

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18356642	
	Filing Date		2023-07-21	
	First Named Inventor	Pratibha S. PILGAONKAR		
	Art Unit			
	Examiner Name			
	Attorney Docket Number	70204.0018USC2		

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	1	"Crystalline 2R, 3S-2-(2,4-Difluorophenyl)-3-(5-Fluoropyrimidin-4-YL)-1-(1H-1,2,4-Triazol-1-YL)-2-Butanol (VRC) In Plate-Like Form and Micronized 2R, 3S-2-(2,4-Difluorophenyl)-3-(5-Fluoropyrimidin-4-YL)-1-(1H-1,2,4-Triazol-1-YL)-2-Butanol Obtained Therefrom", IP.com Number: IPCOM000125373D; IP.com Electronic Publication: May 31, 2005; 14 pgs.	☐
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Signature	/Melissa M. Hayworth/	Date (YYYY-MM-DD)	2024-10-15
Name/Print	Melissa M. Hayworth	Registration Number	45774

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APPLICATION #
18/356,642

RECEIPT DATE / TIME
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70204.0018USC2

Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 4286

FILED BY Keyla Clements

PATENT CENTER # 67574115

FILING DATE 07/21/2023

CUSTOMER # 23552

FIRST NAMED INVENTOR Pratikha S. PILGAONKAR

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Melissa Hayworth

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
702040018USC2IDS20241015.pdf	4	Information Disclosure Statement (IDS) Form (SB08)	1011 KB
Crystalline.pdf	14	Non Patent Literature	2062 KB

Digest

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/356,642	07/21/2023	Pratibha S. PILGAONKAR	70204.0018USC2

CONFIRMATION NO. 4286

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PUBLICATION NOTICE



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Title:ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Publication No.US-2024-0139168-A1

Publication Date:05/02/2024

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18/356,642	07/21/2023	PILGAONKAR et al.	70204.0018USC2

MERCHANT & GOULD P.C. P.O. BOX 2903 MINNEAPOLIS, MN 55402-0903		EXAMINER	
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		ART UNIT	PAPER
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DATE MAILED: 27 April 2024

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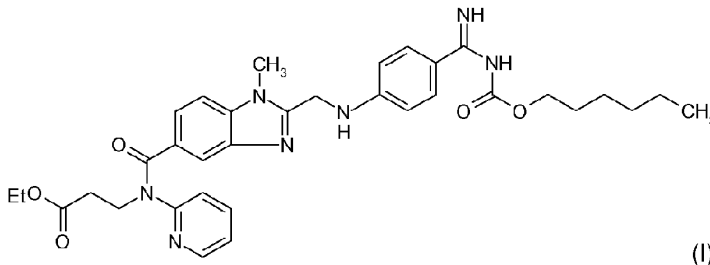
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— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii))

Published:

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

(54) Title: METHOD FOR MANUFACTURING MEDICINAL COMPOUNDS CONTAINING DABIGATRAN

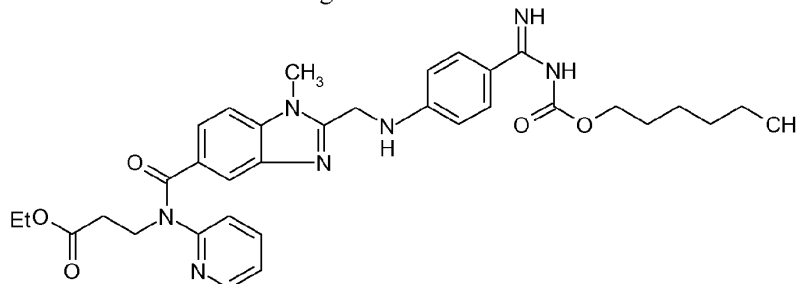


(57) Abstract: The invention relates to an improved process for preparing a new medicament formulation of the active substance dabigatran etexilate of formula I in the form of the methanesulphonic acid salt thereof, and this new medicament formulation as such.

WO 2010/007016 A1

METHOD FOR MANUFACTURING MEDICINAL COMPOUNDS CONTAINING DABIGATRAN

The invention relates to an improved fluidised bed process for preparing a new medicament formulation of the active substance dabigatran etexilate of formula I



5

I

optionally in the form of the pharmaceutically acceptable salts thereof, as well as the new medicament formulation as such.

Background to the invention

- 10 The compound of formula **1** is known from the prior art and was first disclosed in WO98/37075. It is a potent thrombin inhibitor which can be used for example for the post-operative prevention of deep vein thromboses and in stroke prevention, particularly for preventing strokes in patients with atrial fibrillation. WO 03/074056 discloses the methanesulphonic acid addition salt of dabigatran-etexilate (ie: dabigatran etexilate methansulphonate) to be particularly useful.

15

- The compound is usually administered orally. In particular, so-called pellet formulations may be used, as disclosed for example in WO 03/074056. These formulations are compositions, in which an active substance layer containing binder and optionally separating agent and surrounding a core material is applied to the substantially spherical core material, which consists of or contains a pharmaceutically acceptable organic acid. The core layer and the active substance layer are separated from one another by a so-called isolating layer. The schematic structure of an active substance formulation of this kind is shown in Figure 1 of WO 03/074056.

20

- The present invention relates to a process that can be used on an industrial scale for preparing active substance pellets containing dabigatran, which allows the formulation to be manufactured on a large scale. A further aim of the invention is to provide a process which allows the formulation to be manufactured with a reproducible quality.

25

- According to WO 05/028468 the methanesulphonic acid addition salt of dabigatran etexilate exists in different polymorphic forms. It is another aim of the invention to provide for a manufacturing process which allows the manufacture of a pharmaceutical formulation that contains only one polymorphic form of the active ingredient dabigatran etexilat methansulphonate.

30

Detailed description of the invention

According to WO 05/028468 the methansulphonic acid addition salt of dabigatran etexilate exists in different polymorphic forms. Surprisingly it has been found that polymorph I of
5 dabigatran etexilate methanesulphonate is advantageous over polymorph II in view of its crystallisation properties. This allows polymorph I to be easier isolated and handled in and after the manufacturing process of the active ingredient. According to the invention, polymorph I is therefore the preferred polymorph.

- 10 In principle, different polymorphic forms of a substance may be characterized by different properties (including but not limited to stability, efficacy, processing properties during manufacture etc). As a matter of principle it is, therefore, advisable to produce a pharmaceutical composition that contains essentially only one polymorph.
Consequently, the invention relates to manufacturing process which allows the manufacture of a
15 pharmaceutical formulation that contains essentially polymorph I of the active ingredient dabigatran etexilate methanesulphonate.

The process according to the invention is characterised by a series of partial steps. First, the core
20 1 is produced from pharmaceutically acceptable organic acid. Within the scope of the present invention tartaric acid is used to prepare the core 1. The core material 1 thus obtained is then converted into so-called isolated tartaric acid cores 3 by spraying on an isolating suspension 2. A dabigatran suspension 4 prepared subsequently is sprayed onto these coated cores 3 in one or more process steps by means of a coating process. Finally, the active substance pellets 5 thus
25 obtained are packed into suitable capsules.

25 The isolated tartaric acid cores 3 should have a uniform, quasi-spherical geometry. Moreover they should have only minor potential defects in the isolation caused by satellites. The so-called satellites are small particles adhering to the outside of the otherwise rounded pellets and detracting from the otherwise quasi-spherical geometry of the pellets. The ideally spherical
30 shape and low surface roughness is of particular importance for acid-sensitive active substances such as for example dabigatran etexilate, in which defects in the isolation caused by satellites that have broken off or by the excessively rough surface of over-large particles of tartaric acid powder may lead to significantly impaired storage stability and hence durability of the finished
35 product. For this reason, with acid-sensitive active substances it is also essential to apply the isolating layer as such with high reproducibility and consistently high quality.

The core 1 is prepared from tartaric acid particles with a particle size in the range from 0.2-0.8 mm, preferably 0.3-0.7 mm, particularly preferably 0.4-0.6 mm (determined by air jet screening) onto which a solution of tartaric acid and binder is sprayed. The following method is used to

prepare the solution. Tartaric acid is first of all dissolved in water together with a suitable binder, preferably with acacia (gum arabic) at elevated temperature, preferably at a temperature in the range from 30-70°C, particularly preferably in the range from 40-60°C. Preferably, 0.1-0.3 kg, particularly preferably 0.15-0.25 kg, particularly about 0.2 kg acacia are used per
5 kilogram of tartaric acid put in. The amount of water is preferably 0.6-1.0 kg, preferably 0.7-0.9 kg, particularly about 0.8 kg per kilogram of tartaric acid put in.

Preferably, according to the invention, first of all a clear solution of acacia in water is prepared at the above-mentioned temperature. Once this has been obtained, the tartaric acid is then added
10 preferably at constant temperature and while stirring continues. After the addition has ended the mixture is stirred for at least 1 hour, preferably between 3 and 10, particularly preferably 4 - 8, particularly preferably 5 - 6 hours.

The solution thus obtained is sprayed onto tartaric acid particles with a particle size of 0.2-0.8
15 mm, preferably 0.3-0.7 mm, particularly preferably 0.4-0.6 mm. The proportion of particles with the above-mentioned particle size should be at least 90%, preferably at least 95%, particularly preferably at least 97%. For this, the tartaric acid particles are placed in a suitable container. The container is preferably a pan in which the particles are mixed and moved about by the rotation of the pan. Various designs of pan are known in the art and may optionally also be
20 referred to as drum coaters. On this subject reference is made for example to the disclosures of EP 80199, WO 83/03052, WO 95/19713 or WO 06/134133. Within the scope of the present invention pans that may be used in the process according to the invention are optionally also known as horizontal pans.

25 The acid gum solution prepared by the method described hereinbefore is then sprayed onto the particles kept moving by rotation.

Within the scope of the present invention the material supplied for spraying is optionally also referred to as the pellet bed. The term pellet is to be regarded as equivalent to the term particle
30 or core within the scope of the present invention.

According to the invention, preferably 0.8 - 1.6 kg, particularly preferably 1.0 - 1.4 kg, particularly preferably 1.2 kg of the above-mentioned acid gum solution are sprayed on per
35 kilogram of tartaric acid particles supplied.

The amount of supply air in the process according to the invention is dependent on the batch size. The standardised amount of supply air per kilogram of tartaric acid cores supplied according to the invention is preferably in the range from 0.5 - 2 (m³/h)/kg, preferably 0.75 - 1.5

(m³/h)/kg, particularly preferably 0.9 - 1.1 (m³/h)/kg. By the amount of supply air is meant the amount of dry air introduced into the rotating pellet bed per hour.

- If for example 1000 kg tartaric acid cores are placed in one batch, a standardised amount of supply air of 1.0 (m³/h)/kg corresponds to an actual amount of supply air of 1000 m³/h. The temperature of the supply air fed in for drying according to the invention is preferably below 90°C, particularly preferably below 80°C. Ideally the temperature of the supply air should be in the range from 35°-75°C.

- The pellet temperature (the temperature of the pellet bed formed) according to the invention is preferably in the range from 30 - 50°C, particularly preferably 36 - 44°C, ideally 38 - 42°C.

- The differential pressure is preferably 1 - 3 mbar, particularly preferably 1.5 - 2.5 mbar, particularly preferably 1.8 - 2.2 mbar. The differential pressure is the pressure difference between the pan pressure and ambient pressure. The pan should preferably be at reduced pressure so that no acid dust escapes.

- Spraying is carried out at a defined spray rate. By the spray rate is meant the amount of acid gum solution that is sprayed onto the rotating pellet bed per hour. The spray rate is dependant on the batch size in the process according to the invention. The standardised spray rate according to the invention per kilogram of tartaric acid crystals supplied is preferably in the range from 0.2 - 0.4 (kg/h)/kg, preferably 0.25 - 0.35 (kg/h)/kg, particularly preferably 0.28 - 0.32 (kg/h)/kg. If for example 1000 kg tartaric acid crystals are placed in one batch, a standardised spray rate of 0.3 (kg/h)/kg corresponds to an actual spray rate of 300 kg/h.

- After a first portion of the acid gum solution has been sprayed onto the tartaric acid particles of particle size 0.2-0.8 mm and the solution has been distributed by rotating the pan, fine tartaric acid powder is sprinkled onto the moist tartaric acid particles. This tartaric acid powder consists of fine tartaric acid particles with a particle size of < 100 , preferably < 75, particularly preferably < 50 microns (determined by air jet screening). The proportion of particles with the above-mentioned particle size should be at least 85%, preferably at least 90%, particularly preferably at least 94%. According to the invention preferably 0.4 - 1.2 kg, particularly preferably 0.6 - 1.0 kg, particularly preferably 0.8 kg of the above-mentioned tartaric acid powder are used per kilogram of tartaric acid particles supplied. After sprinkling with the above-mentioned tartaric acid powder the material for spraying is dried until a product temperature of about 30-50°C, preferably about 40°C is reached. After this, the acid gum solution is sprayed on again.

To ensure the uniform formation of spherical particles, the spraying on of the acid gum solution and the sprinkling with tartaric acid powder are carried out alternately. The total amounts of acid

gum solution and tartaric acid powder are supplied in at least 100, preferably 150 to 350, particularly preferably 200 to 300, particularly preferably about 250 batches of similar size and the process steps described hereinbefore are repeated a corresponding number of times.

- 5 Once the process has ended, the cores 1 obtained are dried. The drying is preferably carried out at a temperature of 50-70°C, preferably 55-65°C over a period of 24 - 72 hours, preferably 36 - 60 hours.

- After the preparation of the tartaric acid cores 1 so-called isolation of the core material is
10 necessary. An isolating layer is applied around the tartaric acid core, preventing any interaction of active substance with tartaric acid core in the later product.

- The core material is isolated by spraying an isolating suspension 2 onto the tartaric acid cores 1 obtained by the process described hereinbefore. To prepare the isolating suspension 2 ethanol is
15 placed in the batch container and hydroxypropylmethylcellulose and dimethylpolysiloxane are added and dissolved therein with stirring, then talc is added and suspended.

- The use of hydroxypropylmethylcellulose and talc has proved superior to the use of gum arabic and talc, for example. By using hydroxypropylmethylcellulose together with talc it is possible to
20 produce an isolating layer of constant quality in a reproducible manner. This quality and reproducibility has been tested on an industrial scale.

- To prepare the isolating suspension 2, preferably 0.04 - 0.06 kg, particularly preferably 0.046 - 0.05 kg hydroxypropylmethylcellulose are used per kilogram of ethanol. Besides the use of hydroxypropylmethylcellulose it has proved particularly preferable according to the invention to
25 add dimethylpolysiloxane to the isolating suspension 2 to prevent foaming. The amount of dimethylpolysiloxane which is added with stirring to the preparation of the isolating suspension 2 is preferably 0.6 - 1.2 g, particularly preferably 0.8 - 0.9 g per kilogram of ethanol. Finally talc is added and suspended therein with stirring. Preferably 0.04 - 0.06 kg, particularly preferably 0.046 - 0.05 kg talc are used per kilogram of ethanol.

- 30 The isolating suspension 2 thus prepared is sprayed onto the previously prepared tartaric acid pellets 1 in a continuous spray process in a conventional horizontal coater. 0.5 - 0.8 kg, preferably 0.55 - 0.75 kg, particularly preferably 0.6 - 0.7 kg of isolating suspension are sprayed on per kilogram of tartaric acid cores 1 supplied.

- 35 The spraying is carried out at a defined spray rate. By the spray rate is meant the amount of isolating suspension 2 sprayed onto the pellets 1 per hour. The spray rate in the process according to the invention is dependent on the batch size. The standardised spray rate according to the invention is preferably in the range from 0.01 - 0.1 (kg/h)/kg, preferably 0.02 - 0.04

- (kg/h)/kg, particularly preferably 0.025 - 0.035 (kg/h)/kg per kilogram of tartaric acid pellets 1 supplied. If for example 1200 kg tartaric acid cores are placed in one batch, a standardised spray rate of 0.027 (kg/h)/kg corresponds to an actual spray rate of 32 kg/h. If for example 600 kg tartaric acid cores are placed in one batch, a standardised spray rate of 0.035 (kg/h)/kg corresponds to an actual spray rate of 21 kg/h.

During this continuous process the cores are dried continuously with a supply of air at up to 70°C, preferably from 25 - 70°C.

- 10 By the amount of supply air is meant the amount of dry air that is introduced into the rotating pellet bed per hour. The amount of supply air in the process according to the invention is dependant on the batch size. The standardised amount of supply air according to the invention is preferably in the range from 1.0 - 2.5 (m³/h)/kg. Preferably 1.2 - 2.0 (m³/h)/kg, particularly preferably 1.40 - 1.85 (m³/h)/kg per kilogram of tartaric acid cores 2 originally supplied.
- 15 If for example 600 kg tartaric acid cores 2 are placed in one batch, a standardised amount of supply air of 1.83 (m³/h)/kg corresponds to an actual amount of supply air of 1100 m³/h. If for example 1200 kg tartaric acid cores 3 are placed in one batch, a standardised amount of supply air of 1.42 (m³/h)/kg corresponds to an actual amount of supply air of 1700 m³/h.
- 20 The pellets 5 containing active substance are prepared by spraying an active substance suspension 4 onto the isolated tartaric acid cores 3 obtained by the method described hereinbefore. The preparation of the active substance suspension 4 is of particular importance according to the invention as both the homogeneity and the temperature of the active substance suspension 4 are pertinent to the quality of the pellets containing the active substance.
- 25 The active substance suspension 4 is prepared using dabigatran etexilate methanesulphonate in the form of its polymorph I. Polymorph I is characterised inter alia by a melting point of T_{mp.} = 180 ± 3°C (determined by DSC; evaluated using peak maximum; heating rate: 10°C/min). The targeted production of polymorph I is possible for example using the method described in WO
- 30 05/028468 (cf. particularly Example 1). Where the term active substance is used within the scope of the present invention, unless stated otherwise, this is to be understood as being a reference to polymorph I of dabigatran etexilate methanesulphonate.

- In order to prepare the active substance suspension 4 isopropyl alcohol is taken and adjusted to a
- 35 temperature range of 12-22°C under a nitrogen atmosphere. Then hydroxypropylcellulose is sucked into the prepared substance using vacuum or circulatory dispersal with stirring. Preferably the preparation is carried out using a special dispersion device (rotor-stator principle; e.g. Ultra Turrax[®] made by Jahnke & Kunkel or CONTI TDS 4[®] made by Ystral GmbH). Circulatory dispersal denotes that the dispersion device is connected to the batch container and

the prepared isopropyl alcohol is circulated through the disperser. The rotor-stator principle generates the suction vacuum required to suck in the solid. The liquid and solid enter the dispersing chamber by separate routes and are wetted therein during the suction process. As the process takes place during circulation, it is referred to as circulatory dispersal.

- 5 The batch container in which the process takes place is in turn provided with a mixer which achieves the optimum stirring action of the dabigatran etexilate suspension with low energy input (e.g. Visco Jet[®] stirring system made by Visco Jet GmbH or an air jet mixer). Furthermore, the batch container is optionally provided with a double jacket. Isopropyl alcohol is preferably used in substantially anhydrous form (99.5%). The hydroxypropylcellulose is sucked in by vacuum or
- 10 circulatory dispersal at 2000 - 4000 rpm, preferably at 2900 rpm, and incorporated with stirring. The stirring performance of the mixer in the batch container is e.g. 600 rpm. After 30 - 60 minutes the dissolving process is complete. Then the intake of the active substance dabigatran etexilate methanesulphonate and the excipient talc begins, again using vacuum or preferably circulatory dispersion.
- 15 As a result of the dispersion in the circulatory process it is possible to prepare the suspension 4 according to the invention significantly more rapidly than by using conventional stirring techniques.

- Advantageously, the active substance is ground up before the preparation of the suspension. The
- 20 preferred particle size distribution of the active substance is at an X_{90} of less than 14 μm . The characteristic value X_{90} denotes the median value of the particle size below which are found 90% of the quantity of particles with regard to the distribution by volume of the individual particles. The particle sizes may for example be determined within the scope of the present invention by laser diffraction (Fraunhofer diffraction).

- 25 There is then a stirring and swelling phase lasting 30 minutes during which the mixer is operated at a stirring speed of 400 - 800 rpm, preferably 600 rpm. Then the suspension is dispersed for 3 - 10 minutes by the circulatory process at 2000 - 4000 rpm, preferably at 2900 rpm. The dispersing stirring cycle is optionally repeated up to six times.

- 30 To prepare the suspension 4, 0.05 to 0.5 kg, preferably 0.1 to 0.3 kg, particularly preferably 0.15-0.25 kg active substance are used per kilogram of isopropyl alcohol put in. The amount of hydroxypropylcellulose used is 0.01 to 0.1 kg, preferably 0.02 to 0.07 kg particularly preferably 0.03-0.05 kg, per kilogram of isopropyl alcohol put in. The amount of talc used is 0.005 to 0.07
- 35 kg, preferably 0.01 to 0.05 kg, particularly preferably 0.02-0.04 kg, per kilogram of isopropyl alcohol put in.

