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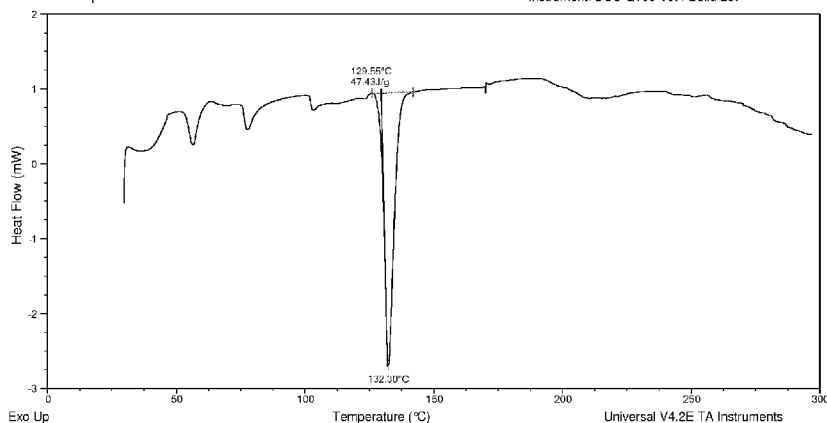
(54) Title: PHARMACEUTICAL COMBINATIONS OF DABIGATRAN AND PROTON PUMP INHIBITORS

Figure 1

Sample: Dabigatran eteksilat
Size: 2.0000 mg
Method: Ramp

DSC

File: \\...Grup4\Lab\atran\08042014\DBG.022
Operator: Yildiz GÜLKOK
Run Date: 08-Apr-2014 10:54
Instrument: DSC Q100 V9.4 Build 287



(57) Abstract: This invention is a novel pharmaceutical composition comprising dabigatran or a pharmaceutically acceptable salt thereof in combination with a proton pump inhibitor for use in the antithrombotic treatment with preventing or reducing the risk of a gastrointestinal disorder.

PHARMACEUTICAL COMBINATIONS OF DABIGATRAN AND PROTON PUMP INHIBITORS

5 Field of Invention

This invention is a novel pharmaceutical composition comprising dabigatran or a pharmaceutically acceptable salt in a combination with a proton pump inhibitor and at least one pharmaceutically acceptable excipient.

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More specifically, this invention relates to pharmaceutical composition comprising dabigatran or a pharmaceutically acceptable salt thereof in combination with a proton pump inhibitor for use in the antithrombotic treatment with preventing or reducing the risk of a gastrointestinal disorder administrated by oral, parenteral, intramuscular or

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Background of Invention

Thrombotic disorders are characterized by formation of a thrombus that obstructs vascular blood flow locally or detaches and embolizes to occlude blood flow downstream. Thrombotic disorders are a major cause of death in the industrialized world.

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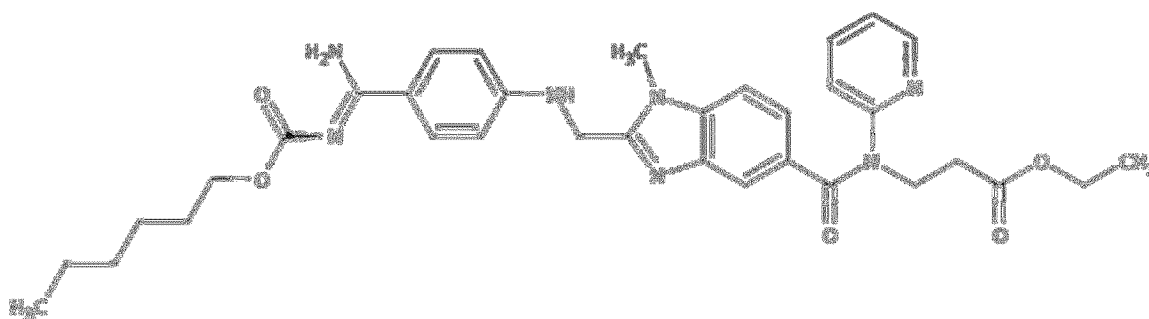
Presently there are numerous antithrombotic drugs which are widely available, they also called as Direct Thrombin Inhibitors (DTIs) which are a class of medication that act as anticoagulants (delaying blood clotting) by directly inhibiting the enzyme thrombin. In another exemplary embodiment, the DTI is univalent. In another exemplary embodiment, the DTI is bivalent. In an exemplary embodiment, the DTI is a member selected from hirudin, bivalirudin (IV), lepirudin, desirudin, argatroban (IV), dabigatran, dabigatran etexilate (oral formulation), melagatran, ximelagatran (oral formulation but liver complications) and prodrugs thereof.

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Dabigatran etexilate (Formula I), which is already known from WO 98/37075, is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-vascular atrial fibrillation.

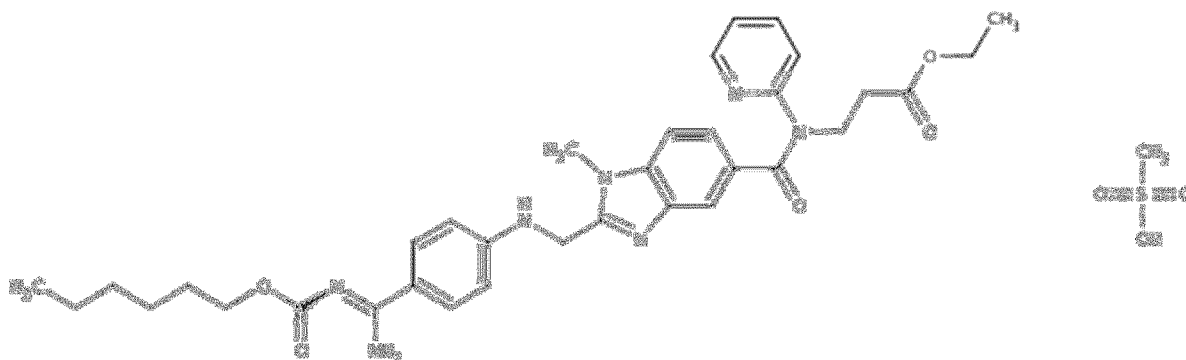
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Formula I: Dabigatran etexilate

- 5 The methane sulphonic acid addition salt of dabigatran etexilate, which is commercially available under the trade name PRADAXA®, is disclosed in EP1870100, also disclosed, pellet composition of dabigatran etexilate mesylate (Formula II). This composition is formulated with a core material consisting of organic acid and an active layer which encloses the core.

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Formula II: Dabigatran etexilate mesylate

- 15 Apart from the mesylate salt of dabigatran etexilate, other acid addition salts of the compound are provided in prior art. For example, WO2012/077136 is directed to the oxalate salt of dabigatran etexilate and besides, its hydrochloride salt is identified in EP1877395. These various form of dabigatran etexilate are prepared to facilitate the development of pharmaceutical composition. An active agent should meet some physicochemical requirements in order to be capable of being used in pharmaceutical compositions. These requirements considerably depend on the physicochemical properties of the active agent used in pharmaceutical composition.
- 20

However, dabigatran etexilate is associated with side effects. The administration of antithrombotic agents, such as dabigatran etexilate, have been associated with gastrointestinal disorders such as ulcers and gastrointestinal bleeding. In addition, the administration of dabigatran etexilate, may make some patients more susceptible to the ulcerogenic effects of ulcerogenic stimuli. It appears that a major factor contributing to the development of these gastrointestinal disorders is the presence of acid in the stomach and upper small intestine. While the mechanisms associated with ulcers and gastrointestinal bleeding are not entirely known, there are many causes of ulcers, including stress, alcohol irritation, *Helicobacter pylori* infection, and the side effects of non-steroid anti-inflammatory drugs. Patients in need of long term antithrombotic drug therapy often may interrupt or not receive such therapy due to gastrointestinal disorders, and as a result, patients are deprived of beneficial antithrombotic drug therapy. There is a need for oral pharmaceutical combination formulations to reduce or eliminate the gastrointestinal disorders associated with use of antithrombotic drugs.

Proton pump inhibitors (PPI) are acid labile compounds useful for inhibiting gastric acid secretion. The problems arisen from this acid labile characteristic of these compounds is overcome by providing a formulation that dissolves in the intestines rather than the acidic environment of the stomach.

Using an antacid or an alkaline excipient with a PPI in the formulation is one method used in the art to reduce the acidity of the gastrointestinal environment. Another one is to provide an enteric coating for the composition comprising the acid labile PPI.

It is known in the state of art that the enteric polymers with acidic nature are not compatible with the proton pump inhibitors and the alkaline excipients used in the formulation. To overcome this problem an inert intermediate layer may be introduced, such as in the prior art. In US 4,853,230 and WO 96/24338 enteric coated formulations with an alkaline active ingredient containing core and a separating layer are described.

Another role of the enteric coating is to provide a modified release. The delivery of the active ingredient to specific sites in the gastrointestinal tract is achieved by enteric coatings. These polymers can also prolong or extend the amount of active ingredient released from the dosage form.

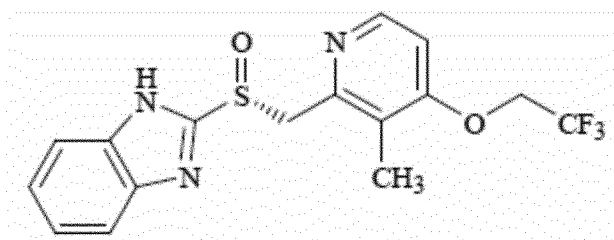
Lansoprazole is a proton pump inhibitor (PPI) which inhibits the stomach's production of gastric acids. Lansoprazole is a racemate 1:1-mixture of the enantiomers dextansoprazole and levansoprazole. Dextansoprazole is an enantiomerically pure active ingredient of a commercial drug as a result of the enantiomeric shift.

