(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 June 2017 (29.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/111637 A1

(51) International Patent Classification:
A61K 9/48 (2006.01) *A61K 31/4439* (2006.01)

(21) International Application Number:
PCT/PL2016/000156

(22) International Filing Date:
23 December 2016 (23.12.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
15460137.1 23 December 2015 (23.12.2015) EP
16460053.8 8 August 2016 (08.08.2016) EP

(71) Applicant: **ZAKLADY FARMACEUTYCZNE POLPHARMA SA** [PL/PL]; ul. Pelplinska 19, 83-200 Starogard Gdanski (PL).

(72) Inventors: **GARBERA, Kamil**; ul. Argentynska 2, 59-220 Legnica (PL). **CICHOCKI, Marek**; ul. Marchołta 51/45, 31-416 Krakow (PL). **SKOCZEN, Przemyslaw**; ul. J. Kasprowicza 37, 83-010 Straszyn (PL).

(74) Agent: **OBRYCKI, Pawel**; Zaklady Farmaceutyczne Polpharma SA, ul. Pelplinska 19, 83-200 Starogard Gdanski (PL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

WO 2017/111637 A1

(54) **Title**: PHARMACEUTICAL COMPOSITION COMPRISING DABIGATRAN OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

(57) **Abstract**: The invention relates to an oral pharmaceutical composition comprising a multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof and an acidic tablet comprising at least one pharmaceutically acceptable organic acid. It also relates to a process for the preparation of the pharmaceutical composition, preferably in the form of capsules and its use in the treatment of venous thromboembolic events and stroke and systemic embolism in adults with non-valvular atrial fibrillation.

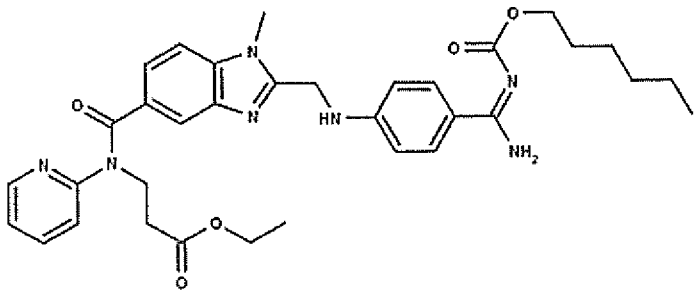
Pharmaceutical composition comprising dabigatran or a pharmaceutically acceptable salt thereof

The invention relates to an oral pharmaceutical composition of the active substance dabigatran or the pharmaceutically acceptable salts thereof, in particular dabigatran etexilate mesylate. It also relates to a process for the preparation of this pharmaceutical composition and to its medical uses, in particular for venous thromboembolic events and stroke and systemic embolism in adults with non-valvular atrial fibrillation.

BACKGROUND ART

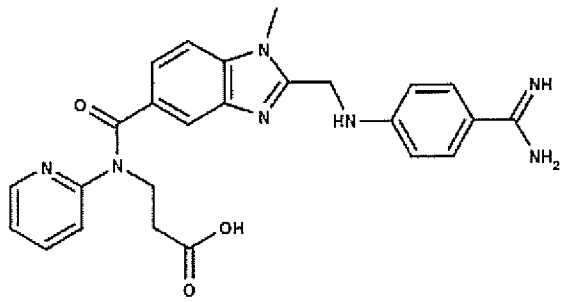
Dabigatran is marketed in the form of pellets in hard hydroxypropyl methylcellulose (HPMC) capsules under the trade name PRADAXA®. The product contains 75, 110 and 150 mg of dabigatran etexilate in the form of methanesulfonate salt (dabigatran etexilate mesylate), and the pellets further contain tartaric acid, acacia (gum arabic), hypromellose (HPMC, hydroxypropyl methylcellulose), dimeticone 350 (dimethylpolysiloxane), talc and hydroxypropyl cellulose (HPC).

Dabigatran etexilate is known as ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate (dabigatran etexilate) and has the chemical structural formula (I):



(I)

It is already known from WO 9837075, which discloses 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]-amino-methyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonyl-ethyl)-amides. The compound of formula (I) is a prodrug of the compound of chemical structural formula (II):



(II)

i.e. the compound of formula (I) is only converted into the active compound of formula (II) after entering the body, by esterase-catalysed in the liver. The compound (II) is known as 3-({2-[(4-carbamimidoyl-phenylamino)-methyl]-1-methyl-1H-benzoimidazole-5-carbonyl}-pyridin-2-yl-amino)-propionic acid. The main indication for the compound of chemical formula (II) is prevention of venous thromboembolic events and stroke and systemic embolism in adults with non-valvular atrial fibrillation.

The solubility of dabigatran, dabigatran etexilate and dabigatran etexilate mesylate in particular is strongly dependant on the pH value with increased solubility at acidic pH. On the other hand, it is chemically unstable in acidic environment and particularly susceptible to hydrolysis of the prodrug. Due to these properties, several attemps have been carried out to provide compositions of dabigatran etexilate that are stable and/or provide desirable in vitro release and bioavailability.

The production of PRADAXA® and the powder layering method according to which it is prepared are described in detail in patent applications WO 03074056, WO 2005018615, WO 2009118321 and WO 2009118322.

WO 03074056 discloses the use of pharmaceutically acceptable organic acids with a water solubility of >1g / 250mL at 20°C, preferably >1g / 160mL at 25°C in solid oral preparations, and in particular methanesulfonic acid addition salt of dabigatran etexilate (dabigatran etexilate mesylate). The disclosed pharmaceutically suitable acids are for example tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid and aspartic acid including the hydrates and acidic salts thereof which are applied to the pellets by powder layering. A preferred embodiment of WO 03074056 is a multi-particulate pharmaceutical form, in particular so-called pellet formulations. The roughly bead-shaped/spherical core portion of the pellet consists of a pharmaceutically acceptable organic acid. Then follows a layer, the so-called isolating layer, which separates the acid core from the layer containing the active substance. The isolating layer is in turn surrounded by the equally spherically shaped layer of the active substance which may in turn be enclosed in a coating which increases the abrasion resistance and shelf life of the pellets.

WO 2005018615 relates to tablets comprising dabigatran etexilate or pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable organic acid and other excipient or filler. However, the absence of physical separation between the dabigatran and the organic acid makes the drug unstable and susceptible to hydrolysis.

WO 2009118321 discloses a process for the preparation of approximately spherical/ball-shaped tartaric acid pellets suitable for the manufacture of drug formulations containing active ingredients, such as dabigatran, the pellets so obtained, and the use thereof as a starting material for the production of drug formulations containing active ingredients. The process is characterized in that in a first step the tartaric acid pellets are produced by powder layering, which are sprayed in a second step with an ethanolic isolation suspension which comprises hydroxypropyl methylcellulose (HPMC).

WO 2009118322 describes a process characterized by a series of partial steps. First, the core is produced from a pharmaceutically acceptable organic acid, preferably tartaric acid by powder layering. The cores are then converted into so-called isolated tartaric acid cores by spraying on an isolating

suspension. A dabigatran etexilate suspension prepared subsequently is sprayed onto these coated cores in one or more process steps by means of a coating process. The preparation of this suspension, which contains dabigatran etexilate mesylate as polymorph I together with talc and hydroxypropyl cellulose in isopropanol, is carried out at temperature not exceeding 30°C. Finally, the active substance pellets thus obtained are packed into suitable capsules.

Later, further attemps have been described in patent applications WO 2012162492, WO 2013110567, WO 2013124340 and WO2015145462.