The ratio of active substance to hydroxypropylcellulose is preferably in the range from 3:1 to 7:1, preferably 4:1 to 6:1, particularly preferably about 5:1, with regard to the mass of the two

constituents in the active substance suspension according to the invention. The ratio of active substance to talc is preferably in the range from 4:1 to 8:1, preferably 5:1 to 7:1, particularly preferably 6:1 to 6.5:1 with regard to the mass of the two constituents in the active substance suspension according to the invention.

- 5 The concentration of the active substance is preferably at 10 - 25 % (w/w), preferably at 11 - 20 % (w/w), particularly preferably at 12 - 19 % (w/w) in the active substance suspension according to the invention. The total concentration of the constituents active substance, hydroxypropylcellulose and talc in the active substance suspension according to the invention is preferably 14 - 40 % (w/w), preferably 15 - 30 % (w/w), particularly preferably 16 - 25 % (w/w).

10

Within the scope of the present invention, unless stated otherwise, concentrations are always given as percent by weight or mass percent.

- Surprisingly it has been found that the temperature selected for the preparation of the suspension
15 4 has a decisive effect on the characteristics of the final product. In order to guarantee that the manufacturing process reproducibly leads to a product with a defined polymorphic form of the active substance, it turned out that the temperature should best be kept below 30°C throughout the entire manufacturing process. If the suspension 4 is produced or even stored at too high a temperature, this may lead to a change in the polymorphic form of the active substance, which
20 may have negatively affect the efficacy of the final formulation. Particularly preferably the temperature of the manufacturing process is in the range from 0 - 30°C, particularly preferably in the range from 5 - 30°C.

- To prevent sedimentation, the suspension is stirred throughout the entire manufacturing process
25 including the spray process. The stirring power of the mixer in the batch container is preferably 300 - 500 rpm, particularly preferably 400 rpm.

- After it has been produced the active substance suspension 4 is stored at below 30°C until further processing is carried out. Preferably the suspension 4 is processed further in the course of not more than 48 h. If the suspension is prepared and stored at 22°C, for example, it is preferably
30 further processed within 60 hours.

- In one aspect the present invention relates to a process for preparing a suspension 4 of the polymorph I of dabigatran etexilate methanesulphonate in isopropyl alcohol, which is characterised in that the temperature during the manufacture and storage of the suspension is
35 always below 30°C, preferably in the range from 0 - 30°C, particularly preferably in the range from 5 - 30°C, the ingredients of the suspension being added by circulatory dispersion.

In another aspect the present invention relates to the suspension 4 of the polymorph I of dabigatran etexilate methanesulphonate in isopropyl alcohol, which may be obtained by the manufacturing process mentioned above.

- 5 In another aspect the present invention relates to the use of the suspension 4 of the polymorph I of dabigatran etexilate methanesulphonate in isopropyl alcohol as starting material for preparing a medicament formulation of dabigatran etexilate methanesulphonate.

- 10 In another aspect the present invention relates to the use of the active substance suspension 4 according to the invention as starting material for preparing a medicament formulation of dabigatran etexilate methanesulphonate, the suspension 4 having been reacted within 48 h at a storage temperature of less than 30°C.

- 15 In another aspect the present invention relates to the use of the active substance suspension 4 according to the invention as starting material for preparing a medicament formulation of dabigatran etexilate methanesulphonate, the suspension 4 having been reacted within 60 h at a storage temperature of less than 22°C.

- 20 To prepare the final active substance formulation 5 the active substance suspension 4 obtained by the above process is sprayed onto the isolated tartaric acid cores 3 described hereinbefore.

- 25 In another aspect the present invention relates to a process for preparing a medicament formulation of dabigatran etexilate methanesulphonate 5, characterised in that the active substance suspension 4 according to the invention is sprayed onto isolated tartaric acid cores 3.

- In another aspect the present invention relates to a medicament formulation of dabigatran etexilate methanesulphonate 5, obtainable by spraying the active substance suspension 4 according to the invention onto isolated tartaric acid cores 3.

- 30 The subsequent preparation of the active substance pellets 5 according to the invention by the fluidised bed method is divided into three process steps:

1. preheating of the starter pellets 3
2. spraying phase (application of the active substance)
3. drying of the active substance pellets 5

- 35 These three process steps are carried out in a fluidised bed apparatus. By a fluidised bed apparatus is meant according to the invention that the product to be coated has a fluid, preferably air, flowing through it. The material put in is set in motion and kept in motion by this fluid, the nature of the movement being controlled by different equipment-specific inserts. Examples of suitable fluidised bed apparatus are GPCG (= Glatt Particle Coater Granulator), Precision Coater

(Aeromatic), Kugelcoater (Hüttlin) or carried out using the Aircoater (Innojet). A so-called Wurster Coater as described for example in EP 0711 593 has proved particularly suitable for carrying out the fluidised bed process according to the invention.

- 5 For the preparation, the isolated tartaric acid starter pellets are placed in the product container, fluidised using process air and at the same time pre-heated. The process air current is generated by a ventilator provided downstream (vacuum method), but may also be generated by the pressure method. The supply air needed may be fed in directly from the outside air and heated or adjusted to a specific moisture level or water content by conditioning. Preferably the moisture
10 level of the supply air is adjusted to 3 g/kg.

The product container is closed off by a perforated base plate in the supply air region. In the exhaust air region a filter cloth or screen insert prevents the pellets from escaping from the product chamber. Once the desired product temperature has been reached the spraying phase is
15 started.

- In the base plate there are one or more spray nozzles. The high degree of perforation in the base plate in the region of the spray nozzles causes the tartaric acid starter pellets 3 which are to be sprayed to be accelerated upwards and thereby sprayed with the active substance suspension
20 according to the co-current principle. The pellets may be forcibly carried by an air current guided vertically through one or more tubes (Wurster-Coater or Precision-Coater), or they may follow a helical or toroidal motion of the process air in the product container and relaxation zone (Kugelcoater or Aircoater). Before and during the falling back of the sprayed pellets the volatile constituents are dried or eliminated. A uniform structure of the active substance layer is ensured
25 by the circulating movement of the pellets. As the tartaric acid starter pellets are relatively small at the start of the process, a low spray pressure and a low spray rate are used to begin with. In the course of the process, the parameters of spray rate and spray pressure as well as supply air volume and supply air temperature are increased step by step to ensure optimum movement of the pellets and optimum product temperature.

- 30 In order to achieve good results in terms of homogeneity and uniformity of the active substance pellets 5 obtained, the product temperature, spray pressure, spray rate, temperature of supply air and amount of supply air in particular should be kept within specified ranges. Monitoring these parameters according to the present invention also ensures limited decomposition of the active
35 substance, a reproducible content of active substance in the pellets 5, associated reduced spray losses and also reduced formation of multiples (clumps of several pellets). A reduced formation of multiples directly influences the yield as clumps would be separated off during the final screening of the active substance pellets 5.

By the product temperature is meant the temperature that prevails in the p, die in the pellet bed. The product container is first of all charged with the isolated tartaric acid pellets 3 described hereinbefore and the isolated tartaric acid pellets 3 are heated. They are preferably heated to a temperature of 30-50°C, preferably 30-48°C, particularly preferably 34-44°C. Once this
5 temperature has been reached, the active substance suspension 4 described hereinbefore is sprayed on.

The temperature of the air supplied according to the invention is preferably below 90°C, particularly preferably below 80°C. Ideally the temperature of the supply air should be in the
10 range from 40°-80°C, particularly preferably between 55-75 °C.

By the spray pressure is meant the pressure of compressed air which is used for atomisation at the nozzle through which the active substance suspension 4 is sprayed on. The spray pressure according to the invention is preferably in the range from 1.0 - 4.0 bar, preferably 1.5 - 4.0 bar,
15 particularly preferably 2.0 - 4.0 bar.

By the spray rate is meant the amount of active substance suspension 4 that is sprayed onto the fluid pellet bed per hour. The spray rate is dependant on the batch size in the process according to the invention. The standardised spray rate according to the invention per kilogram of isolated
20 tartaric acid pellets 3 supplied is preferably in the range from 2 - 30 (g/min)/kg, preferably 4.5 - 30 (g/min)/kg, particularly preferably 6 - 26 (g/min)/kg.
If for example 270.56 kg tartaric acid pellets 3 are placed in a batch, a standardised spray rate of 7.39 (g/min)/kg corresponds to an actual spray rate of about 2000 g/min.

25 By the amount of supply air is meant the amount of dry air that is introduced into the fluid pellet bed per hour. The amount of supply air is dependant on the batch size in the process according to the invention. The standardised amount of supply air per kilogram of isolated tartaric acid pellets 3 supplied according to the invention is preferably in the range from 10 - 30 (m³/h)/kg, preferably 14 - 30 (m³/h)/kg, particularly preferably 18 - 28 (m³/h)/kg.
30 If for example 270.56 kg tartaric acid pellets 3 are placed in one batch, a standardised amount of supply air of 20 (m³/h)/kg corresponds to an actual amount of supply air of 5411 m³/h.

After all the active substance suspension has been sprayed the active substance pellets are dried for a specified length of time, preferably 10-30 minutes, particularly preferably 20 minutes. The
35 product temperature should preferably be adjusted to between 20 and 40°C during the drying. Continuous fluidisation is also ensured during drying.

After the end of the process the product container is emptied gravimetrically and the dabigatran etexilate pellets are screened through a suitable screen, e.g. a vibrating screen (mesh size 1600 μm).

- 5 The amount of active substance suspension 4 sprayed on under the prevailing conditions depends not only on the active substance concentration in the suspension 4 but also on the batch size of the isolated tartaric acid pellets 3 supplied and the desired quantity of active substance per final active substance pellet (so-called charge). Particularly preferably the active substance charge per active substance pellet 5 is in the range from 15 - 50 % (w/w). Particularly preferred active
10 substance pellets 5 according to the invention have a charge of active substance of 20 - 45 % (w/w), particularly preferably 36 - 42 % (w/w).

- If a particularly preferred active substance suspension 4 with an active substance concentration of about 15% (w/w) and an overall concentration of the constituents active substance,
15 hydroxypropylcellulose and talc of about 25 % (w/w) is used according to the invention, a desired charge of for example 40 % of active substance per active substance pellet 5 with a supply of 1 kg of isolated tartaric acid pellets 3 requires the use of about 4.83 kg of active substance suspension 4 according to the invention. It may possibly make sense to use active substance suspension 4 in an excess of up to 5%, to compensate for any spray losses that may
20 occur.

- In the event of a greater charge of the isolated tartaric acid pellets 5 the total weight of the batch and, in the present case, in particular the volume naturally increases constantly during the spraying of the active substance suspension 4. A charge of for example 40% of the isolated
25 tartaric acid pellets 3 with active substance leads to roughly a doubling of the total weight and an increase in bulk density by a factor of approx. 1.4 (i.e. an even greater increase in volume in relation to the mass) of the material for spraying 5. This sharp increase in the mass and particularly the volume of the material for spraying 5 may negatively affect the spray process in large industrial batches, as for example uniform drying of the spray material 5 can no longer be
30 achieved easily or without complex technical procedures.

- In another aspect the present invention relates to a medicament formulation of dabigatran etexilate methanesulphonate 5, obtainable by spraying the active substance suspension 4 according to the invention onto isolated tartaric acid cores 3 by the method described
35 hereinbefore.

To eliminate any clumps that may have formed, the active substance pellets thus obtained are screened through screens of a defined mesh size. The mesh size selected naturally depends on

the charging of the respective active substance pellets. For lower charges, closer-meshed screens may be used.

Finally, the active substance pellets obtained are packed into commercially obtainable capsules,
5 preferably into commercially obtainable HPMC capsules.

The Examples that follow serve to illustrate the present invention in more detail.

Determining the particle sizes of tartaric acid by air jet screening

10

Measuring device and settings:

Measuring device: Air jet screen, e.g. Alpine A 200 LS

Screens: As required

Weight put in: 10g/screen

15 Duration: 1 min/screen, then 1 min each up to the maximum weight loss of 0.1g

Preparation of sample / supply of product:

The substance is transferred into a mortar and any lumps present are destroyed by intensive
pounding. The screen with rubber seal and cover is placed on a balance, set to zero and 10.0 g of
20 the pounded substance are weighed onto the screen.

The screen together with its contents, rubber seal and cover are placed on the device. The timer
is set to 1 minute and the material is treated by air jet screening for this time. Then the residue is
weighed out and documented. This process is repeated until the decrease in the weight of the
residue after air jet screening is < 0.1 g.

25

Example 1 - Preparation of the Starter Pellets

480 kg water are heated to 50°C and 120 kg of acacia (gum arabic) are added with stirring in a
conventional mixing container having a dished end and stirrer. Stirring is continued at constant
temperature until a clear solution is obtained. Once there is a clear solution (usually after 1 to 2
30 hours) 600 kg tartaric acid are added with stirring. The tartaric acid is added at constant
temperature while stirring is continued. After the addition has ended the mixture is stirred for
about another 5 to 6 hours.

1000 kg tartaric acid are added to a slowly rotating (3 revolutions per minute) unperforated
35 horizontal pan with a spraying and powder applying unit (e.g. Driamat 2000/2.5). Before
spraying starts, a sample of the acid is taken for screening analysis. The acid in question is
tartaric acid particles with a particle size in the range from 0.4-0.6 mm.

The acid rubber solution obtained by the above method is sprayed onto the tartaric acid particles
thus provided. During the spraying, the quantity of air supplied is adjusted to 1000m³/h and 35°-

75°C. The differential pressure is 2 mbar and the speed of rotation of the pan is 9 revolutions per minute. The nozzles should be arranged at a distance of 350 – 450 mm from the filling.

The acid rubber solution is sprayed on by alternating with the following steps. After about 4.8
5 kg of the acid rubber solution has been sprayed onto the tartaric acid particles of particle size 0.4-0.6 mm and the solution has been distributed, about 3.2 kg tartaric acid powder are sprinkled onto the damp tartaric acid particles. The tartaric acid powder in question consists of fine tartaric acid particles with a particle size of < 50 microns. In all, 800 kg tartaric acid powder are required. After the said tartaric acid powder has been sprinkled on and distributed the spray
10 material is dried until a product temperature of about 40°C is reached. This is in turn followed by the spraying on of the acid rubber solution.

These cycles are repeated until the acid rubber solution is used up. Once the process has ended the acid pellets are dried in the pan at 3 rpm for 240 minutes. To prevent caking after the drying
15 has finished, an intermittent program is run at 3 rpm for 3 minutes every hour. In the present instance this means that the pan is rotated at 3 rpm for 3 minutes at intervals of one hour and then left to stand. The acid pellets are then transferred into a dryer. They are then dried at 60°C over a period of 48 hours. Finally, the particle size distribution is determined by screen analysis. The particle size with a diameter of 0.6 – 0.8 mm corresponds to the product. This fraction
20 should make up >85%.

Example 2 - Isolation of the Starter Pellets

To prepare the isolating suspension, 666.1 (347.5) kg of ethanol are placed in the mixing container and the hydroxypropylmethylcellulose (33.1 (17.3) kg) is added with stirring at approx.
25 600 rpm and dissolved. Then under the same conditions 0.6 (0.3) kg dimeticone are added. Shortly before use, talc (33.1 (17.3) kg) is added, again with stirring, and suspended.

The acid pellets 1200 (600) kg are poured into the coating apparatus (e.g. GS-Coater Mod. 600/Mod. 1200) and sprayed therein in the rotating pan with the isolating suspension described
30 above in a continuous spraying process lasting several hours at a spraying rate of 32 kg/h for the 1200 kg mixture or 21 kg/h for the 600 kg mixture. The pellets are also dried continuously with an air supply at up to 70°C.

After the GS-Coater has been emptied, the isolated starter pellets are fractionated by screening.
35 The product fraction with a diameter ≤ 1.0 mm is stored and used further.

Example 3 - Preparation of the dabigatran etexilate suspension

The batch container is inertised with nitrogen and nitrogen is passed over it throughout the entire process.

1028.325 kg of isopropyl alcohol are metered into the batch container. The temperature of the isopropyl alcohol must be between 12 and 22°C before the addition of the 50.416 kg hydroxypropylcellulose (Klucel EF) can begin. The dispersing apparatus (CONTI TDS 4[®] made by Ystral GmbH) sucks the hydroxypropylcellulose into the prepared substance by circulatory dispersal. The stirring speed in the batch container is 600 rpm. After 30 min. a sample (100 ml) is taken from the hydroxypropylcellulose and passed through a 250µm screen. If the solution is not clear and still contains recognisable particles, the dissolving process may be extended twice by 15 min. If the solution is clear and free from lumps, the addition of the active substance dabigatran etexilate methanesulphonate can be started. 252.006 kg of the active substance and 40.359 kg talc are sucked in successively by circulatory dispersal. After a stirring phase of 30 minutes the active substance suspension is dispersed for up to 10 minutes at 2900 rpm. Depending on the quality of the active substance suspension the dispersing-stirring cycle may be repeated up to 6 times. The quality of the active substance suspension is monitored by adding 100 ml of active substance suspension through a 500µm screen after each dispersing-stirring cycle. The temperature of the suspension should not exceed 30°C throughout the entire process. The storing and spraying temperature of the finished active substance suspension is adjusted to < 18 °C. If the suspension is stored at below 30°C, it should be further processed within at most 48 h. If for example the suspension is manufactured and stored at 22°C, it may should be further processed within 60 hours. If the suspension is stored for example at 35°C it should be further processed within at most 24 h.

To prevent sedimentation, the active substance suspension is stirred throughout the entire manufacturing and spraying process.

Example 4 - Preparation of the dabigatran etexilate active substance pellets

A fluidised bed apparatus is used (GPCG PRO 300). Spraying is carried out through nozzles 2.2 mm in diameter.

The product container is charged with 270.561 kg of the tartaric acid pellets obtained according to Example 2 and the pellet bed is heated up. Once a pellet bed temperature of 39°C is reached, spraying starts. The suspension prepared according to Example 3 is sprayed on in seven 10-minute spray phases at increasing spray rates of 120 kg/h up to 420 kg/h.

The suspension is stirred constantly. The supply air temperature is not more than 75°C. The amount of supply air is about 7500 m³/h. The spray pressure is in the range from 3 - 4 bar.

Then the pellets are dried in the product container at a supply air temperature of at least 20°C, at most 70°C and with an amount of supply air of 6000 m³/h for a period of about 20 minutes.

The dried pellets are then screened through a vibrating 1.6 mm screen and stored in containers with desiccants until required for further processing.

Example 5 - Examples of formulations

5

The following examples of formulations are then obtained from the active substance pellets obtained according to Example 4 by packing into hydroxypropylmethylcellulose capsules:

Ingredient	amount [mg] per capsule	amount [mg] per capsule
active substance I	86.48 ⁽¹⁾	126.83 ⁽²⁾
Acacia (gum arabic)	4.43	6.50
tartaric acid	88.56	129.9
hydroxymethyl-propylcellulose 2910	2.23	3.27
dimethylpolysiloxane 350	0.04	0.06
talc	17.16	25.16
hydroxypropylcellulose	17.30	25.37
HPMC capsule	60 ⁽³⁾	70 ⁽⁴⁾
Total	276.2	387.1

⁽¹⁾ corresponds to 75 mg of free active substance base

10 ⁽²⁾ corresponds to 110 mg of free active substance base

⁽³⁾ weight of capsule size is about 60 mg

⁽⁴⁾ weight of capsule size is about 70 mg

15 In another aspect the present invention relates to one of the above-mentioned medicament formulations as such.

20 In another aspect the present invention relates to a medicament formulation which contains 60 - 90 mg, preferably 70 - 80 mg, particularly preferably about 75 mg of dabigatran etexilate of formula I. In another aspect the present invention relates to a medicament formulation which contains 90 - 130 mg, preferably 100 - 120 mg, preferably 105 - 115 mg, particularly preferably about 110 mg of dabigatran etexilate of formula I.

25 In another aspect the present invention relates to a medicament formulation which contains 60 - 90 mg, preferably 70 - 80 mg, particularly preferably about 75 mg of dabigatran etexilate of formula I in the form of the polymorph I of its methanesulphonate. In another aspect the present invention relates to a medicament formulation which contains 90 - 130 mg, preferably 100 - 120

mg, preferably 105 - 115 mg, particularly preferably about 110 mg of dabigatran etexilate of formula I in the form of the polymorph I of its methanesulphonate.

5 In another aspect the present invention relates to a medicament formulation which also contains hydroxymethylpropylcellulose, besides dabigatran etexilate of formula I in the form of the polymorph I of its methanesulphonate.

10 In another aspect the present invention relates to a medicament formulation which also contains dimethylpolysiloxane besides dabigatran etexilate of formula I in the form of the polymorph I of its methanesulphonate.