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In prior art, there are many patents including benzimidazoles such as lansoprazole and its R-enantiomer, dextansoprazole in several different pharmaceutical compositions. Crystal form of R-lansoprazole is described in EP1129088.

- 10 One of the the active ingredient from the group of PPI, dextansoprazole is the R-enantiomer of lansoprazole which inhibits gastric acid secretion (a proton pump inhibitor). Its chemical name is (+)-2-[(R)-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulfinyl]-1H-benzimidazole and its chemical structure is shown in the Formula III.

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Formula III: Dextansoprazole

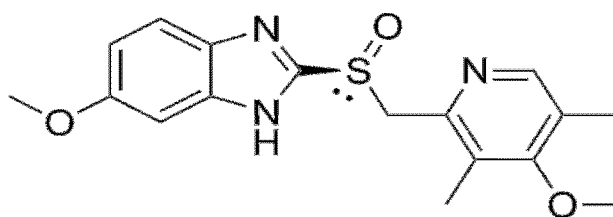
- 20 Delayed release capsule form of dextansoprazole is in the market and it is administered orally in a therapeutic dose of 30 mg and 60 mg.

As other benzimidazole compounds, dextansoprazole has also poor stability and is unstable to acidic medium, humidity, light and sensitive to heating. When orally administered, it may not be able to sufficient activity since it is decomposed by gastric acid and the like. Thus, several problems occur in formulating such compound into oral pharmaceutical dosage forms because of the acidic environmental of the stomach. In particular, it will be rapidly decomposed and change colour under moist conditions or in acidic to neutral aqueous solution.

- 30 Another one from the group of PPI is the compound 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name

omeprazole, and therapeutically acceptable alkaline salts thereof are described in U.S. Pat. No. 4,255,431 to Junggren et al., EP 5129 and EP 124 495, respectively. Omeprazole and structurally similar sulfoxide compounds are known inhibitors of gastric acid secretion and are used as anti-ulcer agents. The sulfur atom of the sulfoxide group in asymmetrically substituted sulfoxides is chiral. Therefore, omeprazole and related sulfoxides exhibit optical isomerism at the sulfur atom of the sulfoxide. In fact, omeprazole exists as a pair of enantiomers; the S (-) enantiomer is referred to as esomeprazole.

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion. Its chemical name is (S)-5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl]-3H-benzimidazole and its chemical structure is shown in the Formula IV. Certain salts of single enantiomers of omeprazole and their preparation are disclosed in WO 94/27988. These compounds have improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and salts thereof.



Formula IV: Esomeprazole

Pharmaceutical compositions that include one or more compounds obtained by the process aspect of the invention are also provided. In particular, in one variant, a pharmaceutical composition that includes the amorphous esomeprazole produced as described in U.S. Pat. No. 2004077869. The more preferred oral solid preparation is a tablet. A tablet may be prepared by direct compression, wet granulation, or molding, of the amorphous form of esomeprazole with a carrier and other excipients in a manner

known to those skilled in the art. The amorphous form of esomeprazole described U.S. Pat. No. 2004077869 may be formulated into typical disintegrating tablet, or into a controlled or extended release dosage forms. Examples of suitable modified release formulation vehicles are disclosed in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 5 3,598,123; and 4,008,719. WO 96/01623 discloses suitable tableted dosage forms of for instance magnesium salts R- and S-omeprazole.

As described above, the major factor contributing to the development of gastrointestinal disorders is the presence of acid in the stomach and upper small intestine. Therefore, 10 the main object of the invention is administering to a patient an oral dosage form including a combination of an antithrombotic agent and a proton pump inhibitor which can reduce a major factor contributing to the development of gastrointestinal disorder in patients. According to the main object, the pharmaceutical compositions of this invention is for the prevention gastrointestinal tract from side effects associated with 15 antithrombotic therapy and provide greater antithrombotic effect with the results in a lower incidence of side effects. According to prior inventions dabigatran etexilate in combination with proton pump inhibitors in particular dextansoprazole or esomeprazole have an additive preventive effect in relief of gastrointestinal disorder and provide greater antithrombotic effect with the results in a lower incidence of side effects.

20 According to the formulation of the present invention it is desired to provide a dosage form comprising in combination a therapeutically effective amount of an antithrombotic agent, specifically dabigatran and a proton pump inhibitor specifically dextansoprazole or esomeprazole which overcomes above described problems. The main challenges 25 when combining those molecules in the same pharmaceutical form are:

- (a) to guarantee the psycho-chemical compatibility between those different active ingredients and/or between the active ingredients and the excipients used; and
- (b) to insure the therapeutical compatibility between those active ingredients regarding their stability characteristics.

30 When dabigatran etexilate is combined with PPI specifically dextansoprazole or esomeprazole in order to minimize or prevent the side effects of the dabigatran etexilate, these two drug substances must be released, dissolved and absorbed harmoniously. For the efficiency of the formulation, an easy dissolution of both drug 35 substances at a desired time is an important factor. In order to minimize or prevent the side effects of dabigatran etexilate; it is very important for the molecule, in which the

molecule is used in combination with the PPIs to release both drug substances at the desired time.

Detailed description of the invention

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The present invention relates to a pharmaceutical composition comprising dabigatran or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof in a combination with a proton pump inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof and at least one pharmaceutically acceptable excipient

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The main object of the present invention is to provide new pharmaceutical compositions comprising a specific direct thrombin inhibitor such as dabigatran etexilate in combination with proton pump inhibitors such as cinprazole, dexlansoprazole, disuprazole, esaprazole, esomeprazole, fuprazole, ilaprazole, lansoprazole, leminoprazole, levolansoprazole, nepaprazole, nilprazole, omeprazole, pantoprazole, picoprazole, pumaprazole, rabeprazole, saviprazole, tenatoprazole, timoprazole, ufiprazole or other benzimidazole derivatives or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof as effective components which overcomes the above described problems in prior art and have additive advantages over them.

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The product in this invention, is used for protecting the gastrointestinal tract from side effects associated with antithrombotic therapy using the oral dosage forms described herein. The invention also relates to protect the gastrointestinal tract from side effects associated with antithrombotic therapy by combination an antithrombotic agent and a proton pump inhibitor. These and other features of the present invention are set forth herein more detailed.

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In one embodiment, the proton pump inhibitor is preferably lansoprazole or omeprazole or an acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof.

30

In one embodiment, the pharmaceutical composition comprises dabigatran or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof and lansoprazole or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof. In a preferred embodiment, lansoprazole is

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present in an amount of between 15 mg and 60 mg. In a more preferred embodiment, lansoprazole is present in an amount of between 15 mg and 30 mg.

5 In one embodiment, the pharmaceutical composition comprises dabigatran or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof in a combination with an enantiomer of lansoprazole which is dextansoprazole. In a preferred embodiment, dextansoprazole is present in an amount of between 10 mg and 75 mg. In a more preferred embodiment, dextansoprazole is present in an amount of 20 mg.

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In one embodiment, the pharmaceutical composition of the present invention comprises dabigatran or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof and omeprazole or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof. According to this embodiment, 15 omeprazole is present in an amount of between 10 mg and 75 mg. In a more preferred preferred embodiment, omeprazole is present in an amount of 20 mg.

In one embodiment, the pharmaceutical composition comprises dabigatran or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph 20 thereof in a combination with an enantiomer of omeprazole which is esomeprazole. In a preferred embodiment, esomeprazole is present in an amount of between 10 mg and 75 mg. In a more preferred embodiment, esomeprazole is present in an amount of 20 mg.

In a preferred embodiment, a pharmaceutically acceptable salt, solvate, hydrate, 25 enantiomer, prodrug or polymorph of dabigatran is the etexilate or etexilate mesylate prodrugs of dabigatran. In another preferred embodiment dabigatran etexilate is present in an amount of between 50 and 250 mg.

In a preferred embodiment dabigatran etexilate or etexilate mesylate present in an 30 amount of between 50 and 250 mg and the dextansoprazole or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof is present in an amount of between 10 and 75 mg.

In another preferred embodiment dabigatran etexilate or etexilate mesylate present in 35 an amount of between 50 and 250 mg and the esomeprazole or a pharmaceutically

acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof is present in an amount of between 10 and 75 mg.

5 According to main object of the invention, pharmaceutical formulations of dabigatran etexilate in a combination with a proton pump inhibitor have a good stability and have improved manufacturing process that is achieved in a technologically simple way which overcomes the above described problems.

10 Yet another object of the present invention is to provide an improved process which is simple, cost-effective and time saving for preparing the pharmaceutical composition of dabigatran or pharmaceutically acceptable salts thereof and one or more PPIs specially esomeprazole and dexlansoprazole.

15 In another embodiment, the oral formulations described herein can be used to treat, prevent or reduce the risk of almost any physiological disorder for which antithrombotic agents are indicated. The methods and formulations provided herein can be administered to any subject in need of therapy including, without limitation, humans, including patients, companion animals, including, but not limited to dogs, cats, ferrets, and birds, food-source animals, including, but not limited to cows, pigs, and sheep, and
20 zoo animals, such as monkeys and other primates, and other similar animal species.

In one embodiment, these pharmaceutical combinations are administered oral, parenteral, intranasal, sublingual, transdermal, transmucosal, ophthalmic, intravenous, pulmonary, intramuscular or rectal administration, and preferably for oral
25 administration. According to this embodiment of the invention, said pharmaceutical composition may be formulated with suitable pharmaceutical diluents, excipients or carriers, suitably selected with respect to a dosage form for oral administration. Examples of dosage forms include tablets, compressed tablets, coated tablets, uncoated tablets, multilayer tablets, buccal tablets, sublingual tablets, effervescent
30 compositions, effervescent tablets, immediate release tablets, modified release tablets, film-coated tablets, orally disintegrating tablets, gastric disintegrating tablets, pills, capsules, hard or soft gelatin capsules, powders, mini tablets, pellets, coated bead systems, granules, microspheres, ion exchange resin systems, sterile solutions or suspensions, steril ocular solutions, aerosols, sprays, drops, ampoules, suppositories,
35 ocular systems, parenteral systems, creams, gels, ointments, dragees, sachets; films,

orally administrable films, solutions, solids; elixirs, tinctures, suspensions, syrups, colloidal dispersions, dispersions, emulsions and thereof.