WO 2012162492 discloses a compressed core for a pharmaceutical dosage form comprising a mixture of (a) at least one pharmaceutically acceptable organic acid, and (b) at least one pharmaceutically acceptable excipient. Such compressed core is useful for the preparation of pharmaceutical compositions containing a drug in which dissolution of the drug is favored in acidic environments, such as dabigatran etexilate and its pharmaceutically acceptable salts.

WO 2013110567 discloses an oral pharmaceutical composition comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof, and at least one water soluble cyclodextrin agent as an excipient.

WO 2013124340 discloses dabigatran etexilate compositions comprising a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient wherein a) the first type of particles comprise the active agent; b) the second type of particles comprise at least one pharmaceutically acceptable organic acid; and c) optionally at least one type of particles are coated with a protective coating layer.

WO2015145462 discloses pharmaceutical composition comprising a) a first component comprising dabigatran or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients; and b) a second component comprising an organic acid; wherein the first component is in the form of a tablet and wherein the composition is in the form of a capsule.

Some of the compositions described in the above patents and/or patent applications contain a tartaric acid core which increases the dissolution rate of dabigatran by modifying the pH of the microenvironment when the pellet is dissolved. On the other hand, dabigatran etexilate is unstable in the presence of tartaric acid; therefore, an isolating layer between the tartaric acid core and API (Active Pharmaceutical Ingredient) layer has to be applied. This is particularly complex since the tartaric acid cores are produced by powder layering of tartaric acid dust onto tartaric acid crystals. The cores produced by such a process are only quasi-spherical and it is very difficult to avoid the formation of satellites which cause defects in the isolating layer. The so-called satellites are small particles adhering to the outside of the otherwise rounded pellets and detracting from the otherwise spherical geometry of the pellets. This lead to impaired storage stability and hence durability of the finished product. Furthermore, protection from humidity during manufacture and storage to prevent hydrolysis of the prodrug forming moieties and polymorphic form transformations is recommended. Also, HPMC capsule shells and expensive packaging materials are necessary to assure adequate stability of the final product.

Other formulations described in the above patents and/or patent applications contain a plurality of particles that involve tedious preparation and/or do not ensure either stability of dabigatran drug and the desired *in vitro* release and bioavailability.

Therefore, need exists to develop alternative solid compositions for oral administration of dabigatran or a pharmaceutically acceptable salt thereof, particularly dabigatran etexilate mesylate, that are stable, easy or convenient to prepare, provide the desired *in vitro* release and biolavailability.

The present inventors provide an alternative oral pharmaceutical compositions comprising a multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof and an acidic tablet comprising at least one pharmaceutically acceptable organic acid. Such compositions ensure the stability of this active compounds in the presence of the organic acid, provide the desired *in vitro* performance, do not have the drawbacks of the prior art and can be produced by an easy, less technologycally demanding

and cost-effective process without affecting the physico-chemical stability of the active compound.

SUMMARY OF THE INVENTION

The inventors have developed an oral pharmaceutical composition which comprises a multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof, preferably dabigatran etexilate mesylate, and an acidic tablet comprising at least one pharmaceutically acceptable organic acid. The pharmaceutical compostion of the present invention ensures the stability of the dabigatran or a pharmaceutically salt thereof in the presence of the organic acid.

Therefore, an aspect of the invention relates to an oral pharmaceutical composition comprising:
a) a multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof; and
b) an acidic tablet comprising at least one pharmaceutically acceptable organic acid.

This oral pharmaceutical composition has the advantage that the dabigatran compound in form of a multi-particulate system removes compression strengths over the active ingredient. This avoids undesired physico-chemical changes over it and sticking and/or picking inconvenients which are associated with compression steps.

A further advantage of this invention is that the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof does not require an isolating coating. This is specially important with active ingredients which are prone to water degradation, like dabigatran.

A further advantage of this invention is that the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof provides bigger surface area in comparison to tablets comprising this active ingredient and makes the active ingredient more bioavailable. Additionally the multi-

particulate system reduces the variability between dosage units.

The oral pharmaceutical compositions of the present invention have the further advantage that they can be prepared through an easy process. Thus, another aspect of the present invention relates to a process for the preparation of the pharmaceutical compositions of the present invention which comprises the following steps:

a) provinding a multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof by:

i) blending dabigatran or a pharmaceutically acceptable salt thereof with at least one pharmaceutically acceptable excipient;

ii) compacting the powder mixture of step i), preferably by roller compaction;

iii) milling the sticks or sheets obtained in step ii) to obtain the granules; and

iv) optionally coating the granules obtained in step iii), preferably by film-coating,

b) providing an acidic tablet comprising at least one pharmaceutically acceptable organic acid by:

i) blending the pharmaceutically acceptable organic acid with at least one pharmaceutically acceptable excipient;

ii) spraying the mixture obtained in step i) with a granulation liquid, preferably water;

iii) kneading the wet mixture obtained in step ii), preferably by high shear granulation;

iv) drying the wet granules obtained in step iii);

v) blending the dried granules obtained in step iv) with at least one extragranular pharmaceutically acceptable excipient;

vi) compresing the granules obtained in step v) to obtain the tablet; and

vii) optionally coating the tablet obtained in step vi), preferably by film-coating.

Another aspect of the present invention relates to a process for the preparation of the pharmaceutical compositions of the present invention which comprises the following steps:

a) providing a multi-particulate system comprising dabigatran or a

pharmaceutically acceptable salt thereof by:

i) blending dabigatran or a pharmaceutically acceptable salt thereof with at least one pharmaceutically acceptable excipient;

ii) wetting the mixture obtained in step i) with a massing liquid, preferably at least one organic solvent, preferably isopropanol, ethanol or mixtures thereof, more preferably isopropanol;

iii) extruding the wet mixture obtained in step ii), through 0,6mm mesh to obtain the wet extrudate, preferably by extruding process;

iv) spheronizing the wet extrudate obtained in step iii) to obtain the pellets, preferably in a roto-spheronizer;

v) drying the pellets obtained in step iv); and

vi) optionally coating the pellets obtained in step v), preferably by film-coating;

b) providing an acidic tablet comprising at least one pharmaceutically acceptable organic acid by:

i) blending the pharmaceutically acceptable organic acid with at least one pharmaceutically acceptable excipient;

ii) spraying the mixture obtained in step i) with a granulation liquid, preferably water;

iii) kneading the wet mixture obtained in step ii), preferably by high shear granulation;

iv) drying the wet granules obtained in step iii);

v) blending the dried granules obtained in step iv) with at least one extragranular pharmaceutically acceptable excipient;

vi) compresing the granules obtained in step v) to obtain the tablet; and

vii) optionally coating the tablet obtained in step vi), preferably by film-coating.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the dabigatran etexilate mesylate release profile of the composition of Examples 1.1b and 1.1a.

FIG. 2 shows the dabigatran etexilate mesylate release profiles of the Examples 2.1a and 2.1b.

DETAILED DESCRIPTION OF THE INVENTION

Unless stated otherwise herein, the percentages given within the scope of the present invention are always percent by weight.

The invention refers to a pharmaceutical composition for oral administration of dabigatran or a pharmaceutically acceptable salt thereof, comprising a multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof and an acidic tablet comprising at least one pharmaceutically acceptable organic acid.

For the purposes of the invention, the term "dabigatran" includes dabigatran, a produg of dabigatran, preferably dabigatran etexilate or any pharmaceutically acceptable salts or derivatives thereof, including polymorphs, hydrates, solvates or amorphous forms. The more preferably compound is dabigatran etexilate and the more preferably salt thereof is dabigatran etexilate mesylate.