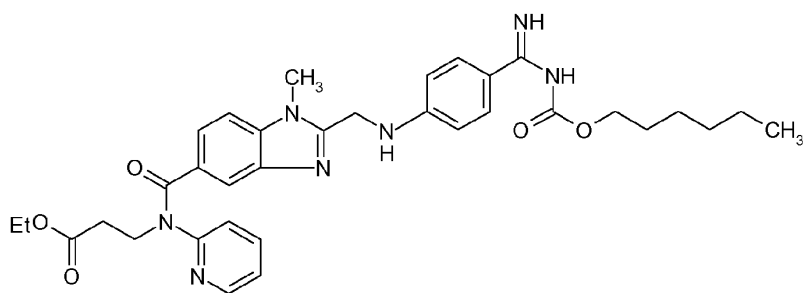
15 In another aspect the present invention relates to a medicament formulation which also contains the constituents gum arabic, tartaric acid, hydroxymethylpropylcellulose, dimethylpolysiloxane, talc as well as hydropropylcellulose, besides dabigatran etexilate of formula I in the form of the polymorph I of its methanesulphonate.

20 In another aspect the present invention relates to a medicament formulation which contains exclusively the constituents gum arabic, tartaric acid, hydroxymethylpropylcellulose, dimethylpolysiloxane and talc as well as hydropropylcellulose, besides dabigatran etexilate of formula I in the form of the polymorph I of its methanesulphonate.

25 In another aspect the present invention relates to a medicament formulation which contains 60 - 90 mg, preferably 70 - 80 mg, particularly preferably about 75 mg of dabigatran etexilate of formula I, for the post-operative prevention of deep vein thromboses and in stroke prevention, particularly for preventing strokes in patients with atrial fibrillation. In another aspect the present invention relates to a medicament formulation which contains 90 - 130 mg, preferably 100 - 120 mg, preferably 105 - 115 mg, particularly preferably about 110 mg of dabigatran etexilate of formula I, for the post-operative prevention of deep vein thromboses and in stroke prevention, particularly for preventing strokes in patients with atrial fibrillation.

Patent Claims

- 5 1) Process for preparing a suspension **4** of the polymorph I of the methanesulphonic acid salt of dabigatran etexilate of formula I



I

characterised in that

- 10 polymorph I of dabigatran etexilate methanesulphonate being characterised by a melting point of $T_{mp.} = 180 \pm 3^{\circ}\text{C}$ (determined by DSC; heating rate: $10^{\circ}\text{C}/\text{min}$) is suspended together with talc in a solution of hydroxypropylcellulose in isopropyl alcohol,

the preparation of the suspension being carried out at a temperature not exceeding 30°C by the

15 circulatory dispersal process.

- 2) Process according to claim 1, characterised in that first of all hydroxypropylcellulose is dissolved in isopropyl alcohol and then polymorph I of dabigatran etexilate methanesulphonate and talc are suspended in this solution.

20

- 3) Process according to claim 1 or 2, characterised in that 0.05 to 0.5 kg dabigatran etexilate methanesulphonate are used per kilogram of isopropyl alcohol put in.

- 4) Process according to one of Claims 1 to 3, characterised in that 0.01 to 0.1 kg
- 25 hydroxypropylcellulose are used per kilogram of isopropyl alcohol put in.

- 5) Process according to one of Claims 1 to 4, characterised in that 0.005 to 0.07 kg talc are used per kilogram of isopropyl alcohol put in.

- 30 6) Suspension **4**, obtainable by the process according to one of claims 1 - 5.

- 7) Suspension **4** according to claim 6, characterised in that the concentration of active substance is 10 - 25 % (w/w).

- 8) Suspension 4 according to claim 6 or 7, characterised in that the overall concentration of the constituents active substance, hydroxypropylcellulose and talc is 14 - 40 % (w/w).
- 5 9) Use of a suspension 4 according to one of claims 6 to 8 as starting material for preparing dabigatran etexilate methanesulphonate pellets 5.
- 10 10) Process for preparing dabigatran etexilate methanesulphonate pellets 5, characterised in that the suspension 4 according to one of Claims 6 to 8 is sprayed onto isolated tartaric acid cores 3 by the fluidised bed method.
- 11) Process for preparing dabigatran etexilate methanesulphonate pellets 5 according to claim 10, characterised in that the product temperature of the pellets 3 supplied is adjusted to 30-50°C.
- 15 12) Process for preparing dabigatran etexilate methanesulphonate pellets 5 according to claim 10 or 11, characterised in that the temperature of the supply air fed in is below 90°C, particularly preferably below 80°C, ideally in the range from 40°-80°C, particularly preferably between 55 and 75°C.
- 20 13) Process for preparing dabigatran etexilate methanesulphonate pellets 5 according to claim 10, 11 or 12, characterised in that the standardised spray rate at which the active substance suspension 4 is sprayed onto the tartaric acid pellets 3 is in the range from 4 - 45 g/min per kilogram of tartaric acid pellets 3 used.
- 25 14) Process for preparing dabigatran etexilate methanesulphonate pellets 5 according to claim 10, 11, 12 or 13, characterised in that the standardised amount of supply air according to the invention is preferably in the range from 10 - 35 (m³/h) per kilogram of tartaric acid pellets 3 used.
- 30 15) Dabigatran etexilate methanesulphonate pellets 5, obtainable by a process according to Claims 10 to 14.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/058900

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/16 A61K47/38 A61K31/4439		
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 practical, search terms used) EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☒ 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 September 2009		Date of mailing of the international search report 10/09/2009
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Fax: (+31-70) 340-3016		Authorized officer Schüle, Stefanie

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/058900

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2009/058900

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2009/058900

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18356642	
	Filing Date		2023-07-21	
	First Named Inventor	Pratibha S. PILGAONKAR		
	Art Unit			
	Examiner Name			
	Attorney Docket Number		70204.0018USC2	

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	Filing Date		2023-07-21	
	First Named Inventor	Pratibha S. PILGAONKAR		
	Art Unit			
	Examiner Name			
	Attorney Docket Number		70204.0018USC2	

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	Filing Date		2023-07-21
	First Named Inventor	Pratibha S. PILGAONKAR	
	Art Unit		
	Examiner Name		
	Attorney Docket Number		70204.0018USC2

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	Filing Date		2023-07-21
	First Named Inventor	Pratibha S. PILGAONKAR	
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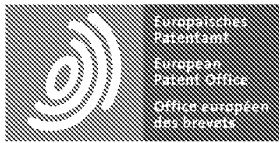
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Espacenet

CN102793699A Medicinal composition containing dabigatran etexilate

Applicants: YIDONG YAN

Inventors: YIDONG YAN

Classifications:

IPC **A61K31/4439; A61K47/22; A61P7/02;**

Priorities: CN201210276279A 2012-08-06

Application: CN201210276279A-2012-08-06

Publication: CN102793699A-2012-11-28

Published as: CN102793699A;**CN102793699B**

Medicinal composition containing dabigatran etexilate

Abstract

The invention relates to a medicinal composition containing dabigatran etexilate. The addition of vitamin C in the prescription can significantly improve the dissolution behavior of the dabigatran etexilate in vitro, wherein the ratio of the vitamin C and the active component dabigatran etexilate by weight, is 1:20-20:1; and through the techniques such as preparing pellets, compacting double-layer sheets of the vitamin C and the dabigatran etexilate respectively, and integrating the two substances into a same pellet one after the other, the two substances are coexistent but separated physically. According to the technique of the invention, double-layer tablets, pellet tablets, pellet (granule) capsules, etc. can be developed.



(12) 发明专利申请

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A1604

(72) 发明人 严轶东

(51) Int. Cl.

A61K 31/4439(2006.01)

A61K 47/22(2006.01)

A61P 7/02(2006.01)

权利要求书 1 页 说明书 5 页 附图 2 页

(54) 发明名称

一种含有达比加群酯的药用组合物

(57) 摘要

本发明涉及一种含有达比加群酯的药用组合物。处方中加入维生素C,可显著提高达比加群酯的体外溶出行为。维生素C与活性成分达比加群酯的重量比为1:20至20:1.可通过分别制备微丸、压制双层片、将两种物质先后整合到同一微丸等技术手段,实现两种成分的共存,但物理学分离。依照本发明说明的技术手段,可开发成双层片、微丸片、微丸(颗粒)胶囊等。

1. 本发明为一种含有达比加群酯的药用组合物,其特征在于,通过处方中整合加入维生素C,而显著促进所述活性成分的溶解和溶出。
2. 权利要求1所述的药用组合物,其特征在于,处方中整合加入的维生素C与药物活性成分的质量比为10 : 20至10 : 1。
3. 权利要求1所述的药用组合物,其特征在于,处方中整合加入的维生素C与药物活性成分的质量比优选为1 : 5至5 : 1。
4. 权利要求1所述的药用组合物,其特征在于,处方中整合加入的维生素C与药物活性成分实现物理学分离。
5. 权利要求2所述的药用组合物,其特征在于,实现物理学分离的途径包括分别制备微丸、压制双层片、将两种物质先后整合到同一微丸中等技术手段。
6. 权利要求1所述的药用组合物,其特征在于,该组合物可开发成双层片、微丸片、微丸(颗粒)胶囊。

一种含有达比加群酯的药用组合物

技术领域

[0001] 本发明涉及一种含有达比加群酯的药用组合物及其制备方法,处方中整合加入维生素 C,属于医药技术领域。

背景技术

[0002] 本发明所述的达比加群酯活性物质的化学结构为 3-[(2-[(4-[(己氧羰基氨基-亚氨基-甲基)-苯基氨基]-甲基)-1-甲基-1H-苯并咪唑-5-羰基)-吡啶-2-基-氨基]-丙酸乙酯。其化学结构如下所示。本化合物具有抑制凝血酶作用及延长该凝血酶时间的作用,它是一种前体药物,它在体内转化成为具有直接抗凝血活性的达比加群,主要适应症为手术后深静脉血栓形成的预防。

发明内容

[0003] 由于达比加群酯在 pH > 4.0 的介质中几乎不溶,故酸性环境有利于主要活性成分达比加群酯从药物制剂中溶出和体内吸收。专利(公开号 CN101632668A)披露:可采用医药上可接受的有机酸,如酒石酸、富马酸、琥珀酸、柠檬酸、苹果酸、谷氨酸或天冬氨酸作为达比加群酯溶解和溶出促进剂。该专利还披露了其口服给药制剂的制备方法。

[0004] 本发明人经过筛选发现:在达比加群酯药物制剂中,整合加入适量维生素 C,可显著促进达比加群酯的溶解和溶出,而且,可显著抑制氧化所致的达比加群酯降解产物的发生。

[0005] 但是,作为一种酸性物质,如果存在即使是少量的水,在长期储存期间,达比加群酯也会出现酸催化的酯键水解,从而导致产生多种降解产物。显然,这不利于药物制剂的稳定性。为克服此缺陷,必须保证达比加群酯和维生素 C 在制剂中保持物理学分离。

[0006] 在国外已上市的药物制剂中,采用的方法是在酸性物质层(酒石酸)和药物层(达比加群酯)之间施加隔离层,此可以是实现不相容物质物理学分离的手段之一。实现物理学分离的方法还包括分别制备微丸、压制双层片等。

[0007] 制备双层片、微丸片等剂型所用的辅料选自业内人士所熟知的辅料,包括但不限于填充剂、粘合剂、崩解剂、润湿剂、润滑剂、助流剂、薄膜衣材料、遮光剂、抗粘剂等。实现制剂生产的技术手段也是制药领域内常用的方法,如湿法制粒、干法制粒、流化床干燥、热风干燥等、微丸、片剂包衣、灌装、包装等。

具体实施方式

[0008] 通过以下实例来进一步说明通过维生素 C 来促进达比加群酯固体药物制剂的溶出和吸收,但并不仅限于以下实例。

[0009] 实施例 1 达比加群酯微丸胶囊或片

[0010] 微丸处方:

[0011]

组分	用量
达比加群酯甲磺酸盐	50g (以达比加群酯计)
维生素 C	150g
微晶纤维素	100g
低取代羟丙基纤维素	4g
羧甲基淀粉钠	8g
硬脂酸镁	2.5g
水	适量
共制成	1000 片

[0012] 包衣处方

[0013]

组分	用量
欧巴代包衣粉 (03K19229 型)	100g
纯化水	加至 1000ml

[0014] 制备方法：

[0015] 1. 达比加群酯甲磺酸盐载药微丸制备

[0016] 将达比加群酯甲磺酸盐、微晶纤维素、低取代羟丙基纤维素分别粉碎，过 100 目筛，混合均匀后，加入适量水制备软材，将该软材置入到挤出滚圆机内，挤成条状物后，置入到抛丸机中，抛丸，控制载药微丸水分，所得微丸可包或不包 HPMC 薄膜衣，备用；

[0017] 2. 维生素 C 微丸制备

[0018] 将维生素、余量微晶纤维素、余量低取代羟丙基纤维素分别粉碎，过 100 目筛，混合均匀后，加入适量水制备软材，将该软材置入到挤出滚圆机内，挤成条状物后，置入到抛丸机中，抛丸，控制载药微丸水分，备用；

[0019] 3. 微丸薄膜包衣

[0020] 取 03K19229 型胃溶欧巴代包衣粉，加水搅拌均匀，制成 10% 浓度的混悬液，即得隔离衣液。取达比加群酯甲磺酸盐含药丸芯于流化床包衣锅中，调节雾化压力和溶液喷速，控制丸芯温度为 30℃～45℃，进行流化床包隔离衣，增至一定量后（约 3%），于 30℃～45℃ 继续干燥 30 分钟，取样检测水分合格后过筛。

[0021] 4. 以上微丸可以直接按照比例混合，装入胶囊中，制得达比加群酯含药微丸胶囊。

[0022] 5. 也可取以上微丸，采用以下步骤制备得到微丸片。取微晶纤维素 PH200，与上述适量两种微丸混合，加入羧甲基淀粉钠、硬脂酸镁，压制微丸片剂。

[0023] 本发明采用丸心载药方式载入药物活性成分，但是，实际应用中，也可以采用空白丸心层积上药、药物混悬液喷雾上药等方式，均能实现类似目的。

[0024] 实施例 2 达比加群酯微丸胶囊或片

[0025] 处方：

[0026]

组分	用量
达比加群酯甲磺酸盐	100g (以达比加群酯计)
维生素 C	20g
微晶纤维素	400g
羧甲基淀粉钠	10g
乳糖	60g
交联聚维酮	8g
硬脂酸镁	7g
水	适量
共制成	1000 片

[0027] 包衣处方

[0028]

组分	用量
欧巴代包衣粉(03K19229 型)	100g
纯化水	加至 1000ml

[0029] 制备方法：

[0030] 1. 达比加群酯甲磺酸盐载药颗粒制备

[0031] 将达比加群酯甲磺酸盐、微晶纤维素分别粉碎，过 100 目筛，混合均匀后，加入适量水制软材，24 目筛制粒，干燥，24 目筛整粒，备用；

[0032] 2. 维生素 C 载药微丸制备

[0033] 将维生素 C、乳糖、微晶纤维素、交联聚维酮分别粉碎，过 100 目筛，混合均匀后，加入适量水制备软材，将该软材置入到挤出滚圆机内，挤成条状物后，置入到抛丸机中，抛丸，控制载药微丸水分，所得微丸可包或不包 HPMC 薄膜衣，备用；

[0034] 3. 微丸薄膜包衣（可选）

[0035] 取 03K19229 型胃溶欧巴代包衣粉，加水搅拌均匀，制成 10% 浓度的混悬液，即得隔离衣液。取含药丸芯于流化床包衣锅中，调节雾化压力和溶液喷速，控制丸芯温度为 30℃～45℃，进行流化床包隔离衣，增至一定量后（约 3%），于 30℃～45℃ 继续干燥 30 分钟，取样检测水分合格后过筛。

[0036] 4. 取步骤 1 所得达比加群酯甲磺酸盐载药颗粒和步骤 2 所得维生素 C 载药微丸，再加入微晶纤维素 PH200、羧甲基淀粉钠、硬脂酸镁，混合均匀后，压片，所得片剂可包衣或不包衣。

[0037] 5. 片剂薄膜包衣（可选）

[0038] 取 03K19229 型胃溶欧巴代包衣粉,加水搅拌均匀,制成 10%浓度的混悬液,即得隔离衣液。取含药片芯于流化床包衣锅中,调节雾化压力和溶液喷速,控制丸芯温度为 30℃~45℃,进行流化床包隔离衣,增至一定量后(约 2%),于 30℃~45℃继续干燥 30 分钟,取样检测水分合格后。

[0039] 6. 或将步骤 1 所得载药颗粒与步骤 2 所得维生素 C 载药微丸,加入微晶纤维素,羧甲基淀粉钠、硬脂酸镁,混合均匀后装胶囊,即得胶囊剂。

[0040] 实施例 3:达比加群酯甲磺酸盐与维生素 C 双层片

[0041] 处方:

[0042]

组分	用量
达比加群酯甲磺酸盐	100g (以达比加群酯计)
维生素 C	500g
微晶纤维素	260g
乳糖	60g
交联聚维酮	8g
硬脂酸镁	7g
水	适量
共制成	1000 片

[0043] 制备方法:

[0044] 1. 达比加群酯甲磺酸盐载药颗粒制备

[0045] 将达比加群酯甲磺酸盐、微晶纤维素分别粉碎,过 100 目筛,混合均匀后,加入适量水制软材,24 目筛制粒,干燥,24 目筛整粒,备用;

[0046] 2. 维生素 C 载药微丸制备

[0047] 将维生素 C、乳糖、微晶纤维素、交联聚维酮分别粉碎,过 100 目筛,混合均匀后,加入适量水制备软材,干燥,24 目筛整粒,备用;

[0048] 3. 将以上两种颗粒按照一定的比例混合,加入交联聚维酮、硬脂酸镁,混合均匀。

[0049] 4. 压片,在双层压片机上压制双层片剂

[0050] 实施例 4:维生素 C 的溶出促进作用考察

[0051] 为考察维生素 C 对达比加群酯甲磺酸盐溶出的促进作用,按照以上实施例 1-3 所述,制备得到受试样品,同时,采用相同的工艺,制备得到不含维生素 C 的各种制剂(仅含有达比加群酯甲磺酸盐,为避免其它因素造成的差异,减除的维生素 C 用量则用微晶纤维素替换,实施例 1 和 2 中仅选择胶囊剂型)。参考 FDA 的溶出度方法,依据达比加群酯剂型而选择溶出试验方法。胶囊剂的溶出试验条件如下:篮法,100rpm,溶出介质:0.01N HCl (pH2.0),溶出介质体积:900 分钟,取样时间:至 45 分钟。片剂的溶出试验方法如下:桨法,100rpm,溶出介质:0.01N HCl (pH 2.0),溶出介质体积:900 分钟,取样时间:至 45 分

钟。

[0052] 根据所得溶出数据,分别绘制溶出曲线图,予以比较。结果如下:

[0053]

		达比加群酯累积释放度 (%)				
		5min	10 min	15 min	30 min	45 min
实施例 1	维生素 C 空白	0.1	3.1	5.4	7.8	12.1
	含维生素 C	8.7	77.4	96.7	99.4	99.2
实施例 2	维生素 C 空白	0.2	5.6	8.6	12.4	15.2
	含维生素 C	4.7	47.8	70.4	85.2	95.5
实施例 3	维生素 C 空白	1.8	4.8	9.7	12.7	17.7
	含维生素 C	45.6	96.2	99.8	98.8	99.4

[0054] 以上结果为平均值, n = 6

[0055] 溶出曲线图如图 1、图 2、图 3 所示。

[0056] 从以上溶出度结果可以看出:处方中维生素 C 与药物活性成分的质量比在 1 : 5 至 5 : 1 范围内,维生素 C 对达比加群酯甲磺酸盐具有很好的溶出促进作用,而且,随着维生素 C 与药物活性成分的质量比的升高,其溶出更为迅速。这是由于维生素含量越高,溶出介质中维生素 C 浓度越大,从而酸度更强所致。