Another object of the invention is to provide a pharmaceutical composition for use in antithrombotic treatment and its use in reducing the risk of stroke and systemic embolism in patients with non-vascular atrial fibrillation and protecting the gastrointestinal tract from side effects associated with antithrombotic therapy.

In a preferred embodiment said pharmaceutical composition is formulated preferably in the form of tablet or capsule or multilayer tablet comprising etexilate or etexilate mesylate pellets of dabigatran and proton pump inhibitor pellets

Dabigatran+PPI DSC Analysis

DSC Analysis: DSC scan of about 2 mg using an automatic thermal analyzer system performed accurately weighed of APIs (Dabigatran etexilate, Dabigatran etexilate mesylate, Esomeprazole, Dexlansoprazole) of 1:1 in ratio respectively. DSC scans performed with 10°C per minute heat flow from 30°C to 300°C. The peak shifting of active ingredients was determined by DSC analysis.

Method Log:

- 1: Pan Type: Aluminum hermetic
- 2: Equilibrate at 30.00 °C
- 3: Ramp 10.00 °C/min to 300.00 °C
- 4: End of method

Results (Thermograms):

Figure 1. Thermogram of Dabigatran etexilate

Figure 2. Thermogram of Dabigatran etexilate mesylate

Figure 3. Thermogram of Esomeprazole

Figure 4. Thermogram of Dexlansoprazole

Figure 5. Thermogram of Dabigatran etexilate: Esomeprazole

Figure 6. Thermogram of Dabigatran etexilate mesylate: Esomeprazole

Figure 7. Thermogram of Dabigatran etexilate:Dexlansoprazole

Figure 8. Thermogram of Dabigatran etexilate mesylate: Dexlansoprazole

Discussion: The characteristic degradation and melting peaks of active ingredients were not determined. It indicates pharmaceutical incompatibility of esomeprazole and dexlansoprazole with Dabigatran etexilate and Dabigatran etexilate mesylate.

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	Melting temperature (°C)	Dabigatran etexilate	Dabigatran etexilate mesylate
Melting temperature (°C)	-	132	180
Esomeprazole	198 (Degradation)	174 The characteristic degradation and melting peaks of both active ingredients were not determined. They're incompatible.	176 The characteristic degradation and melting peaks of both active ingredients were not determined. They're incompatible.
Dexlansoprazole	93	87 The characteristic melting peak of Dabigatran etexilate was not determined. They're incompatible.	82 The characteristic melting peak of Dabigatran etexilate mesylate was not determined. They're incompatible.

According to the pharmaceutical incompatibility problem, the present invention provides a pharmaceutical composition comprising a barrier layer which is present in the middle in such a way that it separates dabigatran etexilate and one of the proton pump inhibitors layers and the dabigatran etexilate and PPI layers are present at the outer or inner part of the barrier layer. By the virtue of the barrier layer, interaction between the dabigatran etexilate and PPI molecules is prevented. Moreover, another important reason is that the formulations of the active substances with different release properties can be provided in the same form with barrier layer. In order to minimize gastric

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damage, enteric coated formulations such that controlled release thereof will be performed with the combination with a barrier layer.

5 In one embodiment of the invention, the bilayer or multilayer tablet may comprise optionally a barrier layer between the two layers wherein the barrier layer is selected from the group consisting of corn starch, lactose, sugar alcohol (D-mannitol, erythritol, etc.), lowsubstituted hydroxypropyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, methylcellulose, hydroxyethyl methylcellulose or mixtures thereof. Thus, the multilayer tablet according to the present
10 invention has two or more layers comprising the dabigatran etexilate and PPI molecules separately and it is characterized in releasing these molecules together and rapidly. The multilayer tablet according to the present invention is formulated in such a way that it increases the pH of the stomach by the dissolution of PPI after the dissolution of dabigatran etexilate that provides less gastrointestinal damage.

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

In a preferred embodiment, said pharmaceutical composition comprises an acid which is selected from a group comprising organic acids or inorganic acids or mixtures thereof

25 Suitable organic acids may comprise but not limited to acetic acid, acrylic acid, adipic acid, aldaric acid, ascorbic acid, azelaic acid, benzoic acid, butyric acid, chloroacetic acid, citric acid, crotonic acid, dimercaptosuccinic acid, formic acid, fumaric acid, gallic acid, glutaric acid, itaconic acid, lactic acid, malic acid, maleic acid, malonic acid, monanoic acid, methacrylic acid, naphthenic acid, oleic acid, oxalic acid, palmitic acid,
30 paracetic acid, propionic acid, pimelic acid, salicylic acid, sebacic acid, succinic acid, stearic acid, sorbic acid, tartaric acid, thiomalic acid, uric acid, glyceric acid, xylonic acid, gluconic acid, neuraminic acid, ulosonic acid, ketodeoxyoctulosonic acid, glucuronic acid, galacturonic acid, iduronic acid, meso-galactaric acid, mucic acid, d-glucaric acid, saccharic acid, glycolic acid, mandelic acid, aspartic acid, glutamic acid,
35 and the like or mixtures thereof.

Organic acids are preferably lactic acid, acetic acid, formic acid, oxalic acid, uric acid, carboxylic acid (adipic acid (dicarboxylic), azelaic acid, butyric acid, crotonic acid, gallic acid, itaconic acid, oleic acid, palmitic acid, propionic acid, sebacic acid, sorbic acid),
5 sugar acid (glyceric acid (3C), xylonic acid (5C), gluconic acid (6C), ulosonic acids), aldaric acids (meso-galactaric acid (mucic acid) (6C), D-glucaric acid (saccharic acid) (6C), mandelic acid) for pharmaceutical composition.

Suitable inorganic acids may comprise but not limited to hydrogen halides and their
10 solutions: hydrofluoric acid (HF), hydrochloric acid (HCl), hydrobromic acid (HBr), hydroiodic acid (HI); halogen oxoacids: hypochlorous acid (HClO), chlorous acid (HClO₂), chloric acid (HClO₃), perchloric acid (HClO₄), and corresponding compounds for bromine and iodine; sulfuric acid (H₂SO₄), fluorosulfuric acid (HSO₃F), nitric acid (HNO₃), phosphoric acid (H₃PO₄), fluoroantimonic acid (HSbF₆), fluoroboric acid
15 (HBF₄), hexafluorophosphoric acid (HPF₆), chromic acid (H₂CrO₄), boric acid (H₃BO₃) and the like or mixtures thereof.

Inorganic acids are preferably hydrogen halides (hydrofluoric acid (HF), hydrobromic acid (HBr), hydroiodic acid (HI)), halogen oxoacids (hypochlorous acid (HClO), and
20 corresponding compounds for bromine and iodine), nitric acid (HNO₃), fluoroboric acid (HBF₄), chromic acid (H₂CrO₄) for pharmaceutical composition.

Suitable buffering agents may comprise but not limited to alkali metal citrate, citric acid/sodium citrate, tartaric acid, fumaric acid, sorbic acid, citric acid, succinic acid,
25 adipic acid, ascorbic acid, glutaric acid, potassium hydrogen tartrate, sodium hydrogen tartrate, potassium hydrogen phthalate, sodium hydrogen phthalate, potassium dihydrogen phosphate, sodium dihydrogen phosphate, disodium hydrogen phosphate, hydrochloric acid/sodium hydroxide or mixtures thereof, and preferably citric acid, fumaric acid, ascorbic acid, sodium dihydrogen phosphate and the like or mixtures
30 thereof.

Suitable stabilizers may comprise but not limited to citric acid, fumaric acid, tartaric acid, sodium citrate, sodium benzoate, sodium dihydrogen phosphate, calcium carbonate, magnesium carbonate, arginine, lysine, meglamine, tocopherol, butylhydroxyanisole
35 (BHA), butylhydroxytoluene (BHT), ascorbic acid, gallic acid esters or the mixtures

thereof, and preferably, citric acid, fumaric acid, arginine and the like or mixtures thereof.

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

Suitable diluents may comprise 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 and the like or mixtures thereof.

Suitable dispersing agents may comprise but not limited to calcium silicate, magnesium aluminum silicate and the like or mixtures thereof.

Suitable lubricants may comprise but not limited to magnesium stearate, calcium stearate, zinc stearate, talc, waxes, boric acid, hydrogenated vegetable oil, sodium chlorate, magnesium lauryl sulfate, sodium oleate, sodium acetate, sodium benzoate, polyethylene glycol, stearic acid, fatty acid, fumaric acid, glyceryl palmito sulphate, sodium stearyl fumarate, sodium lauryl sulphate and the like or mixtures thereof.

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

Suitable disintegrants may comprise but not limited to cross-linked polyvinil pyrrolidone (crospovidone), povidone, cross-linked carboxymethyl cellulose (croscarmellose sodium), low-substituted hydroxypropyl cellulose, pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose,

docusate sodium, guar gum, low substituted hydroxypropyl cellulose, polyacryline potassium, sodium alginate, corn starch, sodium starch glycolate, alginic acid, alginates, ion-exchange resins, magnesium aluminium silica, sodium dodesyl sulphate, poloxamer, sodium glycine carbonate, sodium lauryl sulphate and the like or mixtures thereof.

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

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

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

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

25 Suitable coloring agents may comprise but not limited to ferric oxide, titanium dioxide, Food, Drug & Cosmetic (FD&C) dyes (such as; FD&C blue, FD&C green, FD&C red, FD&C yellow, FD&C lakes), poncau, indigo Drug & Cosmetic (D&C) blue, indigotine FD&C blue, carmoisine indigotine (indigo Carmine); iron oxides (such as; iron oxide red, yellow, black), quinoline yellow, flaming red, carmine, carmoisine, sunset yellow and the like or mixtures thereof.