As used herein, the term “pharmaceutically acceptable salt” refers to any non-toxic salt which can be used for therapeutic purposes. The preparation of pharmaceutically acceptable salts of the compounds of the invention can be carried out by methods known in the art. For instance, they can be prepared from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate pharmaceutically acceptable base or acid in water or in an organic solvent or in a mixture of them. The base compounds and their salts may differ in some physical properties but they are equivalent for the purposes of the present invention. Pharmaceutically acceptable salts are well known in the art. Examples of pharmaceutically acceptable salts, include, without limitation, acetic acid, ascorbic acid, benzenesulfonic acid, citric acid, dichloroacetic acid, formic acid, fumaric acid, glutamic acid, glycolic acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, 3-hydroxypropanoic acid, lactic acid, maleic acid, malonic acid, methanesulfo acid, nitric acid, oxalic acid, 2-oxoglutaric acid, phosphoric acid, propionic acid, sulfuric acid, tartaric acid and p-toluenosulfonic acid.

In one embodiment of the present invention, optionally in combination with one or more features of the various embodiments described above or below, dabigatran is in form of a prodrug, preferably dabigatran etexilate. In another embodiment, dabigatran etexilate is in the form of the mesylate salt, i.e. dabigatran etexilate mesylate.

The dabigatran or the pharmaceutically acceptable salt thereof used in the present invention has a particle size distribution defined by a D90 less than 250 µm, preferably less than 100 µm, more preferably less than 50 µm and further preferably less than 10 µm. The particle size distribution is measured using a laser difraction/scattering method, for example, a MALVERN Mastersizer 2000.

In a particular embodiment of the present invention the dabigatran etexilate is used in the form of polymorphic form I of dabigatran etexilate mesylate (as described in WO 2005028468). In another particular embodiment of the present invention the dabigatran etexilate is used in the form of polymorphic form II of dabigatran etexilate mesylate (as described in WO 2005028468).

The term "oral pharmaceutical composition" includes a pharmaceutical dosage form for oral adminstration in the form of sachets or capsules, comprising the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof and an acidic tablet comprising at least one pharmaceutically acceptable organic acid, preferably in the form of capsules.

The oral pharmaceutical compositions of the present invention may be in the form of a dosage form comprising from 50 mg to 200 mg of dabigatran etexilate mesylate, preferably from 75 mg to 150 mg, more preferably 75 mg, 110 mg or 150 mg.

The term "multi-particulate system" includes a set of solid or semi-solid individual portions. Examples of this multi-particulate system include, without limitation, powder, granules, pellets, beads or minitablets.

In one embodiment of the present invention, optionally in combination with

one or more features of the various embodiments described above or below, the oral pharmaceutical composition comprises a multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof and an acidic tablet comprising at least one pharmaceutically acceptable organic acid wherein the multi-particulate system is in the form of powder, granules, pellets, beads or minitablets. In another embodiment, the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof is in the form of granules. In a preferred embodiment, the multi-particulate system comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof is in the form of granules. In a more preferred embodiment, the multi-particulate system comprising dabigatran etexilate mesylate is in the form of granules. In other embodiment, the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof is in the form of pellets. In a preferred embodiment, the multi-particulate system comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof is in the form of pellets. In a more preferred embodiment, the multi-particulate system comprising dabigatran etexilate mesylate is in the form of pellets.

As used herein, the term "acidic tablet" includes a tablet comprising at least one pharmaceutically aceptable organic acid. The term "organic acid" includes any organic acid or hydrates or acid salts thereof or mixtures thereof which are in a solid state in a room temperature. Examples of pharmaceutically acceptable organic acids include, without limitation, ascorbic acid, aspartic acid, citric acid, erythrobic acid, fumaric acid, gluconic acid, glutamic acid, maleic acid, malic acid, succinic acid and tartaric acid. In one embodiment of the present invention, optionally in combination with one or more features of the various embodiments described above or below, the pharmaceutically acceptable organic acid is selected from a group consisting of ascorbic acid, aspartic acid, citric acid, erythrobic acid, fumaric acid, gluconic acid, glutamic acid, maleic acid, malic acid, succinic acid, tartaric acid or hydrates or acid salts or mixture thereof. In a preferred embodiment, the pharmaceutically acceptable organic acid is maleic acid.

In addition, the multi-particulate system and/or the acidic tablet, optionally further comprise an isolating coating layer. The term "isolating coating layer" includes a layer of a polymeric material disposed on the surface of either in

each solid or semi-solid individual portion that together form the multi-particulate system or of the tablet core of the acidic tablet. This isolating coating layer provides desirable properties to the dosage form, including its protection from environmental conditions, such as light or moisture, and also provides esthetic or taste-masking properties to the dosage form. In the present invention, the isolating coating avoids the direct contact between dabigatran and the organic acid and it is preferably disposed on the surface of the tablet core of the acidic tablet.

In one embodiment of the present invention, optionally in combination with one or more features of the various embodiments described above or below, both the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof and the acidic tablet comprising at least one pharmaceutically acceptable organic acid further comprise an isolating coating layer. In another embodiment, the acidic tablet comprising at least one pharmaceutically acceptable organic acid further comprises an isolating coating layer. In yet another embodiment, the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof may optionally further comprise an isolating coating layer. In a preferred embodiment, only the acidic tablet comprising at least one pharmaceutically acceptable organic acid further comprises an isolating coating layer.

The polymeric pharmaceutically acceptable material used for the isolating coating layer include, without limitation, cellulose derivatives, vinyl derivatives, polymers and copolymers, gums, acrylic or methacrylic acid polymers, copolymers, esters or derivatives thereof, and the like or combinations thereof. Cellulose derivatives that may be employed, include, without limitation, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, ethylcellulose, hydroxypropyl ethylcellulose, carboxymethylethyl cellulose, carboxy ethylcellulose, carboxymethyl hydroxyethylcellulose, hydroxyethylmethyl carboxymethyl cellulose, hydroxyethyl methyl cellulose, carboxymethyl cellulose, methylhydroxyethyl cellulose, methylhydroxypropyl cellulose, carboxymethyl sulfoethyl cellulose, sodium carboxymethyl cellulose, and the like or combinations thereof. Vinyl derivatives, polymers and copolymers thereof that may be employed include, without limitation, copolymers of vinyl

pyrrolidone, copolymers of polyvinyl alcohol (Kollicoat IR), polyvinylpyrrolidone or combinations thereof. Gums that may be employed include, without limitation, gum arabic, alginates, guar gum, locust bean gum, carrageenan, pectin, xanthan gum, gellan gum, maltodextrin, galactomannan, karaya, and the like, or combinations. Acrylic or methacrylic acid polymers, copolymers, esters or derivatives thereof, that may be employed include, without limitation, a) copolymer formed from monomers selected from methacrylic acid, methacrylic acid esters, acrylic acid and acrylic acid esters b) copolymer formed from monomers selected from butyl methacrylate, (2-dimethylaminoethyl)methacrylate and methyl methacrylate c) copolymer formed from monomers selected from ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride or d) copolymers of acrylate and methacrylates with/without quarternary ammonium group in combination with sodium carboxymethylcellulose, e.g. Eudragit® like Eudragit EPO (dimethylaminoethyl methacrylate copolymer; basic butylated methacrylate copolymer), Eudragit RL and RS (trimethylammonioethyl methacrylate copolymer), Eudragit NE30D and Eudragit NE40D (ethylacrylate methymethacrylate copolymer), Eudragit RD 100 (ammoniomethacrylate copolymer with sodium carboxymethylcellulose); or the like or any combinations thereof.

In a preferred embodiment said isolating coating layer comprises copolymers of polyvinyl alcohol. In another preferred embodiment of the present invention, the acidic tablet comprising at least one pharmaceutically acceptable organic acid further comprises an isolating coating layer, wherein the isolating coating layer comprises copolymers of polyvinyl alcohol.