附图说明

[0057] 图 1,实施例 1 制剂溶出曲线比较

[0058] 图 2,实施例 2 制剂溶出曲线比较

[0059] 图 3,实施例 3 制剂溶出曲线比较。

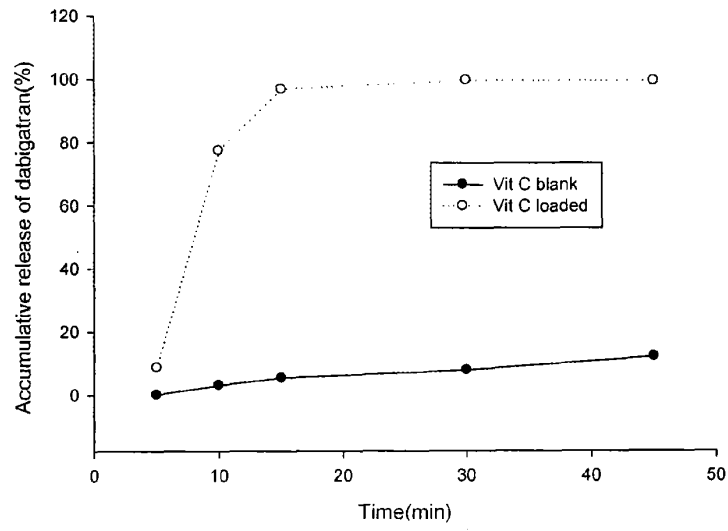


图 1

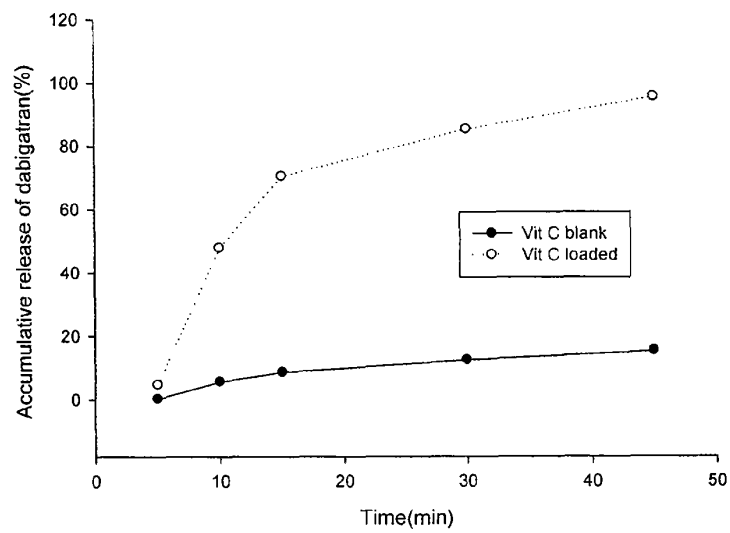


图 2

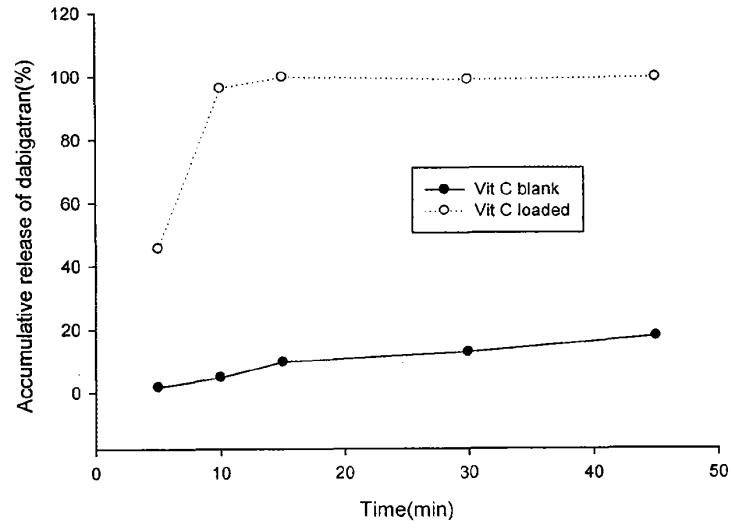


图 3



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Documents

TOTAL DOCUMENTS: 21

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
702040018USC2IDS2.pdf	5	Information Disclosure Statement (IDS) Form (SB08)	1012 KB
WO2012162492A1.pdf	44	Foreign Reference	5556 KB
WO2009118321A1.pdf	18	Foreign Reference	1914 KB
WO2010007016A1.pdf	24	Foreign Reference	2648 KB
CN102793699A1.pdf	10	Foreign Reference	870 KB
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(54) Title: COMPRESSED CORE COMPRISING ORGANIC ACIDS FOR A PHARMACEUTICAL COMPOSITION

(57) Abstract: 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 is described. 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. Also described are pharmaceutical compositions comprising such compressed core.

COMPRESSED CORE COMPRISING ORGANIC ACIDS FOR A PHARMACEUTICAL COMPOSITION

CROSS REFERENCE TO RELATED APPLICATIONS

5 This patent application claims the benefit of U.S. Provisional Patent Application No. 61/489,511 filed May 24, 2011, the disclosure of which provisional application is herein incorporated by reference.

FIELD OF THE INVENTION

10

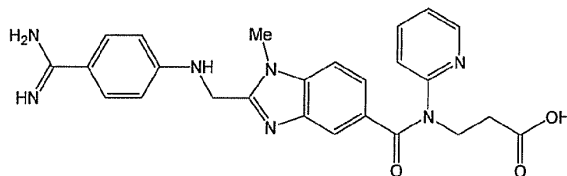
The present invention relates to compressed cores which can be used for pharmaceutical compositions and dosage forms. The compressed cores of the present invention contain an organic acid, and are particularly useful for the preparation of pharmaceutical compositions containing a drug in which dissolution of
15 the drug is favoured in acidic environments.

BACKGROUND OF THE INVENTION

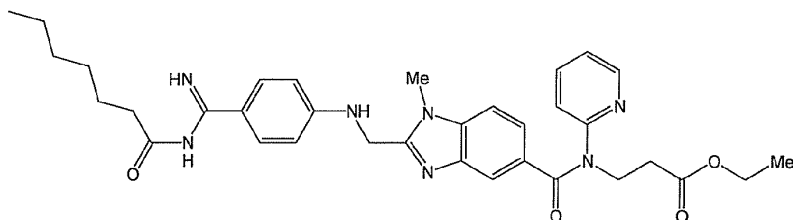
It is known that certain drugs, in particular weakly basic drugs and their salts,
20 demonstrate solubilities that are pH-dependent. In standard matrix formulations, such drugs show a decreased release from the matrix once the formulation enters the higher pH environment of the gastrointestinal tract. The result of this is an unacceptably low, and potentially incomplete, release of the drug from the formulation.

25

Dabigatran, which has the IUPAC name: 3({2-[(4-carbamimidoylphenylamino)methyl]-1-methyl-1H-benzimidazole-5-carbonyl}-pyridin-2-yl-amino)propionic acid, and having the formula:



30 is an example of a drug having such a pH-dependent release profile. Dabigatran in the form of its prodrug, dabigatran etexilate, having the formula:



is an orally administered benzamidine thrombin inhibitor and has activity as an anticoagulant. Dabigatran etexilate (3-[(2-{4-(hexyloxycarbonylaminoiminomethyl)phenylamino)methyl}-1-methyl-1H-benzimidazole-5-carbonyl]pyridine-2-yl-amino]propionate) has use for the prevention of thrombosis, particularly for post-operative deep vein thrombosis, such as in, e.g., hip and knee replacement surgery, and also for the prevention or reduction of risk of stroke and systemic embolism, particularly in patients with non-valvular atrial fibrillation.

10

Dabigatran is described in US 6,087,380. US 2010/0087488, US 2006/0247278 and US 2009/0042948 disclose various salts of dabigatran etexilate.

15

US 2005/0234104, US 2006/0276513, US 2008/0119523 and US 2010/0144796 describe various crystalline forms of dabigatran etexilate and its salts.

20

US 2005/0107438 describes dabigatran etexilate formulations in a dispersed form in an encapsulated lipophilic, pharmaceutically acceptable carrier system, which are said to provide oral formulations that are chemically and physically stable and have good bioavailability.

25

It is known that the solubility of weakly basic drugs, such as dabigatran and dabigatran etexilate, may be increased by the provision of an acidic environment. Hence, the provision of an acidic microenvironment at the intended site of drug release can increase the release rate from the dosage form.

30

For example, US 2005/0038077 describes a matrix tablet comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable organic acids and a pharmaceutically acceptable excipient or filler.

US 2003/0181488 describes oral formulations of dabigatran etexilate, which purport to provide pH-independent bioavailability of the active agent. The formulations contain a pharmaceutically acceptable organic acid having a water solubility of more than 1 g/250 ml at 20°C. The dosage forms are multiparticulate compositions containing pellets prepared by coating tartaric acid crystals of a specific particle size with a solution of tartaric acid dissolved in gum arabic. The coated crystals are sprinkled with powdered tartaric acid prior to screening to a specific size.

The disclosed formulation has disadvantages in particular because the process for its preparation is laborious as it requires several screening steps in order to achieve consistently sized particles for the encapsulated dosage form. Moreover, the multiple screening steps result in wastage of the starting materials and active substance, since the unsuitably sized particles at various stages of the process are discarded. Furthermore, the core preparation requires tartaric acid to be added in three different physical forms.

There is a continuing need to provide new and improved dosage forms of drugs having pH dependent solubilities, such as weakly basic drugs and their salts, including dabigatran. There is a further need to provide simplified and more cost effective processes for the preparation of the dosages forms of such drugs. The present invention addresses this need.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides 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, wherein the pharmaceutically acceptable organic acid is present in an amount of about 50-95% by weight of the core. The core can be used as a component of a multilayer pharmaceutical composition containing a drug having pH dependent solubility. In particular, upon dissolution of the pharmaceutical composition, the core provides an acidic microenvironment in order to facilitate the dissolution of the drug from the pharmaceutical composition.

In a second aspect, the invention provides a process for the preparation of the compressed core comprising:

- (i) admixing the pharmaceutically acceptable acid with the at least one pharmaceutically acceptable excipient to form a mixture, and
- (ii) direct compression of the mixture.

5 In a third aspect of the present invention, there is provided a pharmaceutical composition comprising the compressed core wherein the core is coated with a drug layer comprising a drug having a pH dependent solubility profile, wherein the solubility is greater at acidic pH (i.e. $\text{pH} < 7$), and at least one pharmaceutically acceptable excipient. The composition is preferably in the form of a mini tablet. The
10 mini tablets can be used to prepare a final dosage form, e.g. by encapsulation.

In a fourth aspect, the present invention provides a process for preparing the pharmaceutical composition comprising the compressed core, wherein the process comprises:

- 15 (i) preparing a compressed core by the above process,
- (ii) optionally applying a sub-coat layer over the compressed core,
- (iii) applying a drug layer over the compressed core or sub-coated compressed core, and
- (iv) optionally applying a protective top coat, an extended release coat or
20 a delayed release coat over the drug layer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A is a diagrammatic representation of a compressed core C in
25 accordance with one embodiment of the invention

Figure 1B shows a cross section through the compressed core of Figure 1A

Figure 2 is an enlarged photograph showing a capsule filled with subcoated
30 cores according to an embodiment of the present invention (right) prepared according to Example 3, compared with capsules filled with pellets, such those used in the marketed Pradaxa[®] capsules (left).

Figure 3 is an enlarged photograph showing sub-coated cores according to
35 the present invention (left) prepared according to Example 3, compared with pellets such as those used in Pradaxa[®] (right).

DETAILED DESCRIPTION OF THE INVENTION

5 As used herein, unless otherwise indicated, the term "drug having a pH dependent solubility" refers to a drug that has increased solubility when present in acidic environment (i.e. $\text{pH} < 7$). Typically, the drug has a pK_a in the range of from about 7 to about 14, preferably the pK_a is greater than 7 and less than 12, more preferably the pK_a is greater than 7 and less than 10.

10 As used herein, unless indicated otherwise, percentages refer to a weight percent. Weight percentages given in relation to the dosage form excludes the weight of any capsule shell.

15 As used herein, unless otherwise indicated, references to dabigatran includes references to enantiomers or prodrugs of dabigatran, such as dabigatran etexilate, as well as pharmaceutically salts (preferably mesylate, hydrochloride, maleate, tartrate, salicylate, citrate and malate salts, and particularly the mesylate salt), as well as solvates and hydrates of dabigatran, its enantiomers or prodrugs. The preferred form of dabigatran for any embodiment of the present invention is dabigatran etexilate,
20 preferably in the form of its mesylate salt.

In a first aspect, the present invention provides 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
25 acceptable excipient, wherein the pharmaceutically acceptable organic acid is present in an amount of about 50-95% by weight of the core.

The compressed core can be used in the preparation of pharmaceutical dosage forms of drugs that have a pH dependent solubility, in particular, drugs
30 having a solubilities that are enhanced in acid conditions. The compressed core contains a high concentration of the pharmaceutically acceptable organic acid that on one hand provides an effective acid microenvironment, whilst enabling the resulting dosage form to maintain a compact size, which is desirable for patient compliance. Moreover, the compressed core can be easily and economically manufactured.

35 The compressed core of the invention described in any embodiment of the present invention contains the pharmaceutically acceptable organic acid in a high

concentration, i.e. from about 50 to about 95 wt% of the core. Preferably, the pharmaceutically acceptable acid is present in the core in an amount of about 50 to about 90 wt% of the core, or about 50 to about 85% wt% of the core. Preferably, the pharmaceutically acceptable organic acid is present in an amount of greater than 50
5 wt% of the core. In particularly preferred embodiments, the pharmaceutically acceptable acid is present in an amount of about 60 to about 90 wt%, about 60 to about 85 wt%, about 70 to about 90 wt%, about 70 to about 85 w%, about 80 to about 85wt%, about 80 to about 90 wt%, or about 85%, by weight of the core.

10 In any embodiment of the present invention, the pharmaceutically acceptable organic acid in the compressed core is one which upon administration is capable of producing an acid microenvironment in the gastrointestinal tract (i.e. pH < 7, preferably pH < 5.5, more preferably pH < 5, or pH < 4. The pharmaceutically acceptable organic acid preferably has a pK_a of at least about 2, preferably wherein
15 the pharmaceutically acceptable organic acid has a pK_a of about 5.4 or less, preferably about 4 or less. The pharmaceutically acceptable organic acid preferably has a pK_a of at least about 2.5, preferably at least about 2.9. Particularly, the pharmaceutically acceptable organic acid has a pK_a of about 2.9 to about 5.4.

20 In any embodiment of the present invention, the pharmaceutically acceptable organic acid in the core has an aqueous solubility at 20°C of ≥ 4 grams/litre, particularly ≥ 6 grams/litre, and especially ≥ 10 grams/litre.

Suitable pharmaceutically acceptable organic acids include, but are not
25 limited to, fumaric acid, tartaric acid, citric acid, succinic acid, adipic acid, malic acid, maleic acid, lactic acid, or a mixture of one or more thereof. Of these, fumaric acid, tartaric acid, citric acid, and lactic acid are preferred. Tartaric acid, preferably L-tartaric acid is a preferred pharmaceutically acceptable acid in any embodiment of the present invention.

30 The present invention provides a core containing a pharmaceutically acceptable acid in the form of a compressed minitabiet having a predetermined and uniform size. The cores of the present invention are preferably free of the any pharmaceutically active agent, and contain only the pharmaceutically acceptable acid
35 and pharmaceutically acceptable excipients. Once coated with the drug, the uniformly sized core particles can be easily incorporated into a multiparticulate dosage form, e.g. by filling into a capsule or the like. At the same time, the cores of

the present invention enable a high concentration of the pharmaceutically acceptable acid whilst being surprisingly mechanically stable. For example, typically, the compressed core has a friability of about 0.1% or less, preferably about 0.1%-0.02%, and more preferably about 0.1% to 0.01%. When the cores are used to manufacture
5 a dosage form containing a drug having a pH dependent solubility, the cores dissolve and provide an acid microenvironment for the drug, thereby facilitating dissolution of the drug in the gastrointestinal tract.

Typically, pharmaceutically acceptable organic acids such as fumaric, tartaric,
10 citric, succinic, adipic and malic acids are difficult to compress when incorporated at high concentration. Tartaric acid in particular is not considered to be a highly compressible material. Indeed, in US 2003/0181488, highly concentrated cores containing a pharmaceutically acceptable acid are prepared using crystals of the pure acid, to which a layer containing binder and further acid are applied as a
15 solution by spray coating in a rotating pan. This method suffers from many disadvantages. In particular, at the outset, in order to achieve a narrow particle size range for the cores, the starting crystals of the acid are required to have a narrow particle size range. Moreover, several screening steps are required in order to maintain narrow particle size ranges during the processing of the cores into a dosage
20 form.

The applicant has surprisingly found that pharmaceutically acceptable organic acids, and especially tartaric acid, can be compressed into tablets having small dimensions (i.e. so-called "minitablets") by the inclusion of low concentrations of at
25 least one pharmaceutically acceptable excipient selected from the group consisting of a filler (diluent) and binder, and optionally a lubricant, or a dissolution enhancer. Preferably, the at least one pharmaceutically acceptable excipient selected from the group consisting of a filler (diluent) and binder, and optionally a lubricant. In particular, the pharmaceutically acceptable acid can be in any form, and need not
30 have a particular particle size range or particle size distribution. For example, the pharmaceutically acceptable acid can be in the form of a powder, or pellets. The pharmaceutically acceptable acid can be used directly without further steps (e.g. without a screening step). Preferably, the pharmaceutically acceptable excipient is a filler (diluent), or a mixture of a filler and a lubricant.

35

Suitable fillers (diluent) include microcrystalline cellulose (for example, Avicel PH102 having or PH101), lactose in its various forms (e.g. lactose USP, anhydrous

or spray dried), sorbitol, dextrose, sucrose, mannitol, dibasic calcium phosphate, starch, and mixtures thereof, including mixtures of starch and lactose. Preferred are microcrystalline cellulose (such as Avicel PH102 having a nominal mean particle size of 100 microns), lactose in its various forms (e.g. lactose USP, anhydrous or spray
5 dried), mannitol, dibasic calcium phosphate, starch, and mixtures thereof, including mixtures of starch and lactose. Of these, microcrystalline cellulose, mannitol, lactose, and starch, but particularly microcrystalline cellulose, lactose, and starch, are preferred. Microcrystalline cellulose is an especially preferred pharmaceutically acceptable excipient for use in the cores of the present invention.

10

Suitable binders include cellulose polymers, such as hydroxypropylmethyl cellulose, hydroxypropylcellulose, methylcellulose and hydroxyethyl cellulose, and polyvinylpyrrolidone and polyvinyl alcohol or mixtures thereof.

15

The core may optionally contain one or more lubricants. Examples of suitable lubricants include those selected from the group consisting of sodium stearyl fumarate, stearic acid, magnesium stearate, calcium stearate, zinc stearate, talc, glyceryl behenate, preferably sodium stearyl fumarate, magnesium stearate, calcium stearate and talc, and more preferably magnesium stearate or sodium stearyl

20

fumarate. Magnesium stearate is a particularly preferred lubricant.

As noted above, the pharmaceutically acceptable organic acid is present in a high concentration in the core, i.e. from about 50 to about 95 wt% of the core.

Preferably, the pharmaceutically acceptable acid is present in the core in an amount of about 50 to about 90 wt% of the core, or about 50 to about 85% wt% of the core.

Preferably, the pharmaceutically acceptable organic acid is present in an amount of greater than 50 wt% of the core. In particularly preferred embodiments, the

pharmaceutically acceptable acid is present in an amount of about 60 to about 90 wt%, about 60 to about 85 wt%, about 70 to about 90 wt%, about 70 to about 85

30 wt%, about 80 to about 85 wt%, about 80 to about 90 wt%, or about 85%, by weight of the core. Preferably the remainder is made up of the pharmaceutically acceptable

excipient component (b). Thus, component (b) is preferably present in an amount of about 5-50%, about 10-50%, about 15-50%, about 10-40%, about 15-40%, about 10-30%, about 15-30%, about 20-30%, about 15-20%, about 10-20%, or about 15% by

35 weight of the core.

In any of the above embodiments, a small quantity of lubricant may be added. For example, the lubricant may be present in the core in an amount of about 0.05 to about 2 wt%, preferably about 0.2 wt% to about 0.8 wt%, and more preferably about 0.3 to about 0.7 wt%, and particularly about 0.5 wt% (wt % are relative to the total weight of the core). A dissolution enhancer is generally included when a drug layer is applied. Therefore, when present, the dissolution enhancer is preferably present in an amount of 5-20%w/w of the core.

In any embodiment of the present invention, the weight ratio of the pharmaceutically acceptable acid (a) to the pharmaceutically acceptable excipient (b) in the core, is preferably about 1:1 to about 10 : 1, more preferably about 2 : 1, preferably about 4 : 1 to about 6 : 1. Thus, in a particularly preferred embodiment, the cores contain a pharmaceutically acceptable acid (a) in combination with a filler in a weight ratio of about 2 : 1, preferably about 4 : 1 to about 8 : 1. Optionally a lubricant may be included in a weight ratio of about 1 : 170 to about 1 : 200 relative to the total weight of components (a) and (b).