30 In a preferred embodiment of the present invention, said pharmaceutical composition is in the form of tablet or capsule or multilayer tablet comprising etexilate or etexilate mesylate of dabigatran pellets and proton pump inhibitor pellets and acid pellets which are separate pellets or bilayer or multilayer pellets.

35 In a preferred embodiment of the present invention said dabigatran pellets comprising preferably methacrylic acid-ethyl acrylate copolymer (Eudragit EPO) or polyvinyl

alcohol (PVA) or lactose monohydrate or sugar pellet or polyvinylpyrrolidone (PVP) or dibasic calcium phosphate (DCP) or mixtures thereof as pharmaceutically acceptable excipients

- 5 In a preferred embodiment of the present invention said acid pellets comprising preferably adipic acid or sorbic acid or succinic acid or glutaric acid or nitric acid and as an excipient xanthan gum or isopropyl alcohol (IPA) or sodium alginate or microcrystalline cellulose or mannitol or lactose or silicon dioxide or methacrylic acid–ethyl acrylate copolymer (Eudragit EPO) or polyvinyl alcohol (PVA) or mixtures thereof

10

- In a preferred embodiment of the present invention said proton pump inhibitor pellets comprising preferably sugar pellet or mannitol or sodium starch glycolate or magnesium carbonate or povidone K30 or sucrose or poloxamer 407 or polyvinyl alcohol (PVA) or methacrylic acid–ethyl acrylate copolymer or talc or triethyl citrate or
15 simethicone emulsion or dibasic calcium phosphate (DCP) or polyvinylpyrrolidone (PVP) or methacrylic acid–ethyl acrylate copolymer (Eudragit L100–55) or kollicoat MAE 30DP or polyvinyl acetate (kollidon SR) or dibasic calcium phosphate (DCP) or mixtures thereof as pharmaceutically acceptable excipients

- 20 When these compounds are formulated into pharmaceutical preparations for oral administration, they require special techniques to avoid contact of PPIs with gastric acid of the stomach. One technique most commonly used is to coat these compounds, or its granules or pellets, with an enteric coating. However, the material used in enteric coatings itself is acidic, which can cause the decomposition of the compound. Such
25 decomposition occurs even during the enteric coating process, which results in the coloration of the surface of the drug-containing core.

- Enteric films do not show high flexibility so that compression stress can yield rupturing of the film. It is therefore necessary to use a tableting technique that endorses the
30 compression strain and maintains the acid resistance of the formulation after compression of the granules. Therefore caution is needed to be taken while compressing the tablets especially to form bilayer dosage form.

- In other embodiments, the enteric coating surrounds the antithrombotic agent in the oral
35 dosage form. In still another embodiment, the enteric coating surrounds both the proton pump inhibitor and the antithrombotic agent in the oral dosage form. In some

embodiments, the enteric coating surrounds essentially all of the proton pump inhibitor. In other embodiments, the enteric coating surrounds essentially all of the antithrombotic agent. In still other embodiments, the enteric coating surrounds essentially all of both the proton pump inhibitor and the antithrombotic agent in the oral dosage form. In other
5 embodiments, the oral dosage form does not include an enteric coating. In other
embodiments, the oral dosage form is substantially free of an enteric coating.

In a preferred embodiment of the present invention said proton pump inhibitor pellets
10 comprises enteric coating in an amount of 1% to 20% (w/w) of the total weight of the
pellets preferably in an amount of 2% to 10% (w/w) wherein the enteric coating
dissolves at pH 5.5 or higher.

According to this embodiment, the enteric polymers of the enteric coating layer
composition can be selected from the group comprising of cellulose acetate phthalate,
15 cellulose acetate succinate, hydroxypropyl cellulose, hydroxypropyl cellulose phthalate,
hydroxypropyl ethylcellulose, hydroxypropyl ethylcellulose phthalate, hydroxyl propyl
methyl cellulose , hydroxyl propyl methyl cellulose phthalate, hydroxyl propyl methyl
cellulose acetate succinate, hydroxyethyl cellulose phthalate, methylcellulose phthalate,
polyvinyl acetate, polyvinyl acetate phthalate, polyvinylacetate hydrogen phthalate,
20 cellulose ester phthalates, cellulose ether phthalates, sodium cellulose acetate
phthalate, starch, starch acid phthalate, cellulose acetate butyrate, cellulose acetate
maleate, cellulose acetate trimellitate, cellulose acetate propionate, cellulose acetate
phthalate, styrene maleic acid dibutyl phthalate copolymer, styrene maleic acid polyvinyl
acetate phthalate copolymer, ammonium methacrylate copolymers, hydrogels,
25 carboxyvinyl polymer, sodium alginate, sodium carmellose, calcium carmellose,
polyvinyl alcohol, polyvinyl alcohol-polyethylene glycol mixtures, gelatine,
polyvinylpyrrolidone, microcrystalline cellulose, collagen, ethyl cellulose, carboxymethyl
cellulose, carnauba wax, pectin, carbomer, poloxamer, polyachrylamide, aluminium
hydroxide, bentonit, laponit, setostearyl alcohol, polyoxyethylen-alkyl ethers, hyaluronic
30 acid, guar gum, cocoa oil, paraffin, hydrogenated vegetable oil, cetyl alcohol, stearyl
alcohol, stearic acid, xanthane gum ,shellac or mixtures thereof.

According to the pharmaceutical compositions of the invention may be prepared by
conventional technology well known to those skilled in the art such as direct
35 compression, dry granulation, wet granulation and the like. During direct compression,
active agent and excipients are mixed, sieved and compressed into dosage forms.

During wet granulation, the ingredients are mixed and granulated with a granulation liquid. The granulation process provides agglomerates with a desired homogeneity. The mixture is dried and sieved and optionally mixed with additional excipients. Finally, it is compressed into dosage forms. In addition, this novel pharmaceutical formulation is produced by various technologies such as fluidized bed granulation technique or extrusion/spheronization or spray drying and lyophilization.

Examples:

10 **Example–1: Multilayer Core Pelletization (Organic acid pellets are coated with Dabigatran+PPI pellets)**

Multilayer pellets (organic acid pellets are coated with Dabigatran):

- % 5.0 – 95 Adipic acid or Sorbic acid or Succinic acid or Glutaric acid
- 15 % 0.05 – 50 Xanthan gum
- % 0.05 – 20 Polyvinyl alcohol (PVA) or isopropyl alcohol (IPA)
- % 0.05 – 20 Sodium alginate
- %15.0 – 60 Dabigatran etexilate mesylate (DEM)
- % 0.5 – 40 Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or PVA
- 20

PPI pellets:

- %2.0– 30 Esomeprazole or Dexlansoprazole
- %5.0– 90 Sugar Pellet
- %10.0– 80 Mannitol
- 25 %0.05– 10 Sodium starch glycolate
- %0.5– 30 Magnesium carbonate
- %0.05– 30 Povidone K30
- %0.05– 30 Sucrose
- %0.05– 30 Poloxamer 407
- 30 %0.05– 50 Polyvinyl alcohol (PVA)
- %0.5– 40 Methacrylic acid– Ethyl acrylate copolymer (1:1) dispersion 30%
- %0.5– 30 Talc
- %0.02– 20 Triethyl citrate
- %0.001– 5 Simethicone emulsion

35

Other Excipients:

%0.1 – 0.2 Silicon dioxide

%0.25 – 2.0 Magnesium stearate

- 5 **Production process of multilayer pellets (organic acid pellets are coated with Dabigatran):** Adipic acid or Sorbic acid or Succinic acid or Glutaric acid and Xanthan gum are mixed together. Alcoholic PVA or IPA (isopropyl alcohol) solution is sprayed onto this mixture and pellets produced by fluidized bed pelletizing technique. The pellets are coated with sodium alginate in fluidized bed so acid pellets are manufactured. DEM is dissolved in
- 10 alcoholic Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or Polyvinyl alcohol (PVA) solution. This solution is sprayed onto the acid pellet by fluidized bed pelletizing technique so multilayer pellets are manufactured.

- Production process of PPI pellets:** Esomeprazole/Dexlansoprazole, mannitol, sodium starch glycolate, magnesium carbonate, povidone K30 and sucrose are mixed together.
- 15 Poloxamer 407 and alcoholic PVA solution are added to this mixture. This solution/dispersion is sprayed onto the sugar pellets. Methacrylic acid:Ethyl acrylate copolymer (1:1) dispersion (30%) is prepared with talc, triethyl citrate, simethicone emulsion. This pellets are coated by spraying this mixture.

20

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

- Example–2: Multilayer Core Pelletization (Dabigatran pellets are coated with organic acid+PPI pellets)**
- 25

Multilayer pellets (Dabigatran pellets are coated with organic acid):

%15.0 – 60 Dabigatran etexilate mesylate (DEM)

- %0.5 – 40 Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or Polyvinyl alcohol (PVA)
- 30

%5.0 – 40 Lactose monohydrate

%5.0 – 95 Adipic acid or Sorbic acid or Succinic acid or Glutaric acid

% 0.05 – 50 Xanthan gum

- 35 **PPI pellets:**

%2.0 – 30 Esomeprazole or Dexlansoprazole

%5.0 – 40 Dibasic calcium phosphate (DCP)

%0.1 – 25 Polyvinylpyrrolidone (PVP)

%0.5 – 40 Polyvinyl alcohol (PVA)

5 **Other Excipients:**

%0.1 – 0.2 Silicon dioxide

%0.25 – 2.0 Magnesium stearate

10 **Production process of multilayer pellets (Dabigatran pellets are coated with organic acid):** DEM and lactose monohydrate are mixed together. Alcoholic Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or Polyvinyl alcohol (PVA) solution is sprayed onto this mixture and pellets produced by fluidized bed pelletizing technique. The solution is prepared by adding adipic acid or sorbic acid or succinic acid or glutaric acid and xanthan gum. This solution is sprayed onto the DEM pellets by fluidized bed pelletizing technique
15 so multilayer pellets are manufactured.