In a further embodiment, in addition to the polymeric pharmaceutically acceptable material or any combination thereof, the isolating coating layer may optionally further comprise at least one pharmaceutically acceptable excipient such as, without limitation, plasticizer, anti-tacking agent, pigment, and the like, or combinations thereof. A plasticizer that may be employed includes, without limitation, triethyl citrate, acetyl triethyl citrate, propylene glycol, polyethylene glycol, acetyl tributyl citrate, acetylated monoglycerides, glycerin, triacetin, phthalate esters (e.g., diethyl phthalate, dibutyl phthalate), castor oil, sorbitol and dibutyl seccate or a combination thereof. An anti-

tacking agent that may be employed includes, without limitation, talc, or glyceryl monostearate. A pigment such as, without limitation, titanium dioxide, iron oxide, or a mixture thereof may be employed.

The isolating coating layer may be optionally applied onto at least the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof or the acidic tablet comprising at least one pharmaceutically acceptable organic acid of the present invention in any suitable equipment where coating can be achieved, such as, without limitation, coating pan, conventional film coating apparatus or a fluidized bed apparatus, or the like. Furthermore, in one embodiment, the isolating coating layer can be applied from an aqueous or organic solution or dispersion. In a preferred embodiment the acidic tablet comprising at least one pharmaceutically acceptable organic acid being coated with the isolating coating layer may be coated to a weight gain of about 2% to about 50% by weight, preferably about 2% to about 10%, more preferably about 2% to about 5%. In a further embodiment, the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof being coated with the isolating coating layer may be coated to a weight gain of about 1% to about 50% by weight, preferably about 1% to about 10%, more preferably about 1% to about 5%.

Furthermore, the multi-particulate system and/or the acidic tablet, optionally further comprise one or more pharmaceutically acceptable excipients. In one embodiment, optionally in combination with one or more features of the various embodiments described above or below, the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof may optionally further comprise one or more pharmaceutically acceptable excipients. In another embodiment, the acidic tablet comprising at least one pharmaceutically acceptable organic acid may optionally further comprise one or more pharmaceutically acceptable excipients. In a preferred embodiment, both the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof and the acidic tablet comprising at least one pharmaceutically acceptable organic acid optionally further comprise one or more pharmaceutically acceptable excipients.

As used herein, the expression "pharmaceutically acceptable excipients or carriers" refers to pharmaceutically acceptable materials, compositions or vehicles. Each component must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the pharmaceutical composition. It must also be suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity or other problems or complications commensurate with a reasonable benefit/risk ratio.

In another embodiment, optionally in combination with one or more features of the various embodiments described above or below, these pharmaceutically acceptable excipients may be selected from the group consisting of fillers or diluents, disintegrants, binders, glidants, lubricants, surfactants, colorants and the like or mixtures thereof.

The terms “fillers” or “diluents” as used herein mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of solid dosage formulations. Examples of suitable fillers or diluents include, without limitation, calcium carbonate, calcium phosphate, dibasic calcium phosphate, tribasic calcium sulfate, calcium carboxymethylcellulose, microcrystalline cellulose, dextrin derivatives, dextrin, dextrose, fructose, lactitol, lactose, starch or modified starches, magnesium carbonate, magnesium oxide, maltitol, gluconolactone, maltodextrins, maltose, sorbitol, sucrose, sugar, and xylitol, erythritol, and the like or mixtures thereof.

As used herein, the term "disintegrants" means substances used to promote the composition break up and disperse or dissolve more readily. Examples of suitable disintegrants include, without limitation, cross linked polyvinylpyrolidone such as crospovidone; starches such as maize starch and dried sodium starch glycolate; gums such as maize starch and dried sodium starch glycolate; gums such as alginic acid, sodium alginate, guar gum; croscarmellose sodium; cellulose products such as microcrystalline cellulose and its salts, low-substituted hydroxypropyl cellulose, and the like or mixtures thereof.

As used herein, the term "binders" means substances used to cause adhesion of powder particles in granulations. Examples of suitable binders include, without limitation, cellulose derivatives, such as methylcellulose polymers, hydroxyethyl cellulose, hydroxypropyl cellulose, L-hydroxypropyl cellulose (low substituted), hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose, carboxymethylene, carboxymethyl hydroxyethylcellulose, starches or modified starches, such as corn or potato starch, partially pregelatinized starches, and the like or mixtures thereof.

As used herein, the term "glidants" means substances used to improve the flowability of the solid composition. Examples of suitable glidants include, without limitation, colloidal silica, silicon dioxide, powdered cellulose, talc, tribasic calcium phosphate, and the like and mixtures thereof.

The term “lubricants” as used herein means substances used in solid compositions to reduce friction during compression of the solid dosage. Examples of suitable lubricants include, without limitation, sodium oleate, sodium stearate, sodium benzoate, sodium stearate, sodium chloride, stearic acid, sodium stearyl fumarate, calcium stearate, magnesium stearate, magnesium lauryl sulfate, sucrose esters or fatty acid, zinc, polyethylene glycol, talc, and the like or mixtures thereof.

The term “surfactants” as used herein means substances used to reduce the surface tension of the aqueous solutions comprising them. Examples of suitable surfactants include, without limitation, sodium lauryl sulphate, polyoxyethylen sorbitan fatty acids esters (polysorbate 20, 40, 60, 80), polyoxyethylene stearates, polyoxyglycerides, lauroyol polyoxyglycerides, polyoxyethylene alkyl ethers (macrogol cetostearyl ether, macrogol lauryl ether, macrogol oleyl ether, macrogos stearyl ether), sorbitan esters (sorbitan laureate, sorbitan oleate, sorbitan palmitate, sorbitan stearate), triethyl citrate, and the like or mixtures thereof.

In one embodiment, optionally in combination with one or more features of the various embodiments described above or below, the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof and/or the acidic tablet comprising at least one pharmaceutically acceptable organic

acid, optionally contain one or more fillers or diluents. More particularly, the fillers or diluents are selected from lactose, gluconolactone, microcrystalline cellulose or a mixture thereof.

In one embodiment, optionally in combination with one or more features of the various embodiments described above or below, the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof and/or the acidic tablet comprising at least one pharmaceutically acceptable organic acid, optionally contain one or more disintegrants. More particularly, the disintegrant is crospovidone.

In one embodiment, optionally in combination with one or more features of the various embodiments described above or below, the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof and/or the acidic tablet comprising at least one pharmaceutically acceptable organic acid, optionally contain one or more binders. More particularly, the binders are selected from hydroxypropylcellulose, hydroxypropyl methylcellulose or a mixture thereof.

In one embodiment, optionally in combination with one or more features of the various embodiments described above or below, the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof, optionally contains one or more glidants. More particularly, the glidant is amorphous silica.

In one embodiment, optionally in combination with one or more features of the various embodiments described above or below, the acidic tablet comprising at least one pharmaceutically acceptable organic acid, optionally contains one or more lubricants. More particularly, the lubricant is sodium stearyl fumarate.

In another embodiment, optionally in combination with one or more features of the various embodiments described above or below, the invention relates to an oral pharmaceutical composition comprising or consisting of:

a) a multi-particulate system which comprises:

i) dabigatran, preferably dabigatran etexilate or a pharmaceutically acceptable salt thereof, preferably dabigatran etexilate mesylate;

ii) optionally one or more fillers or diluents, in particular selected from a group consisting of lactose, gluconolactone, microcrystalline cellulose or a mixture thereof;
iii) optionally one or more disintegrants, in particular crospovidone;
iv) optionally one or more binders, in particular hydroxypropylcellulose;
v) optionally one or more glidants, in particular amorphous silica;

b) an acidic tablet which comprises:
i) at least one pharmaceutically acceptable organic acid, in particular maleic acid;
ii) optionally one or more fillers or diluents, in particular microcrystalline cellulose;
iii) optionally one or more disintegrants, in particular crospovidone;
iv) optionally one or more binders, in particular hydroxypropyl methylcellulose;
v) optionally one or more lubricants, in particular sodium stearyl fumarate.