In particularly preferred embodiments, the compressed core consists essentially of a mixture of (a) in an amount of about 50-95 wt% of the pharmaceutically acceptable organic acid and (b) about 5-50 wt% (preferably about 10-20 wt%) of at least one pharmaceutically acceptable excipient. Preferably, in this embodiment, the pharmaceutically acceptable acid component (a) is typically present in an amount of about 60-95% by weight, and (b) is present in an amount of about 5-40% by weight of the core. More preferably, in this embodiment, the compressed core consists essentially of (a) in an amount of about 70-95% by weight, and (b) in an amount of about 5-30% by weight. Even more preferably, the compressed core consists essentially of (a) in an amount of about 80-90% by weight, and (b) in an amount of about 10-20% by weight. Preferably, in these embodiments, the pharmaceutically acceptable excipient consists essentially of a filler and optionally a lubricant, in concentrations (wt%) and weight ratios as discussed above. In these embodiments, the filler can be any of the fillers as described above, although microcrystalline cellulose (e.g. Avicel PH 102) is particularly preferred. In the cores of these embodiments, a small quantity of lubricant as described above (but preferably magnesium stearate), may be added – preferably the lubricant is present in an amount of about 0.2 wt% to about 0.8 wt%, and more preferably about 0.3 to about 0.7 wt%, and particularly about 0.5 wt% (all wt % are relative to the total weight of the core).

5 The compressed cores of the present application as described in any of the above embodiments may be prepared by a process comprising direct compression of a mixture comprising components (a) and (b) and other optional components when present.

10 The compressed cores of the present invention may be further characterised by the absence of an effervescent couple. Such couples are familiar to those skilled on the art as being capable of generating a gas such as carbon dioxide in order to cause the dosage form to fizz and effervesce thereby rapidly releasing the drug from the dosage form.

Thus, a second aspect of the invention provides a process for the preparation of the compressed core of any of the embodiments described herein comprising:

- 15 (i) -- admixing the pharmaceutically acceptable acid as described in any of the above embodiments with the at least one pharmaceutically acceptable excipient as described in any of the above embodiments, to form a mixture, and
- (ii) direct compression of the mixture.

20 The ingredients can be mixed or dry granulated prior to the compression step. The mixing or granulation is advantageously carried out without the use of any process solvent and/or soluble binder. For example, the ingredients for the core may be blended together using, e.g. a diffusion blender (optionally the lubricant, if present, is added after an initial blending step, followed by a further blending step

25 after addition of the lubricant).

Typically, mixture for the direct compression can contain about 0.02 to about 4 wt% water (which may be present in the excipients), about 0.1 to about 4% water, and preferably about 0.5 to about 3% water.

30 The compression is carried out without the addition of a liquid or solvent, i.e. by direct compression. Typically, the mixture is compressed into tablets using a rotary tablet press. The so-formed compressed cores are typically in the form of minitabets which can be used directly as a component of a multilayer pharmaceutical

35 composition or dosage form, i.e. without the need for a screening step.

The compressed cores of the present invention may be essentially cylindrical in shape, and have a diameter of the circular cross section of about 3 mm or less, or about 2 mm or less. Preferably, the cores have a diameter of at least about 1.6 mm. Preferably, the compressed core of any of embodiments described herein have a
5 diameter range of about 1.6 to about 3 mm, , about 1.6 to about 2.8 mm, particularly about 1.7 to about 2.5 mm and about 1.7 mm to about 2.3 mm, about 1.7 to about 2.1 mm, about 1.7 to about 2.0 mm, and particularly about 1.8 mm. The compressed core may also be spherical, or other shapes, depending on the die/punch used to carry out the compression. The spherical or other shaped compressed cores can
10 have the same diameter ranges as set out above.

For example, in a preferred embodiment as shown in Figure 1A, the compressed core C has a cylindrical shape, wherein the circular faces may be convex (shown) or may be flat. Typically, the compressed core has length L of about
15 1.2 mm to about 3 mm, preferably about 1.5 mm to about 2.5 mm and particularly about 2 mm. Figure 1B shows a cross-section through the compressed core of Figure 1A. The diameter $\varnothing$ of the circular cross section of the compressed core can have range of about 1.6 to about 3 mm, about 1.6 to about 2.8 mm, particularly about 1.7 to about 2.5 mm and about 1.7 mm to about 2.3 mm, about 1.7 to about 2.1 mm,
20 about 1.7 to about 2.0 mm, and particularly about 1.8 mm.

In preferred embodiments of the present invention, the compressed core comprises the pharmaceutically acceptable acid, particularly in an amount of 50 wt% to about 90 wt% relative to the weight of the core (preferably wherein the acid is
25 tartaric acid, particularly L-tartaric acid), a filler (particularly microcrystalline cellulose, and especially Avicel PH102), and a lubricant (preferably magnesium stearate). Preferred concentrations of these components in the core are discussed in the preceding passages.

30 The cores having the described sizes are particularly suitable for the preparation of minitables that can be encapsulated to produce the final dosage form, e.g. as a multiparticulate formulation, preferably in the form of encapsulated microtablets. In particular, the cores have a predetermined size and shape. Advantageously, the cores have a uniform size. As such, the use of multiple
35 screening operations during processing of the cores and the dosage form in order to obtain suitably sized core particles having a narrow size distribution is avoided. Therefore, the present process is advantageous as it enables the production of

uniformly sized cores, whilst avoiding the inevitable wastage from screening operations.

The cores of the present invention can be further processed into
5 pharmaceutical dosage forms by providing a layer containing an active agent over the core, e.g. by coating methods. Thus, in a further aspect, the present invention provides a pharmaceutical composition comprising the compressed core as described in any of the above embodiments, wherein the core is coated with a drug layer comprising a drug having a pH dependent solubility profile, wherein the
10 solubility is greater at acidic pH (i.e. $\text{pH} < 7$), and at least one pharmaceutically acceptable excipient.

Preferably, in any embodiment of the present invention, the drug layer comprises an active agent in combination with at least one pharmaceutically
15 acceptable excipient, preferably wherein the pharmaceutically acceptable excipient is selected from the group consisting of a binder, diluent, plasticizer and an anti-tacking (anti-adherent) agent, and mixtures thereof. Optionally, the drug layer comprises an active agent in combination with a binder, a plasticizer, an anti-tacking agent. The drug layer may comprise an active agent, in combination with a binder and an anti-
20 tacking agent. Preferably, the drug layer comprises an active agent, in combination with a binder without an anti-tacking agent. More preferably, the drug layer doesn't comprise talc. Additionally the drug layer may include a dissolution enhancer.

The active agent can be present in a high concentration in the drug layer.
25 Typically, the active agent can be present in a concentration of about 40 to about 90 wt%, about 50 to about 85 wt%, about 60 to about 80 wt%, and particularly about 70 to about 75 wt% relative to the weight of the drug layer. A high concentration of the active agent is desirable from the perspective of ensuring a smaller size of the dosage form.

30

The active agent in the drug layer is a drug that has a pH dependent solubility, in which the solubility of the drug is higher at lower pH. In particular the solubility increases at $\text{pH} < 7$. Typically, the drug has a pK_a in the range of from about 7 to about 14, preferably the pK_a is greater than 7 and less than 12, more
35 preferably the pK_a is greater than 7 and less than 10. Such drugs are weak bases, and include: dabigatran, dabigatran prodrugs (preferably dabigatran etexilate) or pharmaceutically acceptable salts thereof (e.g. dabigatran etexilate mesylate),

solvates or hydrates of dabigatran, dabigatran prodrugs and their pharmaceutically acceptable salts. The drug can also be selected from the group consisting of dipyridamole, aliskiren, fingolimod, and retigabin, and their pharmaceutically acceptable salts, as well as solvates and hydrates of these drugs or their

5 pharmaceutically acceptable salts. In any of the embodiments of the invention, the drug is preferably dabigatran, dabigatran prodrugs (preferably dabigatran etexilate) or pharmaceutically acceptable salts thereof (e.g. dabigatran etexilate mesylate), solvates or hydrates of dabigatran. Dabigatran etexilate mesylate is a particularly preferred drug in the pharmaceutical compositions of any embodiment of the

10 invention.

Suitable binders in the drug layer of the pharmaceutical composition of any embodiment of the present invention include any of the binders mentioned above for the core. For example, suitable binders include those selected from the group

15 consisting of cellulosic polymers such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl cellulose, gelatin, methyl cellulose, pregelatinized starch, acacia, alginic acid, sodium carboxymethyl cellulose gum arabic, polyvinyl pyrrolidone, polyvinyl alcohol, and copolymers of N-vinyl pyrrolidone and vinyl acetate or mixtures thereof. Hydroxypropylmethyl cellulose and

20 hydroxypropyl cellulose (e.g. Klucel LF), or mixtures thereof, are particularly preferred binders for the drug layer, with hydroxypropyl cellulose being especially useful.

In any embodiment of the present invention, the binder in the drug layer can

25 be present in a concentration of about 5 to about 30 wt%, about 5 to about 25 wt% and particularly about 10 to about 18 wt%, relative to the weight of the drug layer.

Preferably, in any embodiment of the present invention, the weight ratio of drug to binder in the drug layer is from about 10 : 1 to about 1 : 1, preferably about 8 :

30 1 to about 2 : 1 and more preferably about 6 : 1 to about 4 : 1.

Suitable plasticizers in the drug layer of the pharmaceutical composition of any embodiment of the present invention can include polyethylene glycol (particularly polyethylene glycol 400), triethyl citrate, tributyl citrate, glycerin, dibutyl sebacate,

35 triacetin and diethylphthalate. Particularly preferred are polyethylene glycol, triethyl citrate, tributyl citrate, dibutyl sebacate, triacetin and diethyl phthalate, or mixtures thereof.

In any embodiment of the present invention, where present in the drug layer, the plasticizer may be present in the drug layer in a concentration of about 2 to about 25 wt%, about 5 to about 15 wt% or about 8 to about 12 wt% relative to the weight of the drug layer.

In any embodiment of the present invention, an anti-tacking agent (anti-adherent) may be included in the drug layer. The anti-tacking agent can include magnesium carbonate, titanium dioxide, microcrystalline cellulose, polyethylene glycol, colloidal silica, corn starch and talc, or mixtures thereof. Talc (especially extra fine talc) is a particularly preferred anti-tacking agent.

Where present in the drug layer, the anti-tacking agent can be employed in a concentration range of about 5 wt% to about 25 wt%, about 8 wt% to about 20 wt%, or about 10 wt% to about 18 wt% relative to the weight of the drug layer.

When present, the dissolution enhancer is preferably present in an amount of 5-20%w/w of the layer or region it is present in i.e. of the core, drug layer or sub-coating layer. Preferably the dissolution enhancer is a pore former contained in the drug layer, preferably such that the weight ratio of dissolution enhancer to drug is from about 1:20 to about 10:1. For example, in the case of a drug-layer containing 150 mg Dabigatran, the preferred amount of a pore-former is from about 3 mg to about 50 mg.

In a particularly preferred embodiment, the drug layer is composed of the active agent as described in any of the above embodiments (e.g. dabigatran, its prodrugs, or pharmaceutically acceptable salts, solvates and hydrates thereof, such as dabigatran etexilate mesylate), in combination with a binder as described above (e.g. a cellulose polymer such as the hydroxyalkyl celluloses including hydroxypropylmethyl cellulose, hydroxypropyl cellulose) and an anti-tacking agent (preferably talc). The concentrations of these components are as set out in the preceding passages.

The drug layer may be applied to the compressed cores as described in any of the embodiments herein by any coating procedure, including by fluid-bed coater, by pan-coating or by spray coating. Preferably, the drug layer and/or the subcoat layer are applied to the compressed cores by pan-coating. Pan-coating is much

more simple, energy efficient and cheaper coating process. Typically, the ingredients for the drug layer are mixed together in, e.g. C₁₋₃ alcohols such as ethanol, isopropanol, or mixtures thereof, and optionally in combinations of the alcohol with purified water to form a coating solution, which can be applied by the above coating methods. Since the cores are of uniform size, there is no need for a screening step following the drug-layer coating step in order to obtain uniform particles.

In certain embodiments of the pharmaceutical compositions of the present invention, it may be preferable to include a subcoat layer between the core containing the pharmaceutically acceptable acid and the drug layer. The inclusion of a subcoat layer is particularly useful for providing a physical barrier to protect certain active agents, including dabigatran, from undesirable interactions with the acid in the core.

When present, the subcoat layer may comprise at least one pharmaceutically acceptable excipient selected from one or more of the group consisting of binder (preferably wherein the binder is a water-soluble polymer), anti-tacking agent, surfactant (emulsifier), dissolution enhancer and plasticizer. The subcoat layer preferably comprises at least one pharmaceutically acceptable excipient selected from one or more of the group consisting of binder (preferably wherein the binder is a water-soluble polymer), anti-tacking agent, surfactant (emulsifier), and plasticizer. Optionally, the subcoat layer does not comprise an anti-tacking agent. In particular, the subcoat layer doesn't comprise talc. Optionally, the sub-coat layer can include a further amount of a pharmaceutically acceptable organic acid such as those described above in the context of the core.

The binder in the subcoat layer may be selected from those binders listed above for the drug layer. Thus, suitable binders for the subcoat layer include cellulosic polymers such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl cellulose, gelatin, methyl cellulose, pregelatinized starch, acacia, alginic acid, sodium carboxymethyl cellulose gum arabic, polyvinyl pyrrolidone, polyvinyl alcohol, and copolymers of N-vinyl pyrrolidine and vinyl acetate, or a mixture thereof. Of these, the cellulosic polymers, e.g. hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl cellulose and methyl cellulose are preferred. Hydroxypropylmethyl cellulose (e.g. HPMC 2910), hydroxypropyl cellulose, hydroxyethyl cellulose and ethyl cellulose or mixtures thereof, are particularly preferred binders for the subcoat layer. Preferably

the binders for the subcoat are hydroxypropylmethyl cellulose and ethyl cellulose or a combination thereof.

5 The binder is typically present in the subcoat layer in a concentration of about 20 to about 95 wt%, about 30 to about 90 wt%, or about 40 to about 90 wt%, relative to the weight of the subcoat layer.

10 Where present in the subcoat layer, the anti-tacking agent can be any of the anti-tacking agents employed in the drug layer. Thus, for example, the anti-tacking agent may include magnesium carbonate, titanium dioxide, microcrystalline cellulose, polyethylene glycol (particularly polyethylene glycol 6000), colloidal silica, corn starch and talc or mixtures thereof. Talc is a particularly preferred anti-tacking agent.

15 Where present in the subcoat layer, plasticizer can be any of the plasticizers employed in the drug layer. Examples of these include polyethylene glycol (particularly polyethylene glycol 400), triethyl citrate, tributyl citrate, glycerin, dibutyl sebacate, triacetin and diethylphthalate. Particularly preferred are polyethylene glycol, triethyl citrate, tributyl citrate, dibutyl sebacate, triacetin and diethyl phthalate, or mixtures thereof, and especially polyethylene glycol and dibutyl sebacate, or a
20 combination thereof.

Typically, the plasticizer may be employed in the subcoat in a concentration of about 5 to about 30 wt%, about 5 to about 20 wt%, or about 8 to about 14 wt%, relative to the weight of the subcoat.

25

Where present in the subcoat, the surfactant or emulsifier is preferably selected from benzalkonium chloride, cetyl alcohol, polysorbate 80, sodium lauryl sulfate and sorbitan esters including sorbitan mono-palmitate or mixtures thereof, and particularly cetyl alcohol or sodium lauryl sulfate, or a combination thereof.

30

The surfactant may be employed in low concentrations, for example about 0.05 to about 6 wt%, typically about 0.1 to about 1 wt% or about 0.2 wt% to about 0.5 wt%.

35 An especially suitable ready-made subcoat in the form of Opadry clear (Colorcon), which contains hypromellose 15 cPS (HPMC 2910), ethyl cellulose

10 cPs, polyethylene glycol 400, dibutyl sebacate, cetyl alcohol and sodium lauryl sulfate.

A dissolution enhancer is generally included when a drug layer is applied.

- 5 Therefore, when present, the dissolution enhancer is preferably present in an amount of 5-20%w/w of the sub-coating layer.

The subcoat layer may be applied in a similar manner to the drug layer. For example the ingredients for the subcoat layer can be mixed together in, e.g. C₁₋₃

- 10 alcohols such as ethanol, isopropanol, or mixtures thereof, and optionally in combinations of the alcohol with purified water, to form a coating solution, which can be applied by the various coating methods as discussed above for the drug layer (e.g. using fluid bed coater).

- 15 In any embodiment of the pharmaceutical compositions described herein, the drug layer may be provided with a further coating. This further coating may be a protective top coat, or a top coat that provides particular release properties, e.g. a extended-release coat or a delayed-release coat, as appropriate for the drug and dosage form.

20

The protective top coat can include a binder, an anti-tacking agent and a plasticizer.

Suitable binders, anti-tacking agents and plasticizers, include those described above for the drug layer or the subcoat layer. The binder can be any of those mentioned including the preferred agents described above in relation to the drug layer or subcoat layer. The binder may be present in the top coat in an amount of about 20 to about 60 wt%, about 30 to about 60 wt%, or about 40 to about 50 wt% relative to the weight of the top coat. The anti-tacking agent can be any of those

- 25 mentioned including the preferred agents described above in relation to the drug layer or subcoat layer. The anti-tacking agent may be present in the top coat in an amount of about 20 to about 60 wt%, about 30 to about 60 wt%, or about 40 to about 50 wt% relative to the weight of the top coat. The plasticizer can be any of those mentioned including the preferred agents described above in relation to the drug layer or subcoat layer. The plasticizer may be present in the top coat in an amount of about 2 to about 40 wt%, about 5 to about 20 wt%, or about 8 to about 12 wt% relative to the weight of the top coat. Particularly preferred is a top coat comprising
- 30
- 35

hydroxypropylmethyl cellulose (especially HPMC 2910), talc and polyethylene glycol (particularly PEG 400).

- As to extended-release coating, this may comprise an extended-release
- 5 polymer, a binder, and a plasticizer. The plasticizer component can be any of the plasticizers mentioned above for the drug layer or the subcoat, and thus includes polyethylene glycol (particularly polyethylene glycol 400), triethyl citrate, tributyl citrate, glycerin, dibutyl sebacate, triacetin and diethylphthalate. Particularly preferred are polyethylene glycol, triethyl citrate, tributyl citrate, dibutyl sebacate,
- 10 triacetin and diethyl phthalate, or mixtures thereof, and especially triethyl citrate. Preferably, the plasticizer can be used in a concentration of about 2 to about 30 wt%, about 5 to about 20 wt%, or about 10 to about 18 wt%, relative to the weight of the extended release coating.
- 15 The binder component can be any of the binders mentioned above for the drug layer or the subcoat, and is preferably selected from the group consisting of cellulosic polymers such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl cellulose, gelatin, methyl cellulose, pregelatinized starch, acacia, alginic acid, sodium carboxymethyl cellulose gum arabic, polyvinyl
- 20 pyrrolidone, polyvinyl alcohol, and copolymers of N-vinyl pyrrolidine and vinyl acetate, or a mixture thereof. Cellulosic polymers, and preferably hydroxypropylmethyl cellulose, hydroxypropyl cellulose and hydroxyethyl cellulose are preferred. Hydroxypropylmethyl cellulose (e.g. HPMC 2910) is especially preferred. The binder is preferably present in a concentration of about 2 to about 30
- 25 wt%, preferably about 5 to about 25 wt%, and particularly about 10 to about 20 wt%, relative to the weight of the extended-release coating.

- Typically the extended-release polymer can selected from the group consisting of ethyl cellulose (e.g. ethylcellulose having a viscosity of about 4 to about
- 30 10 cPs, preferably about 5 to about 9 cPs, and more preferably about 7 cPs), hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA; vinyl alcohol polymer), polymethacrylates, ethyl acrylate-methyl methacrylate copolymers (such as Eudragit RS), hydroxypropyl cellulose (HPC) or a mixture thereof. Preferably, the extended-release polymer is ethylcellulose (such as ethylcellulose having a viscosity
- 35 of about 4 to about 10 cPs, preferably about 5 to about 9 cPs, and more preferably about 7 cPs). The extended-release polymer can be present in a concentration of

about 20 to about 85 wt%, about 40 to about 80 wt%, or about 55 to about 70 wt% relative to the weight of the extended release coating.

5 A suitable delayed release coating may comprise an enteric polymer, a plasticizer and an anti-tacking agent.

Suitable enteric polymers include methacrylate copolymers (e.g. Eudragit L30 D55 – an anionic polymethacrylate), hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate and polyvinylacetate phthalate. The enteric polymer can be used in a concentration of from about 20 to about 85 wt%, about 40 to about 80 wt%, or about 55 to about 70 wt% relative to the weight of the delayed release coating.

15 Suitable anti-tacking agents can include magnesium carbonate, titanium dioxide, microcrystalline cellulose, polyethylene glycol, colloidal silica, corn starch and talc, or mixtures thereof, and preferably talc.