Production process of PPI pellets: Esomeprazole/Dexlansoprazole and DCP and PVP are blended, then by spraying PVA alcoholic/hydroalcoholic solution a wet mass is formed, Pellets produced from this wet mass by extrusion/spheronization pelletizing
20 technique. The pellets are coated by PVA solution in fluidized bed.

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

25 **Example–3: Coated Core Pelletization (Dabigatran pellets+Inorganic acid pellets+PPI pellets)**

inorganic acid pellets:

%0.05 – 10 Nitric acid

30 %5.0 – 40 Microcrystalline cellulose (MCC) or Mannitol or Lactose

%0.1 – 0.2 Silicon dioxide

%0.5 – 40 Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or Polyvinyl alcohol (PVA)

35 **Dabigatran pellets**

%15.0 – 60 Dabigatran etexilate mesylate (DEM)

%5 – 90 Sugar pellet

%0.1 – 25 Polyvinylpyrrolidone (PVP)

%0.5 – 40 Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO or Polyvinyl alcohol (PVA)

5

PPI pellets

%2.0 – 30 Esomeprazole or Dexlansoprazole

%5.0 – 90 Sugar pellet

%0.1 – 25 Polyvinylpyrrolidone (PVP)

10 %0.5 – 40 Methacrylic acid–Ethyl acrylate copolymer (Eudragit L100–55 or Kollicoat MAE 30DP)

%0.5 – 40 Polyvinyl acetate (Kollidon SR)

Other Excipients

15 %0.1 – 0.2 Silicon dioxide

%0.25 – 2.0 Magnesium stearate

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

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

Production process of PPI pellets: Alcoholic solution/dispersion is prepared by adding Esomeprazole/Dexlansoprazole and PVP. Sugar pellets are coated with this solution/dispersion. The sugar pellets which were coated with the active ingredient are coated with Methacrylic acid–Ethyl acrylate copolymer (Eudragit L100–55 or Kollicoat MAE 30DP) and Polyvinyl acetate (Kollidon SR) and then with PVA solution so PPI pellets are manufactured.

Coated PPI pellets and DEM pellets and inorganic acid pellets are mixed. The pellets are first mixed with silicon dioxide and then with magnesium stearate. Finally, the pellets are pressed as tablets or filled into the capsules

5 **Example—4: Multilayer combination pellet (multilayer pellet production)**

%2.0 – 30 Esomeprazole or Dexlansoprazole

%5.0 – 90 Sugar pellet

%0.1 – 25 Polyvinylpyrrolidone (PVP)

10 %0.5 – 40 Methacrylic acid–Ethyl acrylate copolymer (Eudragit L100–55 or Kollicoat MAE 30DP)

%0.5 – 40 Polyvinyl acetate (Kollidon SR)

%15.0 – 60 Dabigatran etexilate mesylate (DEM)

15 %0.5 – 40 Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or Polyvinyl alcohol (PVA)

%5.0 – 40 Lactose monohydrate

%5.0 – 95 Adipic acid or Sorbic acid or Succinic acid or Glutaric acid)

% 0.05 – 50 Xanthan gum

% 0.05 – 20 PVA

20 %0.1 – 0.2 Silicon dioxide

%0.25 – 2.0 Magnesium stearate

Production process multilayer pellets: Alcoholic solution/dispersion is prepared by adding Esomeprazole/Dexlansoprazole and PVP. Sugar pellets are coated with this solution/dispersion. The sugar pellets which were coated with the active ingredient are coated with Methacrylic acid–Ethyl acrylate copolymer (Eudragit L100–55 or Kollicoat MAE 30DP) and Polyvinyl acetate (Kollidon SR) and then with PVA solution so PPI pellets are manufactured. DEM and lactose monohydrate are mixed with alcoholic Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or Polyvinyl alcohol(PVA) solution. This mixture is sprayed onto PPI pellets. The solution is prepared by adding adipic acid or sorbic acid or succinic acid or glutaric acid) and xanthan gum. This solution is sprayed onto the pellets so multilayer pellets are manufactured.

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

Example–5: Multilayer combination pellet (multilayer tablet press)**Multilayer pellets (Dabigatran pellets are coated with organic acid):**

- 5 %15.0– 60 Dabigatran etexilate mesylate (DEM)
 %0.5– 40 Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or Polyvinyl alcohol(PVA)
 %5.0– 40 Laktoz monohidrat
 %5.0 – 95 Adipic acid or Sorbic acid or Succinic acid or Glutaric acid
- 10 % 0.05 – 50 Xanthan gum
 % 0.05 – 20 PVA

PPI pellets:

- %2.0 – 30 Esomeprazole/Dexlansoprazole
- 15 %5.0 – 90 Sugar pellet
 %0.1 – 25 Polyvinylpyrrolidone (PVP)
 %0.5 – 40 Methacrylic acid–Ethyl acrylate copolymer (Eudragit L100–55 or Kollicoat MAE 30DP)
 %0.5 – 40 Polyvinyl acetate (Kollidon SR)
- 20 %0.1– 0.2 Silicon dioxide
 %0.25– 2.0 Magnesium stearate

Production process of multilayer pellets (Dabigatran pellets are coated with organic acid):

- 25 DEM and lactose monohydrate are mixed together. Alcoholic Methacrylic acid–Ethyl acrylate copolymer (Eudragit EPO) or Polyvinyl alcohol(PVA)solution is sprayed onto this mixture and pellets produced by fluidized bed pelletizing technique.The solution is prepared by adding adipic acid (or sorbic acid, succinic acid, glutaric acid) and xanthan gum.This solution is sprayed onto the DEM pellets by fluidized bed pelletizing technique so multilayer pellets are manufactured

30

Production process of PPI pellets: Alcoholic solution/dispersion is prepared by adding Esomeprazole/Dexlansoprazole and PVP. Sugar pellets are coated with this solution/dispersion. The sugar pellets which were coated with the active ingredient are coated with Methacrylic acid–Ethyl acrylate copolymer (Eudragit L100–55 or Kollicoat MAE 30DP) and Polyvinyl acetate (Kollidon SR) and then with PVA solution so PPI pellets are manufactured.

35

The multilayer and PPI pellets first mixed with silicon dioxide and then with magnesium stearate. Finally, the pellets are pressed by multilayer rotary tablet press machine. Or dry coating—intertwined tablets which have PPI pellets on the core are produced with special
5 tablet press machine.

CLAIMS

1. A pharmaceutical composition comprising dabigatran or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof in a combination with a proton pump inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof and at least one pharmaceutically acceptable excipient.
2. The pharmaceutical composition according to claim 1, wherein the proton pump inhibitor is selected from a group comprising cinprazole, dextlansoprazole, disuprazole, esaprazole, esomeprazole, fuprazole, ilaprazole, lansoprazole, leminoprazole, levolansoprazole, nepaprazole, nilprazole , omeprazole, pantoprazole, picoprazole, pumaprazole, rabeprazole, saviprazole, tenatoprazole, timoprazole, ufiprazole or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof.
3. The pharmaceutical composition according to claim 2, wherein the proton pump inhibitor is preferably lansoprazole or omeprazole or an acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof.
4. The pharmaceutical composition according to claim 3, comprising dabigatran or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof and lansoprazole or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof.
5. The pharmaceutical composition according to claim 4, wherein the enantiomer of lansoprazole is dextlansoprazole.
6. The pharmaceutical composition according to claim 3, comprising dabigatran or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof and omeprazole or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof.
7. The pharmaceutical composition according to claim 6, wherein the enantiomer of omeprazole is esomeprazole.

8. The pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph of dabigatran is the etexilate or etexilate mesylate prodrugs of dabigatran.

5

9. The pharmaceutical composition according to claim 5, wherein dabigatran etexilate or etexilate mesylate present in an amount of between 50 and 250 mg and the dexamethasone or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof is present in an amount of between

10

10. The pharmaceutical composition according to claim 7, wherein dabigatran etexilate or etexilate mesylate present in an amount of between 50 and 250 mg and the esomeprazole or a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, prodrug or polymorph thereof is present in an amount of between

15

11. The pharmaceutical composition of any preceding claims, wherein said pharmaceutical composition is formulated as tablets, compressed tablets, coated tablets, uncoated tablets, multilayer tablets, buccal tablets, sublingual tablets, effervescent compositions, effervescent tablets, immediate release tablets, modified release tablets, film-coated tablets, orally disintegrating tablets, gastric disintegrating tablets, pills, capsules, hard or soft gelatin capsules, powders, mini tablets, pellets, coated bead systems, granules, microspheres, ion exchange resin systems, sterile solutions or suspensions, sterile ocular solutions, aerosols, sprays, drops, ampoules, suppositories, ocular systems, parenteral systems, creams, gels, ointments, dragees, sachets; films, orally administrable films, solutions, solids; elixirs, tinctures, suspensions, syrups, colloidal dispersions, dispersions, emulsions and thereof.

25

30

12. The pharmaceutical composition of any preceding claims for use in antithrombotic treatment and reducing the risk of stroke and systemic embolism in patients with non-vascular atrial fibrillation and protecting the gastrointestinal tract from side effects associated with antithrombotic therapy.

35

13. The pharmaceutical composition according to claim 11, wherein said pharmaceutical composition is formulated preferably in the form of tablet or capsule or multilayer tablet comprising etexilate or etexilate mesylate pellets of dabigatran and proton pump inhibitor pellets.

5

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

10

15. The pharmaceutical composition according to claim 14, wherein said pharmaceutical composition comprising an acid which is selected from a group comprising organic acids or inorganic acids or mixtures thereof.