In another embodiment, the acidic tablet of the above embodiment optionally further comprises an isolating coating layer. More particularly, the isolating coating layer comprises copolymers of polyvinyl alcohol.

In another embodiment, the multiparticulate system of the above embodiment is in the form of powder, granules, pellets, beads or minitablets, preferably in the form of granules or pellets.

In another embodiment, optionally in combination with one or more features of the various embodiments described above or below, the invention relates to an oral pharmaceutical composition comprising:

a) a multi-particulate system which comprises:
i) dabigatran, preferably dabigatran etexilate or a pharmaceutically acceptable salt thereof, preferably dabigatran etexilate mesylate;
ii) a filler or diluent, in particular gluconolactone;
iii) a disintegrant, in particular crospovidone;
iv) a binder, in particular hydroxypropylcellulose;

b) an acidic tablet which comprises:
i) at least one pharmaceutically acceptable organic acid, in particular

maleic acid;
ii) a filler or diluent, in particular microcrystalline cellulose;
iii) a disintegrant, in particular crospovidone;
iv) a binder, in particular hydroxypropyl methylcellulose;
v) a lubricant, in particular sodium stearyl fumarate.

In another embodiment, the acidic tablet of the above embodiment further comprises an isolating coating layer. More particularly, the isolating coating layer comprises copolymers of polyvinyl alcohol.

In another embodiment, the multiparticulate system of the above embodiment is in the form of powder, granules, pellets, beads or minitablets, preferably in the form of granules.

In another embodiment, optionally in combination with one or more features of the various embodiments described above or below, the invention relates to an oral pharmaceutical composition comprising:
a) a multi-particulate system which comprises:
i) dabigatran, preferably dabigatran etexilate or a pharmaceutically acceptable salt thereof, preferably dabigatran etexilate mesylate;
ii) one or more fillers or diluents, in particular lactose and gluconolactone;
iii) a disintegrant, in particular crospovidone;
iv) a glidant, in particular amorphous silica;
b) an acidic tablet which comprises:
i) at least one pharmaceutically acceptable organic acid, in particular maleic acid;
ii) a filler or diluent, in particular microcrystalline cellulose;
iii) a disintegrant, in particular crospovidone;
iv) a binder, in particular hydroxypropyl methylcellulose;
v) a lubricant, in particular sodium stearyl fumarate.

In another embodiment, the acidic tablet of the above embodiment further comprises an isolating coating layer. More particularly, the isolating coating layer comprises copolymers of polyvinyl alcohol.

In another embodiment, the multiparticulate system of the above embodiment is in the form of powder, granules, pellets, beads or minitablets, preferably in the form of granules.

In another embodiment, optionally in combination with one or more features of the various embodiments described above or below, the invention relates to an oral pharmaceutical composition comprising:

a) a multi-particulate system which comprises:

i) dabigatran, preferably dabigatran etexilate or a pharmaceutically acceptable salt thereof, preferably dabigatran etexilate mesylate;

ii) one or more fillers or diluents, in particular microcrystalline cellulose and gluconolactone;

iii) a binder, in particular hydroxypropylcellulose;

b) an acidic tablet which comprises:

i) at least one pharmaceutically acceptable organic acid, in particular maleic acid;

ii) a filler or diluent, in particular microcrystalline cellulose;

iii) a disintegrant, in particular crospovidone;

iv) a binder, in particular hydroxypropyl methylcellulose;

v) a lubricant, in particular sodium stearyl fumarate.

In another embodiment, the acidic tablet of the above embodiment further comprises an isolating coating layer. More particularly, the isolating coating layer comprises copolymers of polyvinyl alcohol.

In another embodiment, the multiparticulate system of the above embodiment is in the form of powder, granules, pellets, beads or minitablets, preferably in the form of pellets.

It also forms part of the invention a process for the preparation of the oral pharmaceutical composition as defined above. The multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof is prepared by a dry or wet granulation, preferably by dry granulation. The multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof is also prepared by extrusion-spheronization. The acidic tablet comprising at least one pharmaceutically acceptable organic acid is prepared

by wet, dry granulation or by direct compression, preferably by wet granulation.

In one embodiment of the present invention, optionally in combination with one or more features of the various embodiments described above or below, the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof is prepared by dry granulation, preferable by roller compaction. The process comprises the following steps:

i) blending dabigatran or a pharmaceutically acceptable salt thereof with at least one pharmaceutically acceptable excipient;

ii) compacting the powder mixture of step i), preferably by roller compaction;

iii) milling the sticks or sheets obtained in step ii) to obtain the granules; and

iv) optionally coating the granules obtained in step iii), preferably by film-coating.

In one embodiment of the present invention, optionally in combination with one or more features of the various embodiments described above or below, the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof may also be prepared by wet granulation, preferably by high shear granulation. The process comprises the following steps:

i) blending dabigatran or a pharmaceutically acceptable salt thereof with at least one pharmaceutically acceptable excipient;

ii) spraying the mixture obtained in step i) with a granulation liquid, preferably organic solvent;

iii) kneading the wet mixture obtained in step ii); and

iv) drying the wet granules obtained in step iii);

v) optionally coating the granules obtained in step iv), preferably by film-coating.

In one embodiment of the present invention, optionally in combination with one or more features of the various embodiments described above or below, the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof is prepared by extrusion-spheronization, The process comprises the following steps:

i) blending dabigatran or a pharmaceutically acceptable salt thereof with at least one pharmaceutically acceptable excipient;

ii) wetting the mixture obtained in step i) with a massing liquid, preferably at least one organic solvent, preferably isopropanol, ethanol or mixtures thereof, more preferably isopropanol;
iii) extruding the wet mixture obtained in step ii), through 0.6mm mesh to obtain the wet extrudate, preferably by extruding process;
iv) spheronizing the wet extrudate obtained in step iii) to obtain the pellets, preferably in a roto-spheronizer;
v) drying the pellets obtained in step iv); and
vi) optionally coating the pellets obtained in step v), preferably by film-coating.

The massing liquid used in the process described above is any liquid suitable to prepare the wet mixture between dabigatran or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient. In one embodiment, optionally in combination with one or more features of the various embodiments described above or below, the massing liquid is at least one organic solvent, particularly an alcohol solvent, more particularly an alcohol solvent selected from isopropanol, ethanol or mixtures thereof, and more particularly isopropanol.

In one embodiment of the present invention, optionally in combination with one or more features of the various embodiments described above or below, the acidic tablet comprising at least one pharmaceutically acceptable organic acid is prepared by wet granulation, preferably by high shear granulation. The process comprises the following steps:
i) blending the pharmaceutically acceptable organic acid with at least one pharmaceutically acceptable excipient;
ii) spraying the mixture obtained in step i) with a granulation liquid, preferably water;
iii) kneading the wet mixture obtained in step ii), preferably by high shear granulation;
iv) drying the wet granules obtained in step iii);
v) blending the dried granules obtained in step iv) with at least one extragranular pharmaceutically acceptable excipient;
vi) compresing the granules obtained in step v) to obtain the tablet; and
vii) optionally coating the tablet obtained in step vi), preferably by film-coating.

In one embodiment of the present invention, optionally in combination with one or more features of the various embodiments described above or below, the acidic tablet comprising at least one pharmaceutically acceptable organic acid is prepared by dry granulation, preferable by roller compaction. The process comprises the following steps:

i) blending the pharmaceutically acceptable organic acid with one or more pharmaceutically acceptable excipients;

ii) compacting the powder mixture of step i), preferably by roller compaction;

iii) milling the sticks or sheets obtained in step ii) to obtain the granules; and

iv) optionally coating the granules obtained in step iii), preferably by film-coating.