The plasticizer component of the delayed release coating can be any of the plasticizers mentioned above for the drug layer or the subcoat, and thus includes polyethylene glycol (particularly polyethylene glycol 400), triethyl citrate, tributyl citrate, glycerin, dibutyl sebacate, triacetin and diethylphthalate. Particularly preferred are polyethylene glycol, triethyl citrate, tributyl citrate, dibutyl sebacate, triacetin and diethyl phthalate, or mixtures thereof, and especially triethyl citrate. Preferably, the plasticizer can be used in a concentration of about 2 to about 30 wt%, about 5 to about 15 wt%, or about 7 to about 12 wt% relative to the weight of the delayed release coating.

30 The top coat, extended release coat and the delayed release coat can be applied by the coating procedures described above for the drug layer and the subcoat.

As used above, the term "dissolution enhancer" refers to any excipient that has the ability to function in such a manner. In particular, pore formers, osmotic agents, surfactants and disintegrants are included as suitable dissolution enhancers. Unless explicitly stated otherwise, the dissolution enhancer is present in an amount of from 5-20%w/w of the layer or region it is present in i.e. of the core, drug or su-coating layer.

Preferably, the dissolution enhancer is a pore former such as polyethylene glycol with molecular weight of 200-8000g/mol, lactose or lactose monohydrate, mannitol, sodium chloride, triethyl citrate, low viscosity polyvinyl alcohol, dibasic calcium phosphate and talc. Alternatively, the dissolution enhancer may be a disintegrant such as croscopovidone, croscarmellose sodium, low substituted hydroxypropyl cellulose and sodium starch glycolate in an amount of about 0.5-8%, 1-7%, preferably 2-5% by weight of the total composition.

10 The dissolution enhancer is preferably a pore former. The pore former is preferably a water soluble pharmaceutical excipient which is mixed with at least one polymeric film former (such as the binder discussed above) and optionally with additional component, which can be the drug (if in the drug layer) or excipient, to form a film. The pore former increases the porosity, and thereby the solubility of the
15 resulted film. The preferred ratio between the pore-former and the film-former is from about 1:20 to about 10:1. Preferably the pore former is contained in the drug layer. When the drug layer comprises a pore former, the pore former is in an amount of about 5-20%w/w of the total drug-layer composition. For example, in the case of a drug-layer containing 150 mg Dabigatran, the preferred amount of a pore-former is
20 from about 3 mg to about 50 mg.

According to a further aspect of the present invention, there is provided a process for preparing the pharmaceutical composition as described in any of the above embodiments, comprising
25 (i) preparing a compressed core as described above,
(ii) optionally applying a sub-coat layer over the compressed core,
(iii) applying a drug layer over the compressed core or sub-coated compressed core, and
(iv) optionally applying a protective top coat, an extended release coat or
30 a delayed release coat over the drug layer.

The components of the compressed core, sub-coat layer, drug layer, top coat, extended release coat and delayed release are as discussed in any of the embodiments described above.

35 As the compressed cores can be made to a predetermined and uniform particle size, the cores are particularly suitable for the preparation of multiparticulate

dosage forms of drugs having pH dependent solubility release as discussed above particularly in the form of capsules containing drug-coated minitables. The compressed cores are particularly useful for preparing pharmaceutical compositions of a drug selected from the group consisting of dabigatran, dabigatran prodrugs (preferably dabigatran etexilate) or pharmaceutically acceptable salts thereof (e.g. dabigatran etexilate mesylate), as well as dipyridamole, aliskiren, fingolimod, and retigabin, and their pharmaceutically acceptable salts. In particular, these drugs are characterised by having a pH dependent solubility, i.e. increasing solubility with decreasing pH.

10

Thus, in a further aspect, the present invention provides a multiparticulate dosage form, comprising a plurality of coated cores as defined in any of the embodiments described above. The multiparticulate dosage form can be in the form of capsules filled with the coated cores. The coated cores are typically in the form of minitables having an essentially cylindrical shape (e.g. similar to the compressed cores shown in Figures 1A and 1B). The circular surfaces at each end of the cylinder shape may be convex. The coated cores may have other shapes depending on shape of the compressed core as discussed above. For example, the coated cores can be spherical or other shapes. The circular cross section diameter and length of the coated cores will be slightly larger than the diameter $\varnothing$ and length L of the cores (as shown in Figures 1A and 1B) due to the presence of the coating(s). Preferably, the coated cores have a circular cross section diameter of greater than about 1.6 mm or more, at least about 1.8 mm or more, preferably about 1.6 to about 4 mm, about 2 to about 4 mm, about 2 to about 3 mm, or about 2.4 to about 2.6 mm. Preferably the coated cores have a length of about 2.4 to about 4 mm more preferably, 2.6 to about 3.5 mm and most preferably 2.8. In the case of spherical or other shaped cores, the diameters correspond to the diameters ranges of the circular cross section of the cylindrical cores as set out above. The coated cores (e.g. minitables) are typically larger in size compared with the approximately spherical pellets used in the formulation of dabigatran etexilate marketed under the name Pradaxa® (Figures 2 and 3), which is believed to be manufactured according to the rotating pan-coating process described in US 2003/0181488. In view of their larger size and excellent size uniformity, the tablets of the present invention are easier to fill into capsules for a final dosage form.

35

In particular, in accordance with a further aspect of the present invention, there is provided a process for preparing a pharmaceutical dosage form comprising

filling the pharmaceutical composition according to any embodiment of the invention (e.g. the minitables), or a plurality thereof, into a capsule, preferably wherein the capsule is a hard gelatin capsule or hydroxypropylmethyl cellulose capsule.

5 Moreover, the present invention provides the coated cores containing the drug and the acid in a concentrated form, which enables the cores to be filled into smaller capsules whilst retaining the dosage size, which reduces the problems associated with large dosage forms (e.g. difficulty in swallowing, and hence poor patient compliance).

10

The invention is illustrated by the following examples, which do not limit the scope of the invention. It will be appreciated that various modifications are within the spirit and scope of the invention.

15 Examples

Example 1 (Tartaric acid tablet cores containing tartaric acid powder)

20 L-tartaric acid and microcrystalline cellulose were combined into a blend using a diffusion blender for 5 min. The mixture obtained was then blended with magnesium stearate for additional 3 min. The final mixture was compressed into 1.8 mm tablets (i.e. cylindrical cores wherein the circular cross section is 1.8 mm in diameter) by a rotary tablet press. A batch size of 24,000 tablets was produced with good yield.

25

Table 1 summarizes the composition of the tablets of Example 1:

Table 1. Formulation of tablets of Example 1 by weight	
Component	mg/tab
Tartaric acid powder 75-300 μ m	6.37
Microcrystalline cellulose (Avicel PH 102)	1.09
Magnesium stearate	0.04
Total weight	7.50

30

Example 2 (Tartaric acid tablet cores containing tartaric acid pellets)

Table 2 summarizes the composition of the tablets of Example 2, prepared in a procedure similar to the one described in Example 1:

5

Table 2. Formulation of tablets of Example 2 by weight	
Component	mg/tab
Tartaric acid pellets 400-600 μ m	6.37
Microcrystalline cellulose (Avicel PH 102)	1.09
Magnesium stearate	0.04
Total weight	7.50

Example 3 (Tartaric acid tablet cores coated with hypromellose sub coat)

The tartaric acid cores prepared according to example 1 were coated by a 10% w/w isolating layer, its composition is described in Table 3.

10

The coating was carried out using a small scale pan-coater (7000 tablets/batch)

Table 3. Formulation of tablets of Example 3 by weight	
Component	mg/tab
Core	
Tartaric acid cores (Example 1)	7.50
Coating	
Hypromellose 6 cPs (HPMC 2910)	0.364
Talc extra fine	0.364
Polyethylene Glycol 400	0.082
Ethanol 95% (*)	
Total weight	8.31

(*) Removed during process

15

Figures 2 (capsule on the right) and Figure 3 (capsule on the left) show a comparison of the sub-coated cores prepared according to this process, with the marketed Pradaxa[®] capsules (left in Figure 2 and right in Figure 3)

20

Example 4 (Tartaric acid tablet cores coated with hypromellose sub coat)

The tartaric acid cores prepared according to example 2 were coated by a 10% w/w isolating layer, its composition is described in Table 4.

5

The coating was carried out using a small scale fluid-bed coater (7000 tablets/batch)

<u>Table 4. Formulation of tablets of Example 4 by weight</u>	
<u>Component</u>	<u>mg/tab</u>
<u>Core</u>	
Tartaric acid cores (Example 2)	7.50
<u>Coating- Opadry Clear 21F29126</u>	
Hypromellose 15 cPS (HPMC 2910)	0.575
Ethyl cellulose 10 cPs	0.146
Polyethylene Glycol 400	0.085
Dibutyl Sebacate	0.002
Cetyl Alcohol	0.002
Sodium Lauryl Sulfate	0.001
Ethanol 95% (*)	
Total weight	8.31

(*) Removed during process

10 Example 5 (Tartaric acid tablet cores coated with hypromellose sub coat and a drug layer of Dabigatran ethexilate)

The tartaric acid cores prepared according to example 3 are coated with a 55% w/w drug layer, its composition is described in Table 5.

15

The coating is carried out using a medium-scale pan-coater (70000 tablets/batch)

<u>Table 5. Formulation of tablets of Example 5 by weight</u>	
<u>Component</u>	<u>mg/tab</u>
<u>Core + Subcoat</u>	
Tartaric acid cores (Example 1)	7.50
Subcoat (Example 3)	0.81
<u>Coating-drug layer</u>	

Dabigatran etexilate mesylate (d(0.9) LT 50 um) (*)	7.21
Hydroxypropyl cellulose (Klucel LF)	1.45
Talc extra fine	1.43
Isopropyl Alcohol (**)	
Total weight	18.40

(*) 24 tablets contain 173.0 mg Dabigatran etexilate mesylate, which are equivalent to 150 mg Dabigatran etexilate

(**) Removed during process

5 Example 5a (Tartaric acid tablet cores coated with hypromellose sub coat and a drug layer of Dabigatran ethexilate without talc)

The tartaric acid cores prepared according to example 2 were coated by an isolating layer according to example 3 and further coated with a drug layer, its composition is described in Table 5a:

10

The coating was carried out using a medium-scale pan-coater (70000 tablets/batch)

<u>Table 5a. Formulation of tablets of Example 5a by weight</u>	
<u>Component</u>	<u>mg/tab</u>
<u>Core + Subcoat</u>	
Tartaric acid cores (Example 2)	7.50
Subcoat (Example 3)	0.81
<u>Coating-drug layer</u>	
Dabigatran etexilate mesylate (d(0.9) LT 50 um) (*)	7.21
Hydroxypropyl cellulose (Klucel LF)	1.45
Isopropyl Alcohol (**)	
Total weight	16.97

(*) 24 tablets contain 173.0 mg Dabigatran etexilate mesylate, which are

15 equivalent to 150 mg Dabigatran etexilate

(**) Removed during process

Example 6 (Tartaric acid tablet cores coated with hypromellose sub coat, a drug layer of Dabigatran etexilate and a top- coat)

- 5 The tartaric acid cores prepared according to example 5 are coated with an 8% w/w top-coat; its composition is described in Table 6.

The coating is carried out using a medium-scale pan-coater (70000 tablets/batch).

Table 6. Formulation of tablets of Example 6 by weight	
Component	mg/tab
Core + Subcoat + Drug Layer	
Tartaric acid cores (Example 1)	7.50
Subcoat (Example 3)	0.81
Drug Layer (Example 5)	10.09
Top-Coating layer	
Hypromellose 6 cPs (HPMC 2910)	0.72
Talc extra fine	0.72
Polyethylene Glycol 400	0.16
Ethanol 95% (*)	
Total weight	20.00

- 10 (*) Removed during process

Example 7 (Tartaric acid tablet cores coated with hypromellose sub coat, a drug layer of Dabigatran ethexilate and an extended release coat)

- 15 The tartaric acid cores prepared according to example 5 are coated with a 17% w/w extended release layer; its composition is described in Table 7.

The coating is carried out using a medium-scale pan-coater (70000 tablets/batch).

Table 7. Formulation of tablets of Example 7 by weight	
Component	mg/tab
Core + Subcoat + Drug Layer	
Tartaric acid cores (Example 1)	7.50
Subcoat (Example 3)	0.81
Drug Layer (Example 5)	10.09
Coating - extended release layer	
Ethylcellulose 7 cPs	2.58
Hypromellose 6 cPs (HPMC 2910)	0.56
Triethyl Citrate	0.56
Ethanol 95% (*)	
Isopropyl Alcohol (*)	
Purified water (*)	
Total weight	22.10

(*) Removed during process

Example 8 (Tartaric acid tablet cores coated with hypromellose sub coat, a drug layer of Dabigatran etexilate and an delayed release coat)

5

The tartaric acid cores prepared according to example 5 are coated with a 17% w/w delayed release layer; its composition is described in Table 8.

The coating is carried out using a medium-scale pan-coater (70000 tablets/batch).

10

Table 8. Formulation of tablets of Example 8 by weight	
Component	mg/tab
Core + Subcoat + Drug Layer	
Tartaric acid cores (Example 1)	7.50
Subcoat (Example 3)	0.81
Drug Layer (Example 5)	10.09
Coating- delayed release layer	
Eudragit L-30 D55 (Anionic polymethacrylate)	2.32
Triethyl Citrate	0.33
Talc Extra fine	1.05
Purified water *	

Total weight	22.10
--------------	-------

(*) Removed during process

Example 9 (Encapsulated Tartaric acid tablet cores coated with hypromellose sub coat and a drug layer of Dabigatran Etexilate)

5

The tartaric acid cores prepared according to example 5 are encapsulated into hard-gelatin or hydroxypropylmethyl cellulose capsules using conventional encapsulation machine equipped with an appropriate filling disk according to Table 9:

Table 9. Final capsules of current invention			
Strength (DE)	Fill weight [mg]	Capsule size	# of Coated Tablets/Cap
75 mg	220.8	3	12
150 mg	441.6	1	24

10

Example 10 - Reference Example (Encapsulated commercial pellets)

The capsules described in Example 9 are expected to be bio-equivalent to the commercial drug-layer containing pellets, Pradaxa[®], which can be described by

15 Table 10:

Table 10. Final capsules of PRADAXA[®]			
Strength (DE)	Fill weight [mg]	Capsule size	# of Coated Pellets/Cap
75 mg	215	2	Ca 250
150 mg	430	0	Ca 500

Example 11 – Suitability of Tartaric Acid for Compression

20 The Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed.

The compressibility index and Hausner ratio may be calculated (USP 35–NF 30, General Chapters: <1174> POWDER FLOW:) using measured values for bulk

25 density (P_{bulk}) and tapped density (P_{tapped}) as follows:

$$\text{Compressibility Index} = 100 \times [(P_{\text{tapped}} - P_{\text{bulk}})/P_{\text{tapped}}]$$

$$\text{Hausner Ratio} = (P_{\text{tapped}}/P_{\text{bulk}})$$

5

Alternatively, the compressibility index and Hausner ratio may be calculated by measure (1) the unsettled apparent volume, V_o , and (2) the final tapped volume, V_f , of the powder after tapping the material until no further volume changes occur.

10 The compressibility index and the Hausner ratio are calculated as follows:

$$\text{Compressibility Index} = 100 \times [(V_o - V_f)/V_o]$$

$$\text{Hausner Ratio} = (V_o/V_f)$$

15 By measuring bulk density and tapped density it has been shown that it was not trivial to compress both the tartaric acid pellets and the tartaric acid powder:
85% tartaric acid powder/15% microcrystalline cellulose (Avicel PH102)

	85% tartaric acid powder/15% microcrystalline cellulose (Avicel PH102) R-07506	85% tartaric acid pellets/15% microcrystalline cellulose (Avicel PH102) K-45625
	g/ml	g/ml
Bulk Density	0.75	0.75
Tapped Density	0.88	0.88
Hausner Ratio	1.17	1.17
Carr Index	14.77%	14.77%

20

Claims

1. A compressed core for a pharmaceutical dosage form comprising a mixture of
5 (a) at least one pharmaceutically acceptable organic acid, and (b) at least one pharmaceutically acceptable excipient, wherein the pharmaceutically acceptable organic acid is present in an amount of about 50-95% by weight of the core.
2. The compressed core of claim 1 wherein the pharmaceutically acceptable organic acid is present in an amount of about 50-90%, about 50-85%, about 60-90%,
10 about 60-85%, about 70-90%, about 70-85%, about 80-85%, about 80-90%, or about 85%, by weight of the core.
3. The compressed core of any of claims 1-2, wherein the pharmaceutically acceptable organic acid has a pKa of about 5.4 or less, preferably a pKa of about 2.9 to about 5.4.
- 15 4. The compressed core of any of claims 1-3, wherein the pharmaceutically acceptable organic acid has an aqueous solubility at 20°C of ≥ 4 grams/litre, particularly ≥ 6 grams/litre, and especially ≥ 10 grams/litre.
5. The compressed core of any of claims 1-4, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of fumaric acid, tartaric
20 acid, citric acid, succinic acid, adipic acid, malic acid, maleic acid, lactic acid, or a mixture of one or more thereof, and preferably wherein the pharmaceutically acceptable organic acid is selected from the group consisting of fumaric acid, tartaric acid, citric acid, and lactic acid, and more preferably tartaric acid, especially L-tartaric acid.
- 25 6. The compressed core of any of claims 1-5, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of a filler, binder, and diluent, and lubricant or mixtures thereof, preferably wherein the pharmaceutically acceptable excipient is a filler or a mixture of a filler and a lubricant.
7. The compressed core of any preceding claim wherein the at least one
30 pharmaceutically acceptable excipient is selected from the group consisting of microcrystalline cellulose, lactose, sorbitol, dextrose, sucrose, mannitol, dibasic calcium phosphate, starch, and mixtures thereof, including mixtures of starch and

- lactose, preferably selected from the group consisting of microcrystalline cellulose lactose, mannitol, dibasic calcium phosphate, starch, and mixtures thereof, including mixtures of starch and lactose, and more preferably microcrystalline cellulose, lactose, mannitol, starch, and mixtures thereof, including mixtures of starch and
- 5** lactose.
8. The compressed core of any preceding claim wherein the pharmaceutically acceptable excipient is microcrystalline cellulose.
9. The compressed core of any preceding claim wherein the at least one pharmaceutically acceptable excipient includes a lubricant.
- 10** 10. The compressed core of claim 9 wherein the lubricant is selected from the group consisting of sodium stearyl fumarate, stearic acid, magnesium stearate, calcium stearate, zinc stearate, talc, glyceryl behenate, preferably sodium stearyl fumarate, magnesium stearate, calcium stearate and talc, and more preferably magnesium stearate.
- 15** 11. The compressed core of any preceding claim wherein the pharmaceutically acceptable excipient component (b) is present in an amount of about 5-50%, about 10-50%, about 15-50%, about 10-40%, about 15-40%, about 10-30%, about 15-30%, about 20-30%, about 15-20%, about 10-20%, or about 15%, by weight of the core.
- 20** 12. The compressed core of any preceding claim consisting essentially of a mixture of (a) about 50-95% by weight of a pharmaceutically acceptable organic acid and (b) about 5-50% of at least one pharmaceutically acceptable excipient.
13. The compressed core of claim 12, wherein (a) is present in an amount of about 60-95% by weight, and (b) is present in an amount of about 5-40% by weight.
- 25** 14. The compressed core of claim 13, wherein (a) is present in an amount of about 70-95% by weight, and (b) is present in an amount of about 5-30% by weight.
15. The compressed core of claim 14, wherein (a) is present in an amount of about 80-90% by weight, and (b) is present in an amount of about 10-20% by weight.
- 30** 16. The compressed core of any preceding claim where a lubricant is present in an amount of about 0.05 to about 2 wt%, preferably about 0.2 wt% to about 0.8 wt%, and more preferably about 0.3 to about 0.7 wt%, and particularly about 0.5 wt% relative to the weight of the core.

17. The compressed core of any preceding claim wherein the core is prepared by direct compression of a mixture comprising components (a) and (b).
18. The compressed core of claim 17 wherein the compression is carried out without the addition of a liquid or solvent.
- 5 19. The compressed core of any preceding claim wherein the friability of the core is 0.1% or less, preferably about 0.1%-0.02%, and more preferably about 0.1% to 0.01%
20. The compressed core of any preceding claim wherein the cores have a diameter of about 3 mm or less, or about 2 mm or less.
- 10 21. The compressed core of any of claim 20 wherein the cores have a diameter of at least about 1.6 mm.
22. The compressed core of any of claims 20-21 wherein the cores have a diameter of about 1.6 to about 3 mm, , about 1.6 to about 2.8 mm, particularly about 1.7 to about 2.5 mm and about 1.7 mm to about 2.3 mm, about 1.7 to about 2.1 mm, 15 about 1.7 to about 2.0 mm, and particularly about 1.8 mm.
23. A pharmaceutical composition comprising a compressed core according to any preceding claim wherein the core is coated with a drug layer comprising a drug having a pH dependent solubility profile, wherein the solubility is greater at acidic pH (i.e. pH < 7), and at least one pharmaceutically acceptable excipient.
- 20 24. A pharmaceutical composition according to claim 22 wherein the drug layer further comprises at least one pharmaceutically acceptable excipient, preferably wherein the pharmaceutically acceptable excipient is selected from the group consisting of a binder, diluent, plasticizer and an anti-tacking (anti-adherent) agent, and mixtures thereof, preferably wherein the drug layer contains a binder or a mixture 25 of binders, a plasticizer, and an anti-tacking (anti-adherent) agent, and more preferably a combination of binder and an anti-tacking agent.
25. A pharmaceutical composition according to claim 24 wherein the binder is selected from the group consisting of cellulosic polymers such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl 30 cellulose, gelatin, methyl cellulose, pregelatinized starch, acacia, alginic acid, sodium carboxymethyl cellulose gum arabic, polyvinyl pyrrolidone, polyvinyl alcohol, and copolymers of N-vinyl pyrrolidine and vinyl acetate or mixtures thereof, preferably

hydroxypropylmethyl cellulose and hydroxypropyl cellulose (e.g. Klucel LF) or mixtures thereof, and more preferably, hydroxypropyl cellulose.