15

16. The pharmaceutical composition according to claim 15, wherein the organic acid is selected from a group comprising acetic acid, acrylic acid, adipic acid, aldarcic acid, ascorbic acid, azelaic acid, benzoic acid, butyric acid, chloroacetic acid, citric acid, crotonic acid, dimercaptosuccinic acid, formic acid, fumaric acid, gallic acid, glutaric acid, itaconic acid, lactic acid, malic acid, maleic acid, malonic acid, monanoic acid, methacrylic acid, naphthenic acid, oleic acid, oxalic acid, palmitic acid, paracetic acid, propionic acid, pimelic acid, salicylic acid, sebacic acid, succinic acid, stearic acid, sorbic acid, tartaric acid, thiomalic acid, uric acid, glyceric acid, xylonic acid, gluconic acid, neuraminic acid, ulosonic acid, ketodeoxyoctulosonic acid, glucuronic acid, galacturonic acid, iduronic acid, meso-galactaric acid, mucic acid, d-glucaric acid, saccharic acid, glycolic acid, mandelic acid, aspartic acid, glutamic acid or mixtures thereof.

20

25

17. The pharmaceutical composition according to claim 15, wherein the inorganic acid is selected from a group comprising hydrogen halides and their solutions: hydrofluoric acid (HF), hydrochloric acid (HCl), hydrobromic acid (HBr), hydroiodic acid (HI); halogen oxoacids: hypochlorous acid (HClO), chlorous acid (HClO₂), chloric acid (HClO₃), perchloric acid (HClO₄), and corresponding compounds for bromine and iodine; sulfuric acid (H₂SO₄), fluorosulfuric acid (HSO₃F), nitric acid (HNO₃), phosphoric acid (H₃PO₄), fluoroantimonic acid

30

35

(HSbF₆), fluoroboric acid (HBF₄), hexafluorophosphoric acid (HPF₆), chromic acid (H₂CrO₄), boric acid (H₃BO₃) or mixtures thereof.

5 18. The pharmaceutical composition according to claim 15, wherein said pharmaceutical composition is in the form of tablet or capsule or multilayer tablet comprising etexilate or etexilate mesylate of dabigatran pellets and proton pump inhibitor pellets and acid pellets which are separate pellets or bilayer or multilayer pellets.

10 19. The pharmaceutical composition according to claim 18, wherein said dabigatran pellets comprising preferably methacrylic acid–ethyl acrylate copolymer or polyvinyl alcohol (PVA) or lactose monohydrate or sugar pellet or polyvinylpyrrolidone (PVP) or dibasic calcium phosphate (DCP) or mixtures thereof.

15 20. The pharmaceutical composition according to claim 18, wherein said acid pellets comprising preferably adipic acid or sorbic acid or succinic acid or glutaric acid or nitric acid and as an excipient xanthan gum or isopropyl alcohol (IPA) or sodium alginate or microcrystalline cellulose or mannitol or lactose or silicon
20 dioxide or methacrylic acid–ethyl acrylate copolymer or polyvinyl alcohol (PVA) or mixtures thereof.

25 21. The pharmaceutical composition according to claim 18, wherein said proton pump inhibitor pellets comprising preferably sugar pellet or mannitol or sodium starch glycolate or magnesium carbonate or povidone or sucrose or poloxamer or polyvinyl alcohol (PVA) or methacrylic acid–ethyl acrylate copolymer or talc or triethyl citrate or simethicone emulsion or dibasic calcium phosphate (DCP) or polyvinylpyrrolidone (PVP) or polyvinyl acetate or dibasic calcium phosphate (DCP) or mixtures thereof.

30 22. The pharmaceutical composition according to claim 18 wherein said proton pump inhibitor pellets comprising enteric coating in an amount of 1% to 20% (w/w) of the total weight of the pellets preferably in an amount of 2% to 10% (w/w).

35

Figure 1

Sample: Dabigatran eteksilat
Size: 2.0000 mg
Method: Ramp

DSC

File: \\...\\Grup4\\Dabigatran\\08042014\\DBG.022
Operator: Yildiz GULKOK
Run Date: 08-Apr-2014 10:54
Instrument: DSC Q100 V9.4 Build 287

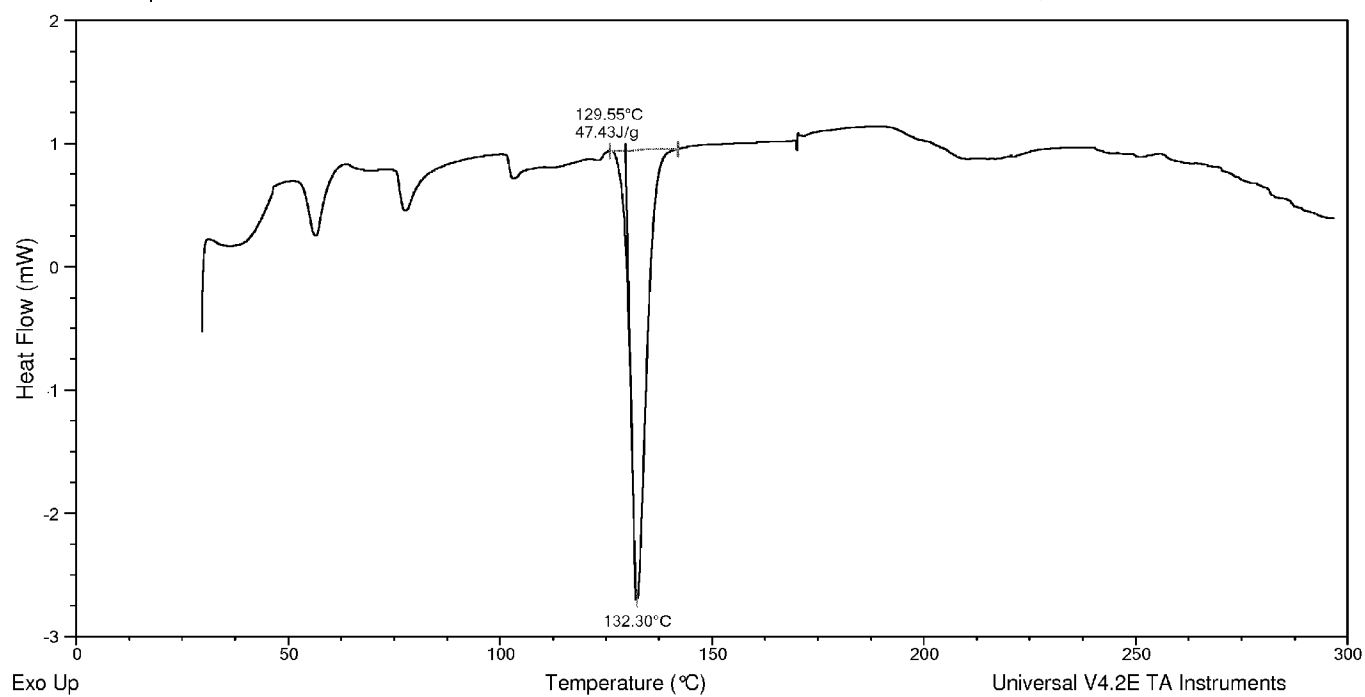


Figure 2

Sample: Dabigatran mesilat
Size: 2.0000 mg
Method: Ramp

DSC

File: \\...\\Grup4\\Dabigatran\\08042014\\DBG.023
Operator: Yildiz GULKOK
Run Date: 08-Apr-2014 11:35
Instrument: DSC Q100 V9.4 Build 287

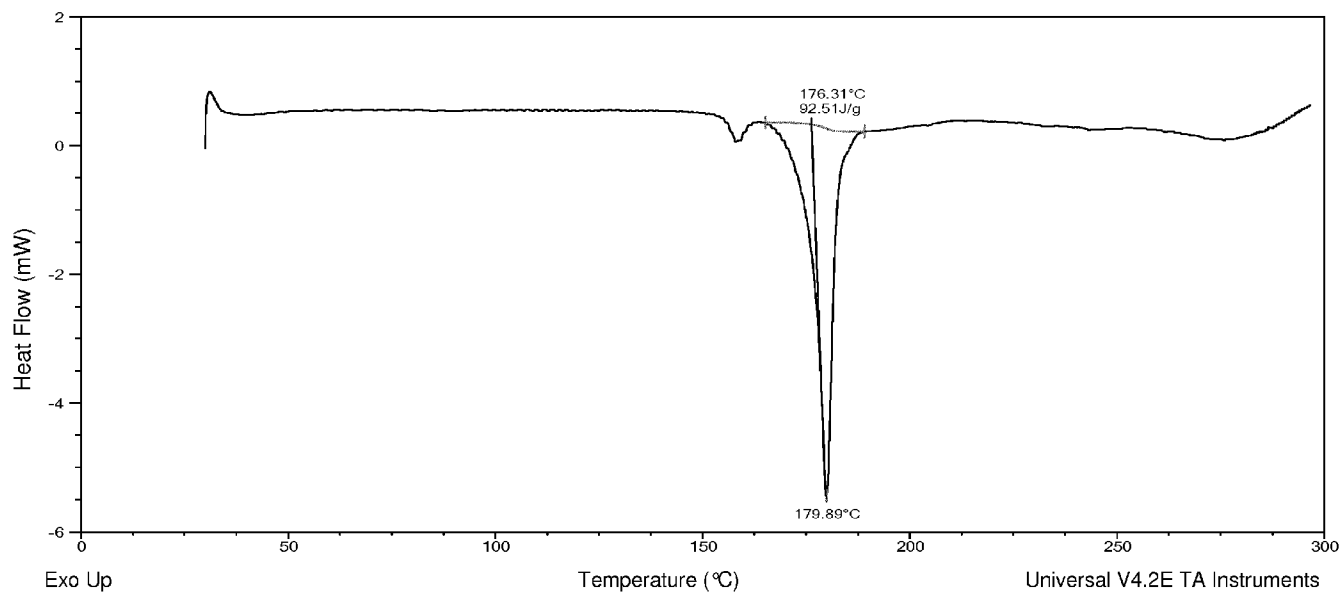


Figure 3

Sample: esomeprazol
Size: 5.0000 mg
Method: Ramp

DSC

File: \\...\\Grup4\\Dabigatran\\eteksilqt.009
Operator: Yildiz GULKOK
Run Date: 20-Feb-2014 15:04
Instrument: DSC Q100 V9.4 Build 287