In one embodiment of the present invention, optionally in combination with one or more features of the various embodiments described above or below, the acidic tablet comprising at least one pharmaceutically acceptable organic acid is prepared by a direct compression. The process comprises the following steps:

i) blending the pharmaceutically acceptable organic acid with at least one pharmaceutically acceptable excipient;

ii) compressing the mixture obtained in step i) to obtain the tablet; and

iii) optionally coating the tablet obtained in step ii), preferably by film-coating.

In a further embodiment of the present invention, the process for preparing the oral pharmaceutical composition of the present invention further comprises the filling in a capsule or a sachet with the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof and the acidic tablet comprising at least one pharmaceutically acceptable organic acid. In another embodiment, the capsule is a hydroxypropyl methylcellulose (HPMC) capsule.

In a further embodiment, the present invention provides the use of the pharmaceutical composition of the present invention for the manufacture of a medicament for preventing venous thromboembolic events in adult patients who have undergone elective total-hip-replacement surgery or total-knee-replacement surgery and/or preveting the risk of stroke and systemic embolism in adults with non-valvular atrial fibrillation.

In still another embodiment the present invention provides a method of preventing venous thromboembolic events in adult patients who have undergone elective total-hip-replacement surgery or total-knee-replacement surgery and/or preveting the risk of stroke and systemic embolism in adults with non-valvular atrial fibrillation, comprising administering to the subject in need thereof the pharmaceutical compositions of the present invention.

For the purposes of the present invention, the expressions "obtainable", "obtained" and similar equivalent expressions are used interchangeably and, in any case, the expression "obtainable" encompasses the expression "obtained".

The following examples and drawings are provided by way of illustration, and they are not intended to be limiting of the present invention. Furthermore, the present invention covers all possible combinations of particular and preferred embodiments described herein.

EXAMPLES

Example 1. Preparation of capsules comprising dabigatran granules and a maleic acid tablet

Preparation of dabigatran granules by roller compaction

Dabigatran etexilate mesylate was seived through 1,0 mm mesh. The rest of the excipients were added after seiving through 1,0mm mesh and the mixture were blended to provide an homogeneous mixture. Then, the mixture was compacted by roller compaction and later milled to obtain the desired granules. Optionally, these granules may be coated with an isolating coating layer.

Preparation of acidic tablet by wet granulation

The organic acid together with the rest of excipients (except lubricant) were sieved through 1,0 mm mesh and placed into a high shear granulator. The mixture was granulated with water and dried in a fluid bed. After dry screening the blend, it was blended with extragranular excipients and compressed into

tablet cores. The tablet cores were coated with a isolating coating layer comprising copolymers of polyvinyl alcohol.

Preparation of the capsules

Final hydroxypropyl methylcellulose (HPMC) capsules were filled with the adequate amount of granulate and one film-coated acidic tablet.

A HPMC capsule was obtained with the following composition:

Example 1.1a (150mg dabigatran etexilate)

Granulate	**[%]**	**mg/capsule**
Dabigatran etexilate mesylate	45.00	173.00
Gluconolactone	45.00	173.00
Crospovidone (XL10)	5.00	19.25
Hydroxypropyl cellulose (Klucel LF)	5.00	19.25
Total	**100.00**	**384.50**

Acidic tablet		**[%]**	**mg/tabl.**
Intra-granular	Maleic acid	71.43	105.00
	Hydroxypropyl methylcellulose (E5)	3.81	5.60
Extragranular	Crospovidone XL	9.52	14.00
	Microcrystalline cellulose (PH200)	8.57	12.60
	Sodium stearyl fumarate (PRUV)	1.91	2.80
Coating	copolymers of polyvinyl alcohol (Kollicoat IR)	4.76	7.00
Total		**100.00**	**147.00**

Total capsule filling	**531.50mg**

Example 1.1b (150mg dabigatran etexilate)

Granulate	**[%]**	**mg/capsule**
Dabigatran etexilate mesylate	52.00	173.00
Gluconolactone	25.00	83.17
Crospovidone (XL10)	5.00	16.63
Lactose anhydrous (DCL 21)	10.00	33.27
Amorphous silica (Syloid Al-1FP)	8.00	26.62
Total	**100.00**	**332.69**

Acidic tablet		**[%]**	**mg/tabl.**
Intra-granular	Maleic acid	71.43	105.00
	Hydroxypropyl methylcellulose (E5)	3.81	5.60
Extragranular	Crospovidone XL	9.52	14.00
	Microcrystalline cellulose (PH200)	8.57	12.60
	Sodium stearyl fumarate (PRUV)	1.91	2.80
Coating	copolymers of polyvinyl alcohol (Kollicoat IR)	4.76	7.00
Total		**100.00**	**147.00**

Total capsule filling	**479.69mg**

Example 1.2. Dabigatran drug release

Dissolution test was performed in 900mL of dissolution media (distilled water) at 37°C at a rotation speed of 100 rpm. Samples were removed after 5, 10, 15, 30, 45, 60, 90 minutes from test initiation and analyzed for dabigatran etexylate by HPLC (acetonitrile buffer pH 7.0).

The following table shows the results for different samples, wherein "average" relates to dissolved amount of dabigatran etexilate mesylate as a percentage [%] and "RSD" is the relative standard deviation.

Conditions:	Distilled water	T 37°C 100 RPM	baskets 900 ml			
Product:	PRADAXA 150mg		Example 1.1a		Example 1.1b	
Time (min)	average	RSD	average	RSD	average	RSD
5	0	0	0	0	0	0
10	3.5	107.4	0	173.2	4.2	134.2
15	17.2	55.0	6.8	112.6	32.9	76.2
30	66.2	22.3	65.1	7.4	64.2	36.5
45	79.4	13.5	77.0	3.4	73.6	28.2
60	85.1	10.5	81.8	2.6	78.2	23.6
90	89.8	7.0	85.9	1.8	81.5	19.2

The capsules of examples 1.1a and 1.1b showed adequate dissolution profile when compared with PRADAXA.

Example 2. Preparation of capsules comprising dabigatran pellets and a maleic acid tablet

Preparation of dabigatran pellets by extrusion-spheronization process

Dabigatran etexilate mesylate was seived through 1,0 mm mesh. The rest of the excipients were added after seiving through 1,0mm mesh and the mixture were blended to provide an homogeneous mixture. Then, the mixture was wetted with isopropanol to obtain the desired uniform wet mass. In the next step the wet mixture was extruded through 0,6mm mesh. The obtained wet extrudate was spheronized in a roto-spheronizer equipment. Then the obtained pellets were dryied. Optionally, these pellets may be coated with an isolating coating layer.

Preparation of acidic tablet by wet granulation

The organic acid together with the rest of excipients (except lubricant) were sieved through 1,0 mm mesh and placed into a high shear granulator. The mixture was granulated with water and dried in a fluid bed. After dry screening the blend, it was blended with extragranular excipients and compressed into tablet cores. The tablet cores were coated with a isolating coating layer comprising copolymers of polyvinyl alcohol.

Preparation of the capsules

Final hydroxypropyl methylcellulose (HPMC) capsules were filled with the adequate amount of pellets and one film-coated acidic tablet.