26. A pharmaceutical composition according to any of claims 24-25 wherein the
5 binder in the drug layer is present in a concentration of about 5 to about 30 wt%, about 5 to about 25 wt% and particularly about 10 to about 18 wt%, relative to the weight of the drug layer
27. A pharmaceutical composition according to any of claims 24-26 wherein the
10 weight ratio of drug to binder in the drug layer is from about 10 : 1 to about 1 : 1, preferably about 8 : 1 to about 2 : 1 and more preferably about 6 : 1 to about 4 : 1.
28. A pharmaceutical composition according to any of claims 24-27 wherein the plasticizer is selected from the group consisting of polyethylene glycol (preferably polyethylene glycol 400), triethyl citrate, tributyl citrate, glycerin, dibutyl sebacate, triacetin and diethylphthalate, preferably, polyethylene glycol, triethyl citrate, tributyl
15 citrate, dibutyl sebacate, triacetin and diethyl phthalate, or mixtures thereof.
29. A pharmaceutical composition according to any of claims 24-28 wherein the plasticiser is present in the drug layer in a concentration of about 2 to about 25 wt%, about 5 to about 15 wt% or about 8 to about 12 wt% relative to the weight of the drug layer.
- 20 30. A pharmaceutical composition according to any of claims 24-29 wherein the anti-tacking agent is selected from the group consisting of magnesium carbonate, titanium dioxide, microcrystalline cellulose, polyethylene glycol, colloidal silica, corn starch and talc, or mixtures thereof, and preferably wherein the anti-tacking agent is talc.
- 25 31. A pharmaceutical composition according to any of claims 24-30 wherein the anti-tacking agent is present in an concentration range of about 5 wt% to about 25 wt%, about 8 wt% to about 20 wt%, or about 10 wt% to about 18 wt% relative to the weight of the drug layer.
32. A pharmaceutical composition according to any of claims 23-31 wherein the
30 compressed core and the drug layer are separated by a subcoat layer.
33. A pharmaceutical composition according to claim 32 wherein the subcoat layer comprises at least one pharmaceutically acceptable excipient, preferably

selected from one or more of the group consisting of binder (preferably wherein the binder is a water-soluble polymer), anti-tacking agent, surfactant (emulsifier), and plasticizer.

34. A pharmaceutical composition according to claim 33 wherein the binder in the subcoat layer is selected the group consisting of cellulosic polymers such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl cellulose, gelatin, methyl cellulose, pregelatinized starch, acacia, alginic acid, sodium carboxymethyl cellulose gum arabic, polyvinyl pyrrolidone, polyvinyl alcohol, and copolymers of N-vinyl pyrrolidone and vinyl acetate, or a mixture thereof, preferably wherein the binder is a cellulosic polymer or a mixture of cellulosic polymers including hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl cellulose and methyl cellulose, more preferably wherein the binder is selected from the group consisting of, hydroxypropylmethyl cellulose (e.g. HPMC 2910), hydroxypropyl cellulose, hydroxyethyl cellulose and ethyl cellulose or mixtures thereof, and most wherein the binder is selected from hydroxypropylmethyl cellulose and ethyl cellulose or a combination thereof.

35. A pharmaceutical composition according to any of claims 33-34 wherein the binder is present in the subcoat layer in a concentration of about 20 to about 95 wt%, about 30 to about 90 wt%, or about 40 to about 90 wt%, relative to the weight of the subcoat layer.

36. A pharmaceutical composition according to any of claims 33-35 wherein the anti-tacking agent is selected from the group consisting of magnesium carbonate, titanium dioxide, microcrystalline cellulose, polyethylene glycol, colloidal silica, corn starch and talc and mixtures thereof, and preferably wherein the anti-tacking agent is talc.

37. A pharmaceutical composition according to any of claims 33-36 wherein the plasticizer is selected from the group consisting of polyethylene glycol (particularly polyethylene glycol 400), triethyl citrate, tributyl citrate, glycerin, dibutyl sebacate, triacetin and diethylphthalate, preferably wherein the plasticizer is selected from the group consisting of polyethylene glycol, triethyl citrate, tributyl citrate, dibutyl sebacate, triacetin and diethyl phthalate, or mixtures thereof, and particularly polyethylene glycol and dibutyl sebacate, or a combination thereof.

38. A pharmaceutical composition according to any of claims 33-37 wherein the plasticizer is present in a concentration of about 5 to about 30 wt%, about 5 to about 20 wt%, or about 8 to about 14 wt%, relative to the weight of the subcoat.
- 5 39. A pharmaceutical composition according to any of claims 33-38 wherein the surfactant or emulsifier is selected from the group consisting of benzalkonium chloride, cetyl alcohol, polysorbate 80, sodium lauryl sulfate and sorbitan esters including sorbitan mono-palmitate, or mixtures thereof, and particularly cetyl alcohol or sodium lauryl sulfate, or a combination thereof.
- 10 40. A compressed core according to any of claims 1-22 or a pharmaceutical composition according to any of claims 23-39 further comprising a dissolution enhancer, said dissolution enhancer preferably being a pore former, osmotic agent, disintegrant or surfactant.
41. A pharmaceutical composition according to claim 40, where in the pore
15 former is present in an amount of about 5-20%w/w of the layer or core it is present in.
42. A pharmaceutical composition according to any of claims 40 or 41 wherein the dissolution enhancer is present in the drug layer.
43. A pharmaceutical composition according to any of claims 40-42, wherein the dissolution enhancer is a pore former.
- 20
44. A pharmaceutical composition according to any of claims 22-43 wherein the drug layer is coated with a protective top coat, an extended-release coat or a delayed-release coat.
45. A pharmaceutical composition according to claim 44 wherein the extended-
25 release coat comprises an extended-release polymer.
46. A pharmaceutical composition according to claim 45 wherein the extended-release polymer is selected from the group consisting of ethyl cellulose (e.g. ethylcellulose having a viscosity of about 4 to about 10 cPs, preferably about 5 to about 9 cPs, and more preferably about 7 cPs), hydroxypropyl methylcellulose
30 (HPMC), polyvinyl alcohol (PVA; vinyl alcohol polymer), polymethacrylates, ethyl acrylate-methyl methacrylate copolymers (such as Eudragit RS), hydroxypropyl cellulose (HPC) or a mixture thereof, and preferably wherein the extended-release

polymer is ethylcellulose (particularly ethylcellulose having a viscosity of about 4 to about 10 cPs, preferably about 5 to about 9 cPs, and more preferably about 7 cPs).

47. A pharmaceutical composition according to any of claims 45-46, wherein the extended-release layer further comprises a binder or a plasticizer or a mixture thereof.

48. A pharmaceutical composition according to any of claims 23-47 wherein the drug is selected from the group consisting of dabigatran, dabigatran prodrugs such as dabigatran etexilate, dipyrindamole, aliskiren, fingolimod, and retigabine, or prodrugs thereof, and pharmaceutically acceptable salts of the drugs or prodrugs.

49. A multiparticulate dosage form, comprising a plurality of coated cores as defined in any of claims 23-48.

50. A multiparticulate dosage form according to claim 49 wherein the multiparticulate dosage form comprises a plurality of pharmaceutical compositions as defined in any of claims 23-49 wherein the compositions are filled into capsules, preferably hard gelatin or HPMC capsules.

51. A multiparticulate dosage form according to claim 49 or claim 50, wherein the drug is dabigatran etexilate, preferably dabigatran etexilate mesylate.

52. A multiparticulate dosage form according to claim 47 wherein the dosage form provides from 25 mg to 300 mg, preferably from 50 mg to 250 mg, and more preferably about 75 to about 220 mg, and most preferably 75 mg, 110 mg, 150 mg or 220 mg of dabigatran etexilate, preferably wherein the drug is in the form of dabigatran etexilate mesylate).

53. A process for the preparation of the compressed core of any of claims 1-22 comprising:

(i) admixing the pharmaceutically acceptable acid with the at least one pharmaceutically acceptable excipient to form a mixture, and

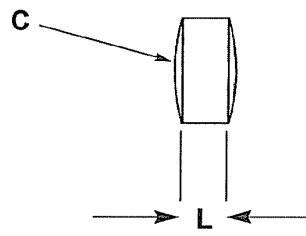
(ii) direct compression of the mixture.

54. A process according to claim 53, wherein the final blend for direct compression is prepared without the addition of a liquid or solvent.

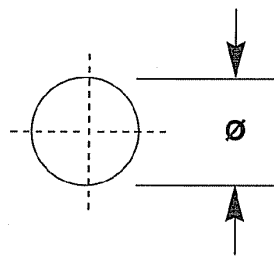
55. A process for preparing the pharmaceutical composition according to any of claims 23-48 comprising:

- (i) preparing a compressed core by the process of any of claims 49-50, and
 - 5 (ii) optionally applying a sub-coat layer over the compressed core,
 - (iii) applying a drug layer over the compressed core or sub-coated compressed core, and
 - (iv) optionally applying a protective top coat, an extended release coat or a delayed release coat over the drug layer.
- 10 56. A process according to claim 55 wherein the composition or a plurality thereof is filled into a capsule, preferably wherein the capsule is a hard gelatin capsule or hydroxypropylmethyl cellulose capsule.
57. A process according to claim 56 wherein the capsule provides a 75 mg, 110 mg, 150 mg or 220 mg dose of the drug (preferably dabigatran, more preferably
- 15 dabigatran etexilate, and most preferably in the form of dabigatran etexilate mesylate).

Figure 1



(1A)



(1B)

Figure 2

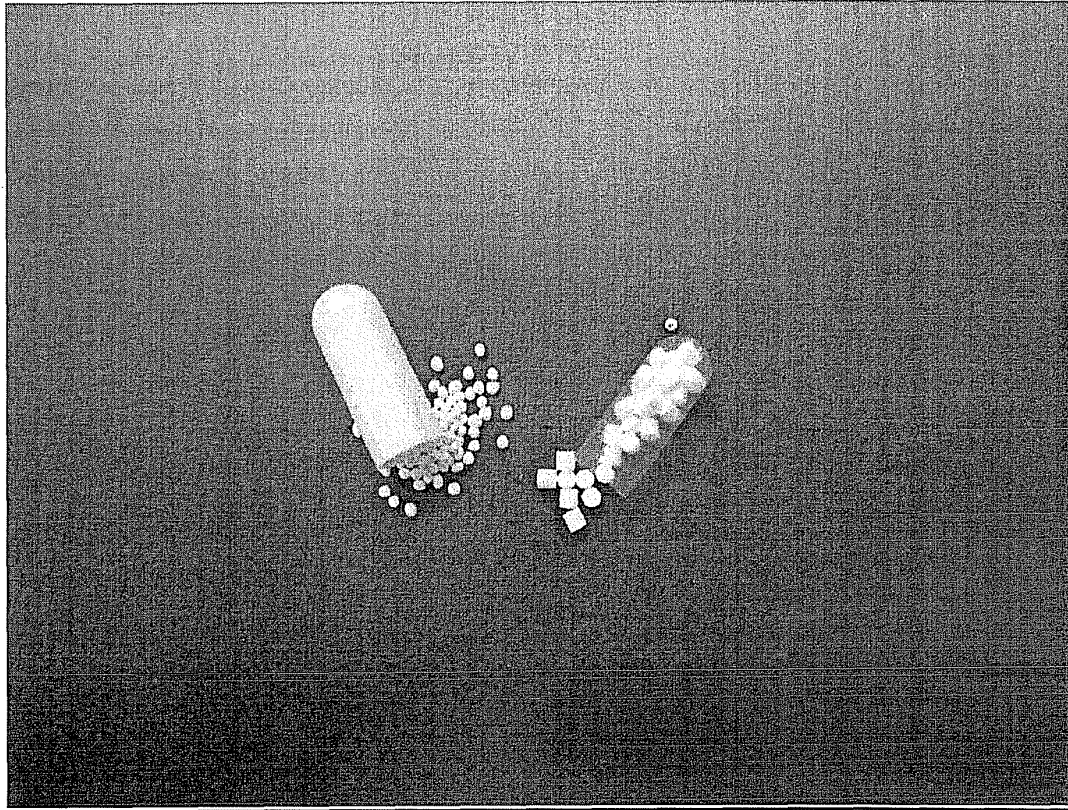
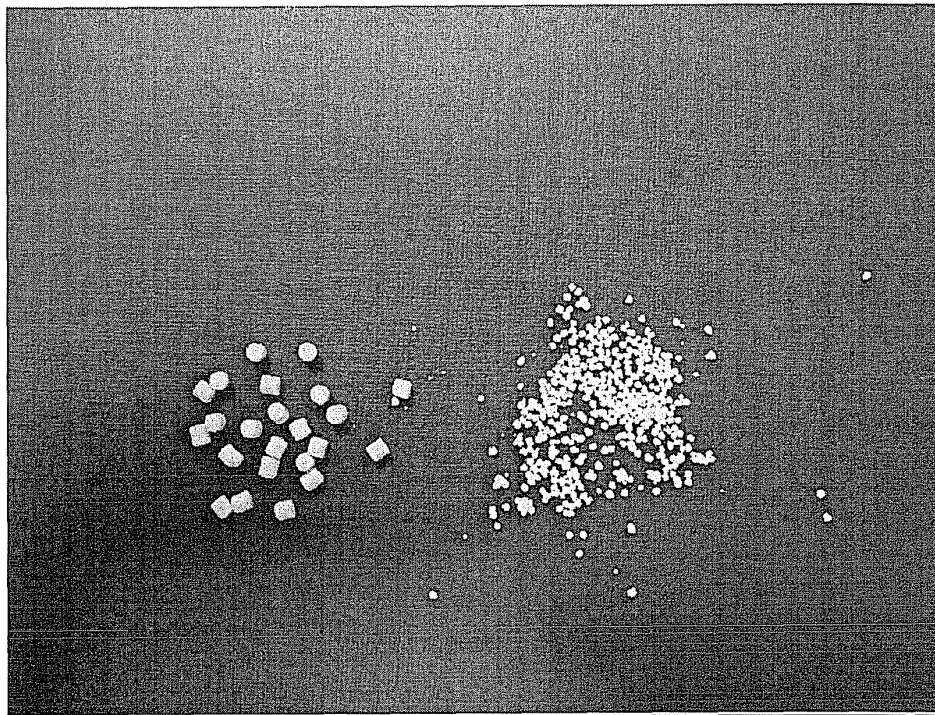


Figure 3



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/039327

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20
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, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

☒ See patent family annex.

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1

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Information on patent family members

International application No

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International application No

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(74) Agent: **SEVINC, Erkan**; Istanbul Patent A.S., Plaza-33, Büyükdere Cad. 33/16, 34381 Sisli/İstanbul (TR).

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(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).

(54) Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN

(57) Abstract: The present invention relates to pharmaceutical compositions for an oral administration comprising a first component comprising dabigatran etexilate free base or pharmaceutically acceptable salts of dabigatran etexilate and a second component comprising an organic acid.

WO 2019/132839 A1

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN

Technical Field

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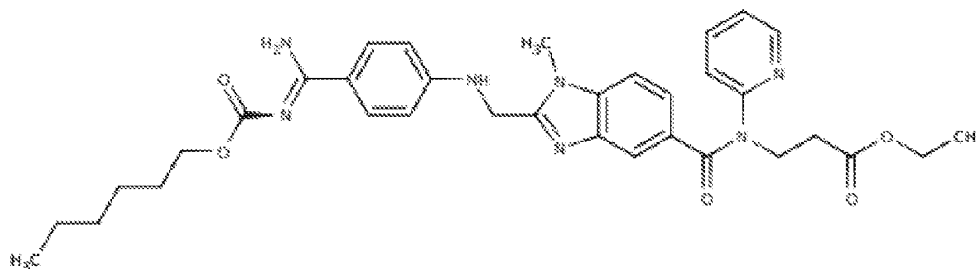
The present invention relates to pharmaceutical compositions for an oral administration comprising a first component comprising dabigatran etexilate free base or pharmaceutically acceptable salts of dabigatran etexilate and a second component comprising an organic acid.

10

Background of the Invention

Dabigatran etexilate (Formula 1), 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-valvular atrial fibrillation. Thrombin is a multifunctional enzyme which converts fibrinogen to fibrin, cross-linking fibrin monomers via activation of factor XIII and augmenting further thrombin production via the activation of factors V and VIII. It also activates platelets, generates anticoagulant activity via activation of protein C and initiates numerous cellular processes.

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Formula 1: Dabigatran etexilate

The methane sulphonic acid addition salt of dabigatran etexilate, which is commercially available under the trade name PRADAXA® immediate release capsule (in the strength of 75, 110, 150 mg), is disclosed in EP1870100, wherein also disclosed, pellet formulation of dabigatran etexilate methanesulphonate. This composition is formulated with a core material consisting of organic acid and an active layer which encloses the core. Each PRADAXA® capsule contains the following inactive ingredients: acacia, dimethicone,

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hypromellose, hydroxypropylcellulose, tartaric acid, carrageenan, potassium chloride, talc, titanium dioxide, and gelatin.

5 Apart from the methanesulfonate 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.

10 It is known that the solubility of weakly basic drugs, such as dabigatran etexilate and dabigatran etexilate salt, is pH-dependent and may be increased by the provision of an acidic environment. Therefore, weakly basic drugs are formulated with an acidic excipient.

15 Patent application EP1658056 discloses a conventional tablet formulation comprising dabigatran etexilate, organic acid with a solubility in water of $> 1 \text{ g} / 250 \text{ ml}$ at 20°C together with conventional excipients and fillers. But in the patent application EP1658056, there is no insulating layer between the active agent and the organic acid.

20 Dabigatran etexilate is also less stable in acidic environment. To avoid this stability problem, many solutions were offered in the prior art. Separating layer between the acidic core and the active substance layer is the most preferred way. In this invention, the separating layer is used and in comparison to prior art, the composition of this invention is more stable since the active agent is not in the outer layer of the composition.

25 WO03/074056 discloses a composition contains the following components: a core material comprising an organic acid, an insulating layer which separates the acid core from the layer containing the active substance and an active agent layer.

30 Patent application WO2012001156 relates to a process for the preparation of a solid oral dosage form comprising dabigatran etexilate. In this application, the pellets comprise a neutral core comprised of sucrose, microcrystalline cellulose or starch, or a commercially available tartaric acid pellet; the tartaric acid layer, the isolating layer, the active pharmaceutical ingredient layer and, optionally, an overcoat.

35 Patent application WO2013124340 discloses dabigatran etexilate compositions comprising a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein the first type of particles comprises the

active agent; the second type of particles comprise at least one pharmaceutically acceptable organic acid; and optionally at least one type of particles are coated with a protective layer. In this patent application, the invention provides a quick dissolution particularly at earlier time points as compared to formulation having one type of particles/pellets.

Thus, there is still a need in the art to develop stable and bioavailable pharmaceutical formulations comprising dabigatran etexilate free base or pharmaceutically acceptable salts of dabigatran etexilate with a long shelf-life and a pH independent release by a simplified and cost-effective process. By this need, the formulation has been developed to overcome the solubility and stability problems of dabigatran etexilate in a safe manner disclosed above.

Detailed Description of the Invention

The main object of the present invention is to provide pH-independent pharmaceutical compositions for oral administration comprising dabigatran etexilate free base or pharmaceutically acceptable salts of dabigatran etexilate and at least one pharmaceutically acceptable excipient.

A further object of the present invention is to provide stable pharmaceutical compositions which are not prone to phase transformation and degradation.

A further object of the present invention is to provide pharmaceutical compositions which have desired chemical and polymorphic stability.

Another object of the present invention is to provide pharmaceutical compositions which are easy to prepare.