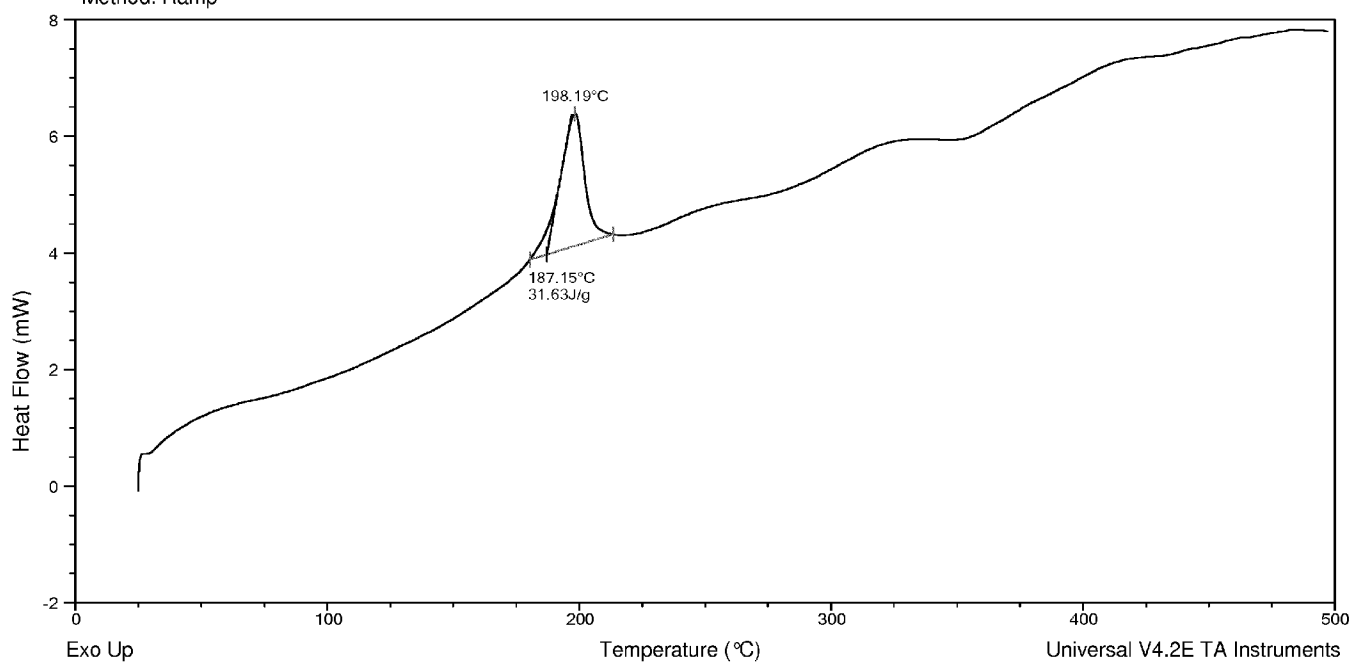


Figure 4

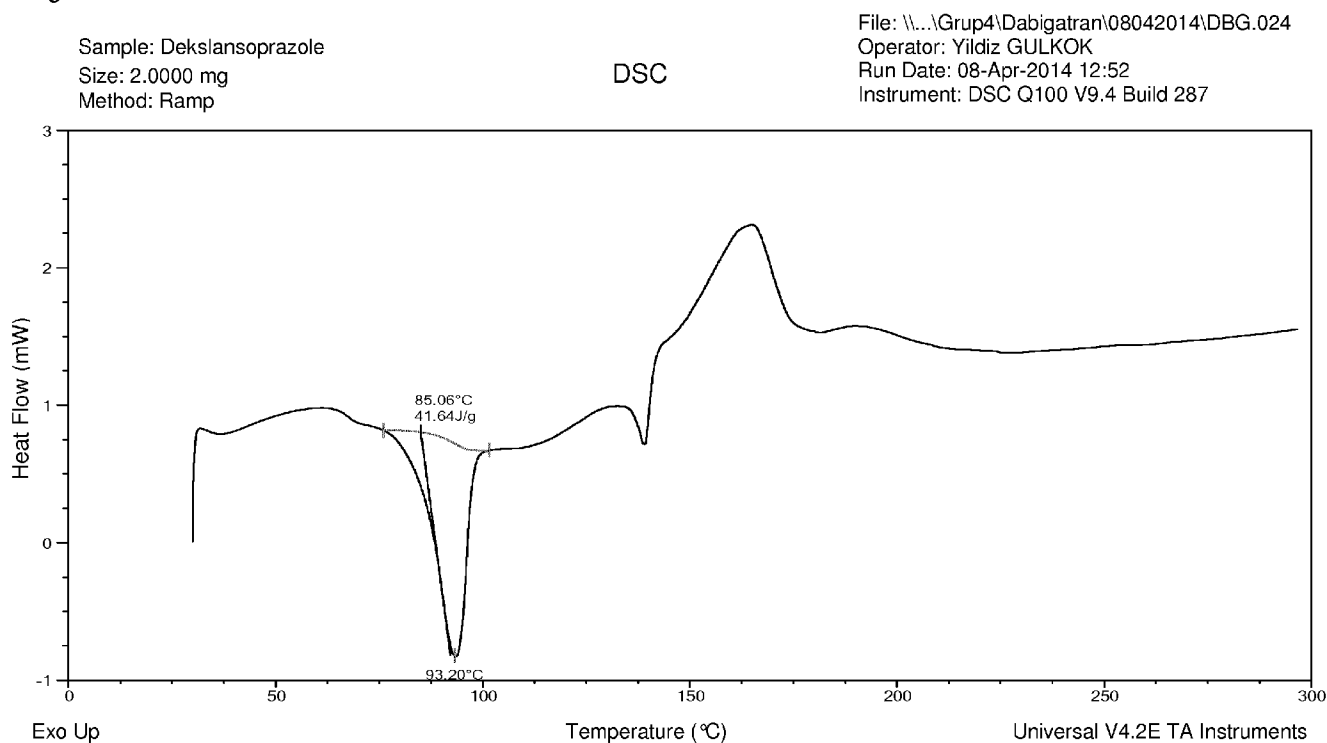


Figure 5

Sample: esomeprazol+dabigatran etexilat
Size: 2.0000 mg
Method: Ramp

DSC

File: \\...\Dabigatran\New Folder\DBG.005
Operator: Yildiz Gulkok
Run Date: 27-Mar-2014 22:07
Instrument: DSC Q100 V9.4 Build 287

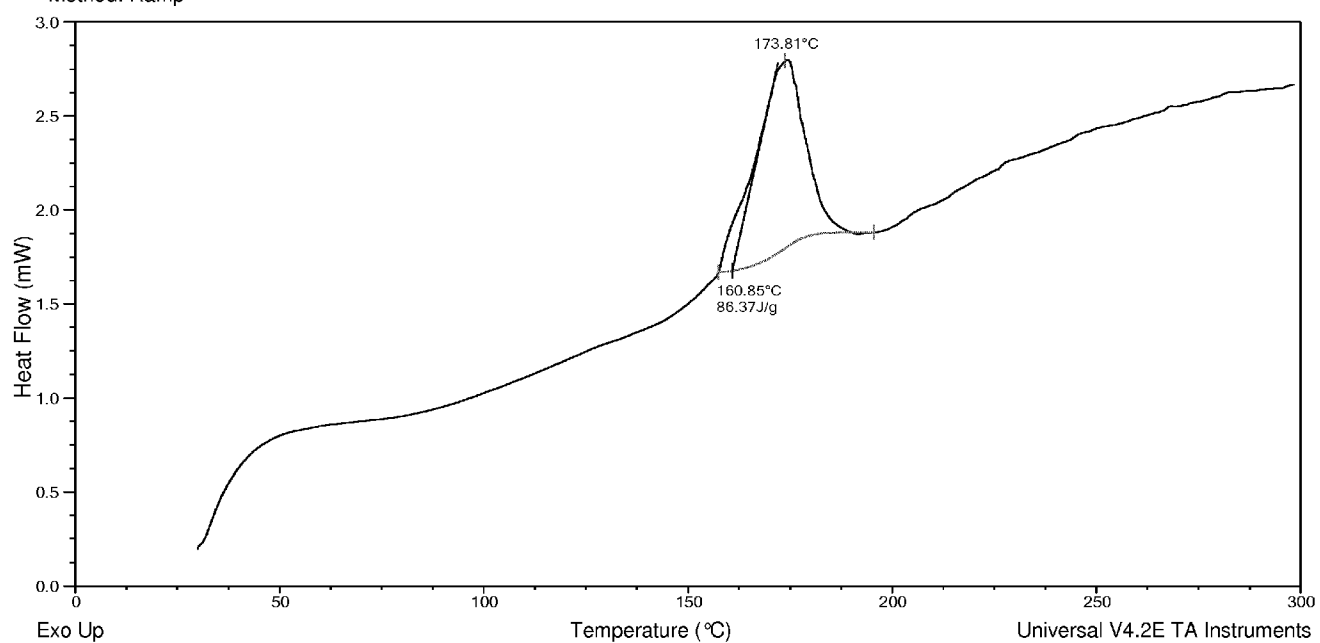


Figure 6

Sample: esomeprazol+DBGeteksilat mesilat
Size: 2.0000 mg
Method: Ramp

DSC

File: \\...\\Dabigatran\\New Folder\\DBG.005
Operator: Yildiz Gulkok
Run Date: 27-Mar-2014 22:07
Instrument: DSC Q100 V9.4 Build 287