A HPMC capsule was obtained with the following composition:

Example 2.1a (150mg dabigatran etexilate)

Pellets	**[%]**	**mg/capsule**
Dabigatran etexilate mesylate	50.00	173.00
Gluconolactone	35.00	121.10
Hydroxypropyl cellulose (Klucel LF)	5.00	17.30
Microcrystalline cellulose (PH101)	10.00	34.60
Total	**100.00**	**346.00**

Acidic tablet		**[%]**	**mg/tabl.**
Intra-granular	Maleic acid	71.43	120.00
	Hydroxypropyl methylcellulose (E5)	3.81	6.40
Extragranular	Crospovidone XL	8.57	14.40
	Microcrystalline cellulose (PH200)	9.52	16.00
	Sodium stearyl fumarate (PRUV)	1.91	3.20
Coating	copolymers of polyvinyl alcohol (Kollicoat IR)	4.76	8.00
Total		**100.00**	**168.00**

Total capsule filling	**514.00mg**

Example 2.1b (150mg dabigatran etexilate)

Pellets	**[%]**	**mg/capsule**
Dabigatran etexilate mesylate	40.00	173.00
Gluconolactone	45.00	194.60
Hydroxypropyl cellulose (Klucel LF)	5.00	21.60
Microcrystalline cellulose (PH101)	10.00	43.25
Total	**100.00**	**346.00**

Acidic tablet		**[%]**	**mg/tabl.**
Intra-granular	Maleic acid	71.43	120.00
	Hydroxypropyl methylcellulose (E5)	3.81	6.40
Extragranular	Crospovidone XL	8.57	14.40
	Microcrystalline cellulose (PH200)	9.52	16.00
	Sodium stearyl fumarate (PRUV)	1.91	3.20
Coating	copolymers of polyvinyl alcohol (Kollicoat IR)	4.76	8.00
Total		**100.00**	**168.00**

Total capsule filling	**514.00mg**

Dissolution test was performed in 900mL of dissolution media 0.01N HCl at 37°C at a rotation speed of 100 rpm. Samples were removed after 10, 15, 30, 45, 60, 90 minutes from test initiation and analyzed for dabigatran etexylate by HPLC.

The following table shows the results for different samples, wherein "average" relates to dissolved amount of dabigatran etexilate mesylate as a percentage [%] and "RSD" is the relative standard deviation.

Conditions:	Distilled water	T 37°C 100 RPM	baskets	900 ml		
Product:	PRADAXA 150mg		Example 2.1a		Example 2.1b	
Time (min)	average	RSD	average	RSD	average	RSD
10	18.4	54.2	41,3	37	52,9	47,8
15	70.0	21.3	75,7	4,2	68,9	34,7
20	87.0	16.9	85,4	3,4	78,5	21,7
30	97.0	6.6	94	2,6	90,2	8,1
45	101.0	1.6	96,5	1,4	95,8	3,0
60	102.2	0.9	96,6	1,2	97,7	0,9
90	102.3	1.1	96,7	1,3	98,4	0,3

The capsules of examples 2.1a and 2.1b showed adequate dissolution profile when compared with PRADAXA.

CLAIMS

1. An oral pharmaceutical composition comprising:
a) a multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof; and
b) an acidic tablet comprising at least one pharmaceutically acceptable organic acid.

2. The pharmaceutical composition according to claim 1 wherein the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof is in the form of powder, granules, pellets, beads or minitablets, preferably granules or pellets.

3. The pharmaceutical composition according to claims 1 or 2 wherein the acidic tablet comprising at least one pharmaceutically acceptable organic acid further comprises an isolating coating layer.

4. The pharmaceutical composition according to claim 3 wherein the isolating coating layer comprises copolymers of polyvinyl alcohol.

5. The pharmaceutical composition according to any of the preceding claims wherein the dabigatran, is dabigatran etexilate or a pharmaceutically acceptable salt thereof, preferably dabigatran etexilate mesylate.

6. The pharmaceutical composition according to any of the preceding claims wherein the pharmaceutically acceptable organic acid is selected from a group consisting of ascorbic acid, aspartic acid, citric acid, erythrobic acid, fumaric acid, gluconic acid, glutamic acid, maleic acid, malic acid, succinic acid and tartaric acid or hydrates or acid salts thereof, preferably maleic acid.

7. The pharmaceutical composition according to any of the preceding claims wherein the multi-particulate system and/or the acidic tablet further comprise one or more pharmaceutically acceptable excipients.

8. The pharmaceutical composition according to claim 7 wherein the pharmaceutically acceptable excipient is selected from a group consisting of

fillers or diluents, binders, disintegrants, surfactants, glidants, lubricants, or mixtures thereof.

9. The pharmaceutical composition according to any of the preceding claims, comprising:

a) a multi-particulate system which comprises:

i) dabigatran, preferably dabigatran etexilate or a pharmaceutically acceptable salt thereof, preferably dabigatran etexilate mesylate;

ii) optionally one or more fillers or diluents, in particular selected from a group consisting of lactose, gluconolactose, or a mixture thereof;

iii) optionally one or more disintegrants, in particular crospovidone;

iv) optionally one or more binders, in particular hydroxypropylcellulose;

v) optionally one or more glidants, in particular amorphous silica; or

i) dabigatran, preferably dabigatran etexilate or a pharmaceutically acceptable salt thereof, preferably dabigatran etexilate mesylate;

ii) optionally one or more fillers or diluents, in particular gluconolactone, microcrystalline cellulose or a mixture thereof;

iv) optionally one or more binders, in particular hydroxypropylcellulose;

b) an acidic tablet which comprises:

i) at least one pharmaceutically acceptable organic acid, in particular maleic acid;

ii) optionally one or more fillers or diluents, in particular microcrystalline cellulose;

iii) optionally one or more disintegrants, in particular crospovidone;

iv) optionally one or more binders, in particular hydroxypropyl methylcellulose;

v) optionally one or more lubricants, in particular, sodium stearyl fumarate.

10. The pharmaceutical composition according to claim 9, wherein the acidic tablet further comprises an isolating coating layer, preferably copolymers of polyvinyl alcohol.

11. The pharmaceutical composition according to any of preceding claims wherein the pharmaceutical composition is in the form of a capsule, preferably hydroxypropyl methylcellulose (HPMC) capsule, or a sachet.

12. A process for preparing the oral pharmaceutical composition according to any of the preceding claims wherein the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof is prepared by dry granulation or extrusion-spheronization and the acidic tablet comprising at least one pharmaceutically acceptable organic acid is prepared by wet granulation.

13. The process according to claim 12 wherein the multi-particulate system comprising dabigatran or a pharmaceutically acceptable salt thereof is prepared by a process comprising:
i) blending dabigatran or a pharmaceutically acceptable salt thereof with at least one pharmaceutically acceptable excipient;
ii) compacting the powder mixture of step i), preferably by roller compaction;
iii) milling the sticks or sheets obtained in step ii) to obtain the granules; and
iv) optionally coating the granules obtained in step iii), preferably by film-coating; or
i) blending dabigatran or a pharmaceutically acceptable salt thereof with at least one pharmaceutically acceptable excipient;
ii) wetting the mixture obtained in step i) with a massing liquid, preferably at least one organic solvent, preferably isopropanol, ethanol or mixtures thereof, more preferably isopropanol;
iii) extruding the wet mixture obtained in step ii), through 0,6mm mesh to obtain the wet extrudate, preferably by extruding process;
iv) spheronizing the wet extrudate obtained in step iii) to obtain the pellets, preferably in a roto-spheronizer;
v) drying the pellets obtained in step iv); and
vi) optionally coating the pellets obtained in step v), preferably by film-coating.

14. The process according to claim 12 wherein the acidic tablet comprising at least one pharmaceutically acceptable organic acid is prepared by a process comprising:
i) blending the pharmaceutically acceptable organic acid with at least one pharmaceutically acceptable excipient;
ii) spraying the mixture obtained in step i) with a granulation liquid, preferably water;

iii) kneading the wet mixture obtained in step ii), preferably by high shear granulation;
iv) drying the wet granules obtained in step iii);
v) blending the dried granules obtained in step iv) with at least one extragranular pharmaceutically acceptable excipient;
vi) compresing the granules obtained in step v) to obtain the tablet; and
vii) optionally coating the tablet obtained in step vi), preferably by film-coating.

