelatin.

11. The pharmaceutical composition according to claim 1, wherein the organic acid is selected from a group comprising citric acid, tartaric acid, gallic acid, orotic acid, p-coumaric acid, hippuric acid, ferulic acid, vanillic acid, fumaric acid, maleic acid, succinic acid, malic acid, glutamic acid, aspartic acid, oxalic acid, lactic acid, formic acid, acetic acid, propionic acid, caproic acid, benzoic acid, carbonic acid, adipic acid or mixtures thereof.

12. The pharmaceutical composition according to claim 11, wherein the organic acid is citric acid or tartaric acid or mixtures thereof.

13. The pharmaceutical composition according to any of the preceding claims, wherein the weight ratio of the direct thrombin inhibitor to the organic acid is between 0.6 and 8.0 or between 0.75 and 3.0, between 1.0 and 5.0.

14. The pharmaceutical composition according to any of the preceding claims, wherein the composition is further comprising at least one pharmaceutically acceptable excipient which is selected from fillers, disintegrants, diluents, dispersing agents, binders, lubricants, glidants, plasticizers, preservatives, sweeteners, flavorings, melting components, coloring agents, solvents or mixtures thereof.

15. The pharmaceutical composition according to claim 6, comprising the first formulation and the second formulation wherein,

a) the first formulation comprising

30.0 - 80% by weight of dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof;
5.0 - 50.0% by weight of microcrystalline cellulose;
1.0 - 30.0% by weight of hydroxypropyl methyl cellulose;
0.1 - 3.0% by weight of colloidal silicon dioxide;
1.0 - 15.0% by weight of croscarmellose sodium;
0.1 - 5.0% by weight of magnesium stearate, and

b) the second formulation comprising

10.0 - 50.0% by weight of citric acid or tartaric acid pellets or coated (isolated) citric acid or tartaric acid pellets or powder mixture containing citric acid or tartaric acid;
in percentages by weight based on the total weight of the composition.

16. The pharmaceutical composition according to claim 7, comprising the first formulation and the second formulation wherein,

a) the first formulation comprising

10.0 - 50.0% by weight of citric acid or tartaric acid pellets or coated (isolated) citric acid or tartaric acid pellets or powder mixture containing citric acid or tartaric acid, and

b) the second formulation comprising

30.0 - 80.0% by weight of dabigatran etexilate in the form the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates, hydrates or esters thereof;
5.0 - 50.0% by weight of microcrystalline cellulose;
1.0 - 30.0% by weight of hydroxypropyl methyl cellulose;
0.1 - 3.0% by weight of colloidal silicon dioxide;
1.0 - 15.0% by weight of croscarmellose sodium;
0.1 - 5.0% by weight of magnesium stearate;
in percentages by weight based on the total weight of the composition.

17. A process for preparation of the pharmaceutical composition according to claim 15 or 16, wherein the process comprising the following steps:

a. Preparing the first formulation in the form of mini tablets or granules or pellets or powder or beads or capsules or mixtures thereof;
b. Preparing the second formulation in the form of mini tablets or granules or pellets or powder or beads or capsules or mixtures thereof;
c. Filling the second formulation into the second capsule and;
d. Coating the second capsule with at least one water-soluble polymer
e. Inserting the second capsule into the first capsule and subsequently filling the first formulation into the first capsule.

18. The process for preparation of the pharmaceutical composition according to claim 1, wherein the process for coating the second capsule comprising the following steps:

a) Mixing hydroxypropyl methyl cellulose with water,
b) Adding polyethylene glycol (PEG) and then mixing to obtain suspension solution,
c) Then, coating the second capsule with the suspension solution.