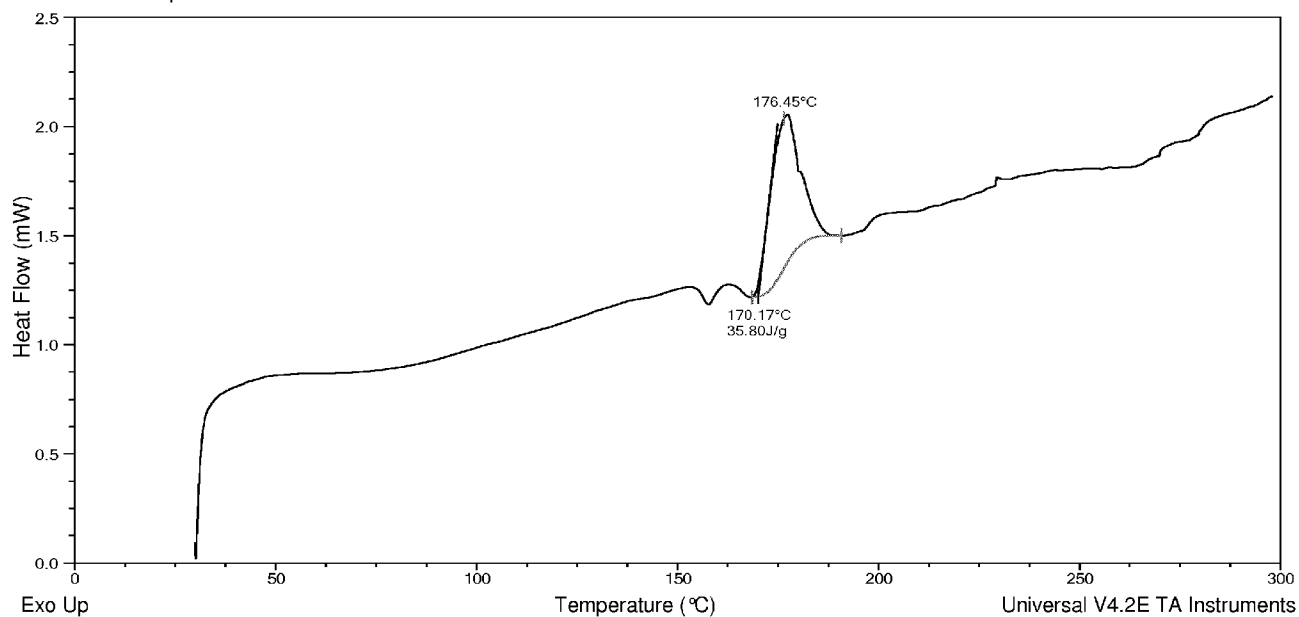


Figure 7

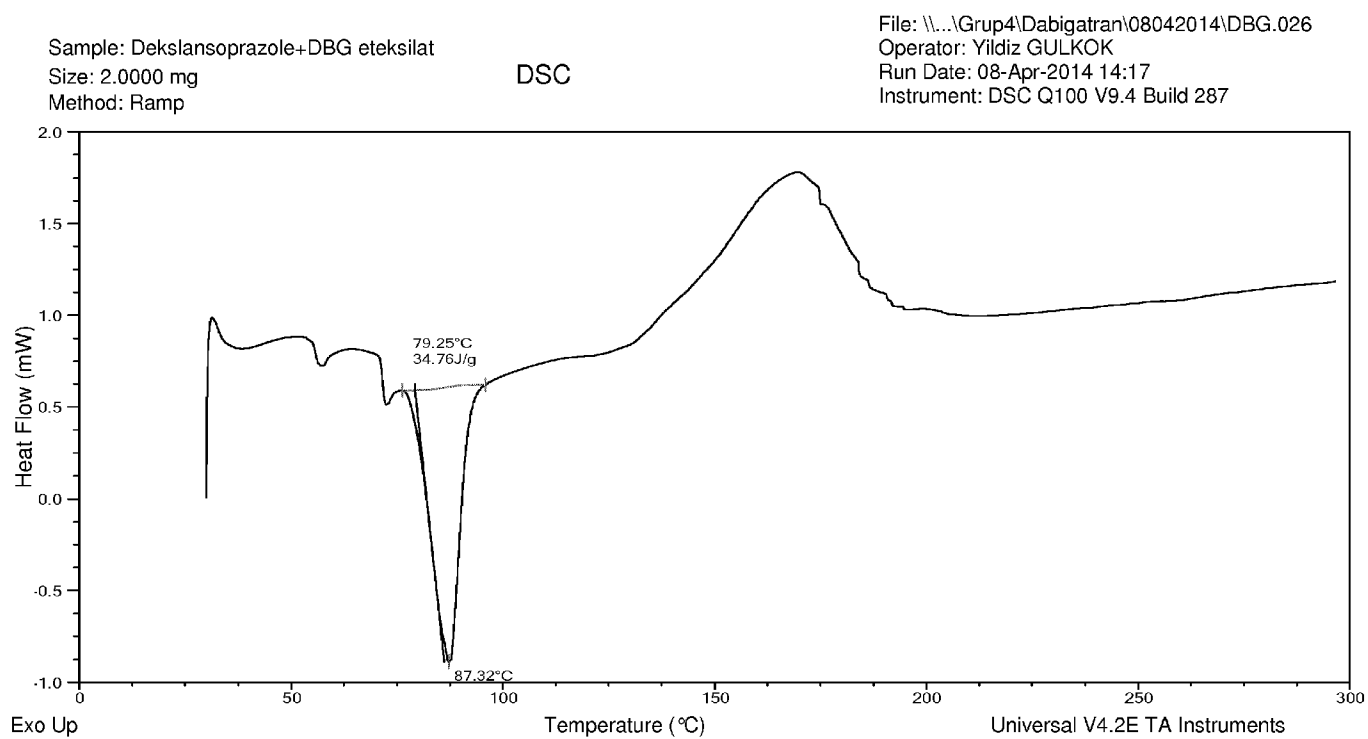
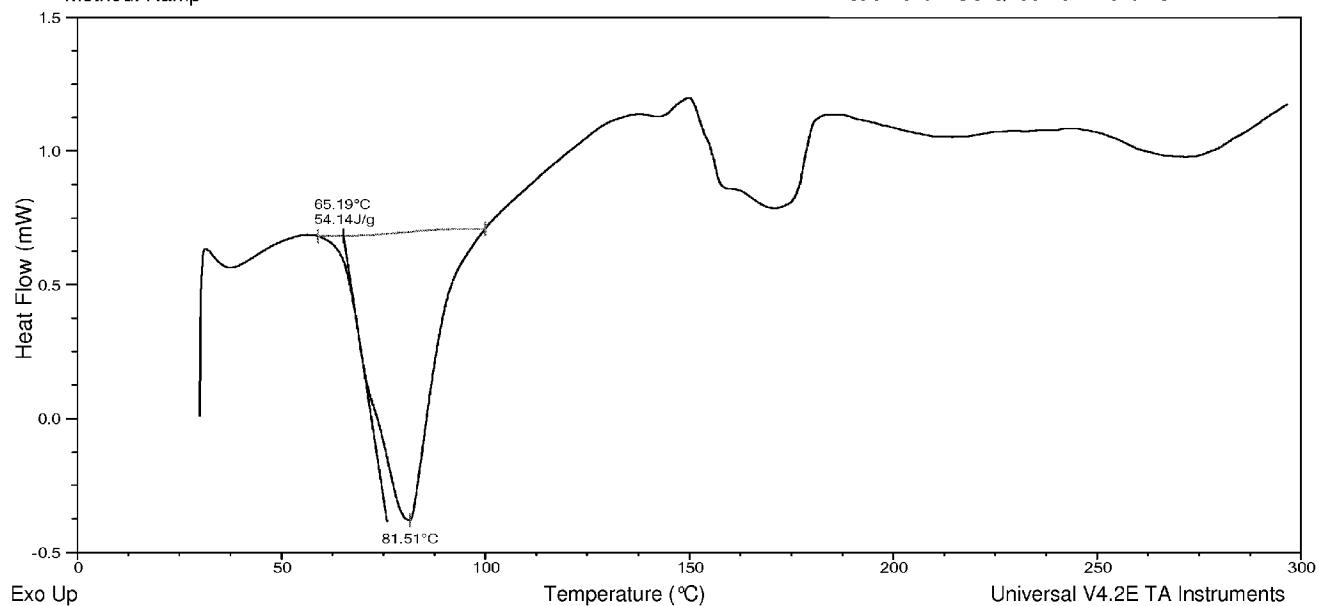


Figure 8

Sample: Dekslanso+DBGeteksilatmesilat
Size: 2.0000 mg
Method: Ramp

DSC

File: \\...\\Grup4\\Dabigatran\\08042014\\DBG.025
Operator: Yildiz GULKOK
Run Date: 08-Apr-2014 13:35
Instrument: DSC Q100 V9.4 Build 287



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/057702

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/4439 A61K9/20 A61K9/24
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

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

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AGEWALL ET AL: "Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy", EUROPEAN HEART JOURNAL, vol. 34, 2013, pages 1708-1715, XP002731551,	1-22
Y	page 1712 ----- -/--	13-22



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

1 June 2015

Date of mailing of the international search report

09/06/2015

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Authorized officer

Albayrak, Timur

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/057702

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NIRANJAN KOTTALA ET AL: "Evaluation of the Performance Characteristics of Bilayer Tablets: Part I. Impact of Material Properties and Process Parameters on the Strength of Bilayer Tablets", AAPS PHARMSCITECH, SPRINGER NEW YORK LLC, US, vol. 13, no. 4, 14 September 2012 (2012-09-14), pages 1236-1242, XP035148020, ISSN: 1530-9932, DOI: 10.1208/S12249-012-9845-9 page 1236 -----	13-22