15. The process according to any of the claims 12 to 14 which further comprises filling a capsule, preferably a hydroxypropyl methylcellulose (HPMC) capsule, or a sachet with the composition as defined in any of the claims 1 to 10.

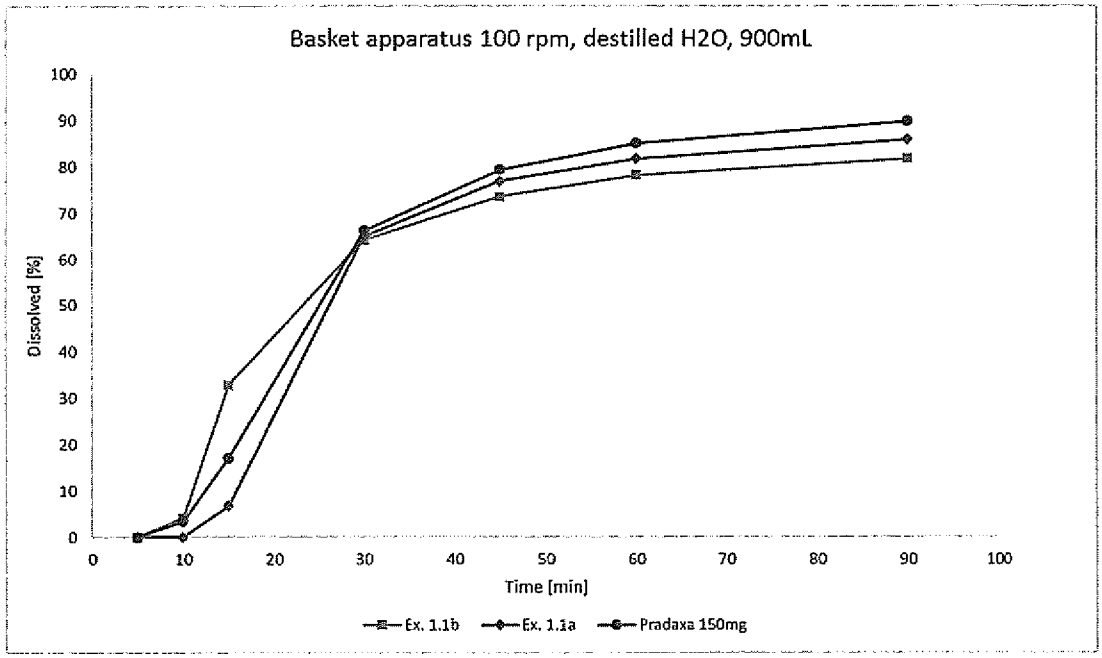

Basket apparatus 100 rpm, destilled H2O, 900mL
Dissolved [%]
Time [min]
Ex. 1.1b
Ex. 1.1a
Pradaxa 150mg

FIG. 1

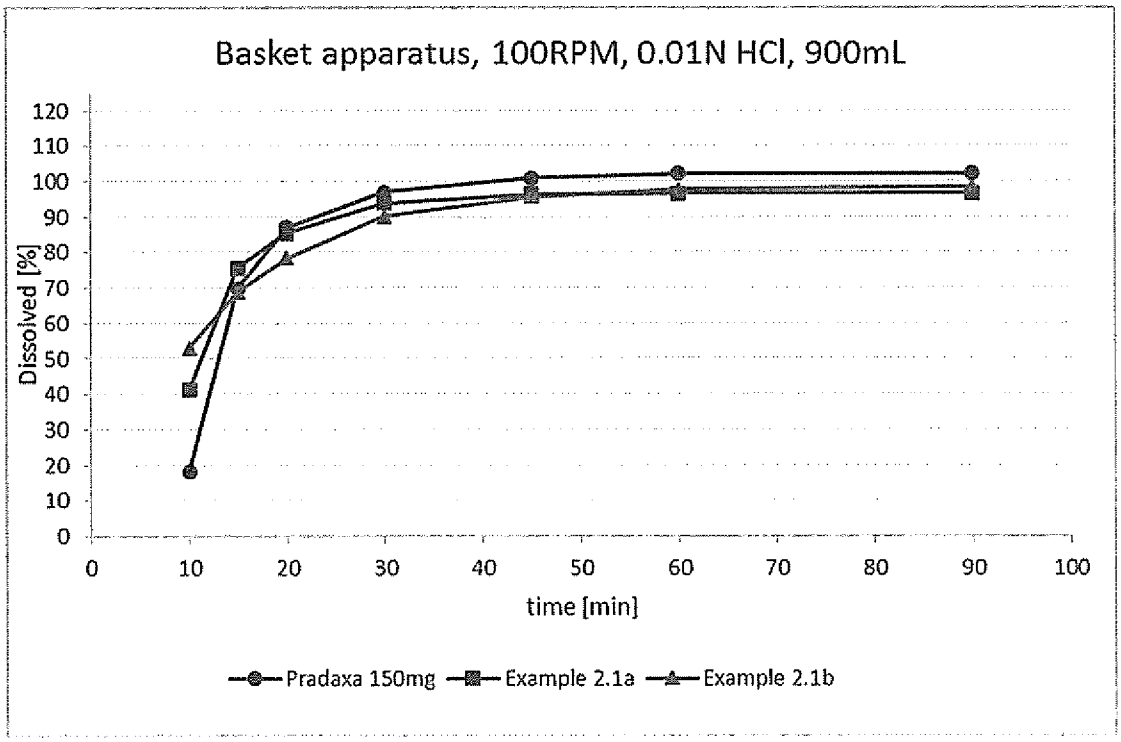

Basket apparatus, 100RPM, 0.01N HCl, 900mL
Dissolved [%]
time [min]
Pradaxa 150mg
Example 2.1a
Example 2.1b

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2016/000156

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/48 A61K31/4439
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, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/124340 A1 (ESTEVE LABOR DR [ES]) 29 August 2013 (2013-08-29) page 3, line 22 - page 16, line 21; claims 1-20; examples 1-3; tables 1-8, 17,18	1-15
X	WO 2012/162492 A1 (TEVA PHARMA [IL]; TEVA PHARMA [US]; HARONSKY ELINA [IL]; ARIELI DAFNA) 29 November 2012 (2012-11-29) page 3, line 26 - page 4, line 20 page 7, lines 21-34; claims 1-22; examples 1-6	1-15
X	WO 2015/145462 A1 (CADILA HEALTHCARE LTD [IN]) 1 October 2015 (2015-10-01) page 3, line 20 - page 6, line 16; claims 1-16; example 1; table 1	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2017	06/03/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Toulacis, C

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/PL2016/000156

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013124340 A1	29-08-2013	AU 2013224146 A1	28-08-2014
		CA 2864423 A1	29-08-2013
		CN 104114158 A	22-10-2014
		EP 2817000 A1	31-12-2014
		HK 1203832 A1	06-11-2015
		JP 2015511241 A	16-04-2015
		KR 20140135216 A	25-11-2014
		NZ 628301 A	31-07-2015
		RU 2014138036 A	20-04-2016
		US 2015030680 A1	29-01-2015
		WO 2013124340 A1	29-08-2013
WO 2012162492 A1	29-11-2012	EA 201391758 A1	30-06-2014
		JP 2014517843 A	24-07-2014
		US 2012301541 A1	29-11-2012
		WO 2012162492 A1	29-11-2012
WO 2015145462 A1	01-10-2015	NONE	