According to this present invention, the pharmaceutical composition for oral administration comprising:

- a. a first component comprising dabigatran etexilate or pharmaceutically acceptable salts of dabigatran etexilate and at least one pharmaceutically acceptable excipient
 - b. a second component comprising an organic acid and at least one pharmaceutically acceptable excipient
- wherein the first component is in the form of minitables.

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

5 The term “mini tablet”, as used herein, refers to small tablets with a diameter equal to or less than 6 mm that are typically filled into a capsule or further compressed into larger tablets.

10 Mini tablets have many advantages. Due to increased surface in relation to volume, the drug can be released more efficiently incase of mini-tablets. Some benefits of mini-tablets include excellent size uniformity, regular shape and a smooth surface. In mini tablets, smooth surface offers an excellent substrate for coating with polymeric systems. It can be concluded that pharmaceutical mini-tablets offer several advantages when compared to single unit dosage forms and are also good substitutes for granules and pellets. They have well defined size, shape, surface, low degree of porosity and high mechanical
15 strength. The mini tablets have round shape and smooth surface to ease coating process. Due to significant smaller dimensions of the mini tablets, when compared to normal tablets, they pass through the stomach at a more even rate. As a result, the concentration of the drug in the blood can be easily reproduced. It has been found that, dissolution and stability problems are overcome by using mini tablet form.

20 In one embodiment, mini-tablets have a diameter more than 3 mm. Preferably this value is between 3 mm and 5 mm, more preferably between 3 mm and 4 mm, more preferably 3 mm and 3.5 mm.

25 According to this embodiment, it has been found that these specific mini-tablet thickness ranges are important for stability of the composition. Furthermore, when the mini-tablets have a diameter mentioned here, process for the preparation of mini-tablets and process for the filling mini-tablets into the capsule get easy.

30 In one embodiment, mini-tablets comprise one coating layer for ensuring the stability of the composition.

Homogen coating which is very important for ensuring stability of the composition, is provided by choosing these specific mini-tablet thickness ranges. A further advantage of
35 these ranges is simplified coating process. During the development study of the invention,

it has been found that when the mini-tablets have a diameter mentioned above, homogen coating process is easier than usual for this invention.

5 In one embodiment, the second component is in the form of pellets or minitables or granules or beads or capsules.

In a preferred embodiment, the second component is in the form of pellets.

In one embodiment, the second component is free of dabigatran etexilate.

10 According to another embodiment, dabigatran etexilate free base or a pharmaceutically acceptable salt of dabigatran etexilate is present in an amount of between 30 to 350 mg, preferably 50 to 300 mg and more preferably it is 50 to 250 mg.

15 In one embodiment, the composition comprises dabigatran etexilate free base or pharmaceutically acceptable salts of dabigatran etexilate in an amount of between 20.00% and 80.00% by weight of the first component, preferably between 30.00% and 70.00%, more preferably between 40.00% and 60.00%.

20 According to one embodiment, the organic acid is selected from a group comprising tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid or aspartic acid or hydrates or salts thereof.

In a preferred embodiment, the organic acid is citric acid.

25 Choice of the organic acid is important for the desired dissolution profile of the composition since the dissolution of dabigatran should be pH independent. It has been found that, using citric acid ensures effective dissolution profile, especially when the second component which is free of dabigatran, is in the form of pellets.

30 According to these embodiments, the amount of the organic acid is between 70.00% and 99.00% by weight of the second component., preferably between 85.00% and 99.00%.

35 In one embodiment, wherein said at least one pharmaceutically acceptable excipient is selected from disintegrants, fillers, binders, lubricants, glidants, coating agents, solvents, anticaking agents.

Suitable fillers are selected from a group comprising microcrystalline cellulose, lactose, mannitol, spray-dried mannitol, starch, dextrose, sucrose, fructose, maltose, sorbitol, xylitol, inositol, kaolin, inorganic salts, calcium salts, polysaccharides, dicalcium phosphate, sodium chloride, dextrates, lactitol, maltodextrin, sucrose-maltodextrin mixture, trehalose, sodium carbonate, sodium bicarbonate, calcium carbonate, polyols, dextrose, maltitol or mixtures thereof.

In one embodiment, the filler is present in an amount of between 10.0 % and 80.0% by weight of the first component.

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In one preferred embodiment, the filler is selected from microcrystalline cellulose, lactose or mixtures thereof.

Selection of microcrystalline cellulose and lactose as the fillers also helps improving the stability of the composition. Furthermore, when the weight ratio of microcrystalline cellulose to lactose is between 0.20 and 5.00, the improvement in the stability of the composition is more distinct.

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

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In a preferred embodiment, the binder is croscarmellose sodium.

According to these embodiments, the amount of binder is between 1.00% and 20.00%, preferably between 2.00% and 10.00% by weight of the first component.

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Suitable glidants are selected from colloidal silicon dioxide, talc, aluminium silicate or mixtures thereof.

In a preferred embodiment, the glidant is colloidal silicon dioxide.

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Suitable disintegrants are selected from a group comprising hydroxypropyl methylcellulose, starch, sodium starch glycolate, microcrystalline cellulose, crospovidone (cross-linked polyvinyl pyrrolidone), povidone, poloxamer, 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, alginic acid, alginates, ion-exchange resins, magnesium aluminium silica, sodium dodecyl sulphate, sodium glycine carbonate, or mixtures thereof

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In a preferred embodiment, the disintegrant is hydroxypropyl methylcellulose.

It has been found that, using hydroxypropyl methylcellulose in the compositions according to this invention, takes part in ensuring the desired dissolution profile.

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According to these embodiments, the amount of disintegrants is between 1.00% and 15.00% by weight of the first component, preferably between 3.00% and 7.00%.

Suitable anticaking agents are selected from a group comprising talc, magnesium silicate, magnesium trisilicate, magnesium oxide, hydroxypropyl cellulose, hydroxyethyl cellulose, hydrophobic colloidal silica, guar gum, colloidal silicon dioxide, calcium silicate, calcium phosphate or mixtures thereof.

In a preferred embodiment, the anticaking agent is talc.

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According to these embodiments, the amount of anticaking agent is between 0.01% and 10.00% by weight of the second component., preferably between 0.10% and 5.00%, more preferably between 0.10% and 2.00%

Suitable lubricants are selected from a group comprising magnesium stearate, sodium stearyl fumarate, 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 palmitostearate, sodium lauryl sulphate or mixtures thereof.

In a preferred embodiment, the lubricant is magnesium stearate.

According to these embodiments, the amount of the lubricant is between 0.10% and 5.00% by weight of the first component, preferably between 0.50% and 2.00%.

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Suitable salts of dabigatran etexilate are selected from a group comprising mesylate, maleate, malonate, citrate, tosylate, esylate, tartrate, oxalate or camphor sulfonate.

Preferably suitable salts of dabigatran etexilate are selected from maleate, malonate, 10 citrate, tosylate, esylate, tartrate, oxalate, camphor sulfonate.

In one preferred embodiment, the active agent is in the form of free base.

It has been found that, when dabigatran etexilate free base is used in this composition, 15 desired chemical and polymorphic stability of the formulation is provided.

Example 1: Capsule comprising dabigatran mini tablets and acid pellets

Dabigatran mini tablets	% by weight
Dabigatran etexilate free base or or pharmaceutically acceptable salts of dabigatran etexilate	20.00-70.00
Microcrystalline cellulose	10.00-50.00
Croscarmellose sodium	2.00-10.00
Lactose	10.00-30.00
Colloidal silicon dioxide	0.50-3.00
Hydroxypropyl methylcellulose	1.00-15.00
Magnesium stearate	0.10-5.00
Total first component (mini tablets)	100
Acid pellets	% by weight
Citric acid	70.00-99.00
Talc	0.01-10.00
Hydroxypropyl methylcellulose	5.00-30.00
Total second component (pellets)	100

The pharmaceutical compositions mentioned above are prepared by following these steps:

- 5 a. Weighing, sieving and mixing dabigatran etexilate free base or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, croscarmellose sodium, lactose and colloidal silicon dioxide
- b. Granulating the mixture with water
- c. Drying the granules in an oven at 50°C and sieving them
- d. Adding magnesium stearate to the mixture and mixing 1-2 more minutes
- 10 e. Compressing the mixture into mini tablets
- f. Suspending hydroxypropyl methylcellulose and talc in ethanol to form isolation solution
- g. Coating citric acid pellets having a diameter in the range of 0.4 mm and 0.6 mm with the isolation solution to form isolated pellets
- 15 h. Filling the mini-tablets and isolated pellets into the capsules

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CLAIMS:

1. A pharmaceutical composition comprising:
 - a. a first component comprising dabigatran etexilate or pharmaceutically acceptable salts of dabigatran etexilate and at least one pharmaceutically acceptable excipient
 - b. a second component comprising an organic acid and at least one pharmaceutically acceptable excipientwherein the first component is in the form of minitables.
2. The pharmaceutical composition according to claim 1, wherein the second component is in the form of pellets or minitables or granules or beads or capsules or their mixtures.
3. The pharmaceutical composition according to claim 1, wherein the mini-tablets have a diameter more than 3 mm, preferably this value is between 3 mm and 5 mm, more preferably between 3 mm and 4 mm, more preferably 3 mm and 3.5 mm.
4. The pharmaceutical composition according to claim 3, wherein said mini-tablets comprise one coating layer.
5. The pharmaceutical composition according to claim 1, wherein the composition comprising dabigatran etexilate free base or pharmaceutically acceptable salts of dabigatran etexilate in an amount of between 20.00% and 80.00% by weight of the first component.
6. The pharmaceutical composition according to claim 1, wherein the organic acid is selected from a group comprising tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid or aspartic acid or hydrates or salts thereof.
7. The pharmaceutical composition according to claim 6, wherein the organic acid is citric acid.
8. The pharmaceutical composition according to claim 5, wherein the amount of the organic acid is between 70.00% and 99.00% by weight of the second component.

- 5 9. The pharmaceutical composition according to claim 1, wherein said at least one pharmaceutically acceptable excipient is selected from disintegrants, fillers, binders, lubricants, glidants, coating agents, solvents or anticaking agents or mixtures thereof.
- 10 10. The pharmaceutical composition according to claim 9, wherein the filler is selected from a group comprising microcrystalline cellulose, lactose, mannitol, spray-dried mannitol, starch, dextrose, sucrose, fructose, maltose, sorbitol, xylitol, inositol, kaolin, inorganic salts, calcium salts, polysaccharides, dicalcium phosphate, sodium chloride, dextrates, lactitol, maltodextrin, sucrose-maltodextrin mixture, trehalose, sodium carbonate, sodium bicarbonate, calcium carbonate, polyols, dextrose, maltitol or mixtures thereof, preferably the fillers are microcrystalline cellulose and lactose.
- 15 11. The pharmaceutical composition according to claim 10, wherein the amount of fillers is between 10.00% and 80.00% by weight of the first component.
- 20 12. The pharmaceutical composition according to claim 11, wherein the filler is selected from microcrystalline cellulose, lactose or mixtures thereof.
- 25 13. The pharmaceutical composition according to claim 12, wherein the weight ratio of microcrystalline cellulose to lactose is between 0.20 and 5.00.
- 30 14. The pharmaceutical composition according to claim 9, wherein the disintegrant is selected from a group comprising hydroxypropyl methylcellulose, starch, sodium starch glycolate, microcrystalline cellulose, crospovidone (cross-linked polyvinyl pyrrolidone), povidone, poloxamer, cross-linked carboxymethyl cellulose (croscarmellose sodium), low-substituted hydroxypropyl cellulose, pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose, docusate sodium, guar gum, polyacryline potassium, sodium alginate, alginic acid, alginates, ion-exchange resins, magnesium aluminium silica, sodium dodecyl sulphate, sodium glycine carbonate, or mixtures thereof.
- 35 15. The pharmaceutical composition according to claim 14, wherein the amount of disintegrants are between 1.00% and 15.00% by weight of the first component, preferably between 3.00% and 7.00%.

16. The pharmaceutical composition according to claim 15, wherein the disintegrant is hydroxypropyl methylcellulose.
- 5 17. The pharmaceutical composition according to claim 9, wherein the anticaking agent is selected from a group comprising talc, magnesium silicate, magnesium trisilicate, magnesium oxide, hydroxypropyl cellulose, hydroxyethyl cellulose, hydrophobic colloidal silica, guar gum, colloidal silicon dioxide, calcium silicate, calcium phosphate or mixtures thereof, preferably the anticaking agent is talc.
- 10 18. The pharmaceutical composition according to claim 17, wherein the amount of anticaking agent is between 0.01% and 10.00% by weight of the second component.
- 15 19. The pharmaceutical composition according to any of the preceding claims, comprising:
- 20 20.00% to 80.00% dabigatran etexilate free base or or pharmaceutically acceptable salts of dabigatran etexilate
10.00% to 50.00% microcrystalline cellulose
1.00% to 20.00% croscarmellose sodium
10.00% to 30.00% lactose
0.5% to 3.00% colloidal silicon dioxide
- 25 1.00% to 15.00% hydroxypropyl methylcellulose
0.1% to 5.00% magnesium stearate
by weight of the first component
- 30 70.00% to 99.00% citric acid
0.01% 10.00% talc
5.00% to 30.00% hydroxypropyl methylcellulose
by weight of the second component
- 35 20. The process for preparation of the pharmaceutical composition according to claim 19, wherein the process comprising the following steps:
- a. Weighing, sieving and mixing dabigatran etexilate free base or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, croscarmellose sodium, lactose and colloidal silicon dioxide

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- b. Granulating the mixture with water
- c. Drying the granules in an oven at 50°C and sieving them
- d. Adding magnesium stearate to the mixture and mixing 1-2 more minutes
- e. Compressing the mixture into mini tablets
- 5 f. Suspending hydroxypropyl methylcellulose and talc in ethanol to form isolation solution
- g. Coating citric acid pellets having a diameter in the range of 0.4 mm and 0.6 mm with the isolation solution to form isolated pellets
- h. Filling the mini-tablets and isolated pellets into the capsules

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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/00 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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015/157618 A1 (KANDI CHANDRASHEKHAR [IN] ET AL) 11 June 2015 (2015-06-11) paragraph [0097] - paragraph [0098]; example 3B -----	1-6,8-20
X	WO 2015/145462 A1 (CADILA HEALTHCARE LTD [IN]) 1 October 2015 (2015-10-01) example 1 -----	1-12,14, 15,17-20
X	KR 2017 0070635 A (HANMI PHARM IND CO LTD [KR]) 22 June 2017 (2017-06-22) figure 1; example 1 -----	1-12,14, 15,17-20

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2015157618	A1	11-06-2015	NONE	

WO 2015145462	A1	01-10-2015	NONE	

KR 20170070635	A	22-06-2017	NONE	

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(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES
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(81) Bestimmungsstaaten (soweit nicht anders angegeben, für jede verfügbare nationale Schutzrechtsart): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Erklärungen gemäß Regel 4.17:

— hinsichtlich der Berechtigung des Anmelders, ein Patent zu beantragen und zu erhalten (Regel 4.17 Ziffer ii)

Veröffentlicht:

— mit internationalem Recherchenbericht (Artikel 21 Absatz 3)



WO 2009/118321 A1

(54) Title: METHOD FOR MANUFACTURING ACID PELLETS

(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG VON SÄUREPELLETS

(57) Abstract: The invention relates to an improved method for producing approximately spherical/ball-shaped tartaric acid pellets suitable for the manufacture of drug formulations containing active ingredients, and to the pellets so obtained as such and the use thereof as a starting material for the production of drug formulations containing active ingredients.

(57) Zusammenfassung: Die Erfindung betrifft ein verbessertes Verfahren zur Herstellung von annähernd sphärischen/kugelförmigen Weinsäurestarterpellets, die zur Herstellung von wirkstoffhaltigen Arzneimittelformulierungen geeignet sind, sowie die so erhältlichen Pellets als solche und deren Verwendung als Ausgangsmaterial zur Herstellung wirkstoffhaltigen Arzneimittelformulierungen.

Verfahren zur Herstellung von Säurepellets

- Die Erfindung betrifft ein verbessertes Verfahren zur Herstellung von annähernd sphärischen/kugelförmigen Weinsäurestarterpellets, die zur Herstellung von wirkstoffhaltigen
- 5 Arzneimittelformulierungen geeignet sind, sowie die so erhältlichen Pellets als solche und deren Verwendung als Ausgangsmaterial zur Herstellung wirkstoffhaltigen Arzneimittelformulierungen.

Hintergrund der Erfindung

- 10 Aus dem Stand der Technik sind Pellets, d.h. kleine runde Kügelchen als Grundlage für pharmazeutische Darreichungsformen bekannt. Häufig werden sogenannte „neutrale“ Pellets bestehend aus Maisstärke und Saccharose als Grundlage für pharmazeutische Darreichungsformen in Pelletform verwendet. Ebenfalls möglich ist die Verwendung von Starterpellets, welche überwiegend aus einer organischen Säure bestehen. Eine solche
- 15 Pelletformulierung ist beispielsweise in der WO 03/074056 offenbart. Bei diesen Formulierungen handelt es sich um Zusammensetzungen bei denen auf ein annähernd sphärisches Kernmaterial, das aus der pharmazeutisch akzeptablen organischen Säure besteht oder diese enthält, eine binde- und gegebenenfalls trennmittelhaltige Wirkstoffschicht, die das Kernmaterial umschließt, aufgetragen ist. Die Kernschicht und die Wirkstoffschicht sind dabei
- 20 durch eine so genannte Isolierschicht voneinander getrennt. Der schematische Aufbau einer solchen Wirkstoffformulierung ist in Figur 1 der WO 03/074056 dargestellt.

- Die Herstellung von solchen Säurestarterpellets mit der erwünschten annähernd kugelförmigen/sphärischen Geometrie erweist sich jedoch unerwartet als schwierig.
- 25 Insbesondere kann es immer wieder zu starken Abweichungen von der gewünschten kugelförmigen Symmetrie, etwa zu Agglomeraten aus einer größeren Kugel mit außen anhaftenden kleineren Klümpchen, sogenannte Satelliten. Bei Pelletformulierungen, in denen der Starterpellet von einer säureempfindlichen Wirkstoffschicht umschlossen wird, können diese Satelliten nach Auftragen der Isolierschicht abbrechen und dadurch Fehlstellen in der Isolierung
- 30 verursachen. Dies wiederum wirkt sich nachteilig auf die Lagerstabilität der Wirkstoffpellets aus.

- Es ist Aufgabe der vorliegenden Erfindung so genannte Starterpellets bereitzustellen, die eine gleichmäßige, kugelähnliche Geometrie aufweisen. Darüber hinaus sollten sie nur geringfügig potentielle Fehlstellen in der Isolierung durch Satelliten aufweisen. Von besonderer Bedeutung
- 35 ist die möglichst ideale Kugelform und eine geringe Oberflächenrauigkeit für säureempfindliche Wirkstoffe, bei denen Fehlstellen der Isolierung durch abgebrochene Satelliten oder durch zu rauhe Oberfläche zu großer Weinsäurepulverpartikel zu deutlich verschlechterten Lagerstabilitäten und damit Haltbarkeiten des fertigen Produkts führen kann. Aus diesem Grund

ist es bei säureempfindlichen Wirkstoffen auch erforderlich, die Isolierschicht als solche in hoher Reproduzierbarkeit und gleichbleibend guter Qualität aufzubringen.

Detaillierte Beschreibung der Erfindung

- 5 Die vorliegende Erfindung betrifft ein Verfahren zur Herstellung von Starterpellets, welche die vorstehend genannte Aufgabe lösen.

Das erfindungsgemäße Verfahren ist durch eine Reihe von Teilschritten gekennzeichnet. Zunächst erfolgt die Herstellung des Kerns 1 aus pharmazeutisch akzeptabler organischer Säure.

- 10 Im Rahmen der vorliegenden Erfindung gelangt zur Herstellung des Kerns 1 Weinsäure zur Anwendung. Das so erhaltene Kernmaterial 1 wird anschließend durch Aufsprühen einer Isoliersuspension 2 in so genannte isolierte Weinsäurekerne 3 überführt. Im Rahmen der vorliegenden Erfindung werden die isolierten Weinsäurekerne 3 gegebenenfalls auch als isolierte Weinsäurepellets 3 oder auch als Starterpellets bezeichnet.

- 15 Die Herstellung der Kerns 1 erfolgt aus Weinsäurepartikeln mit einer Partikelgröße im Bereich von 0,2-0,8 mm, bevorzugt 0,3-0,7 mm, besonders bevorzugt 0,4-0,6 mm (bestimmt durch Luftstrahlsiebung) auf die eine Lösung aus Weinsäure und Bindemittel aufgesprüht wird. Zur Herstellung der Lösung wird wie folgt vorgegangen. Weinsäure wird zunächst gemeinsam
20 mit einem geeigneten Bindemittel, bevorzugt mit Acacia (Gummi Arabicum) bei erhöhter Temperatur, vorzugsweise bei einer Temperatur im Bereich von 30-70°C, besonders bevorzugt im Bereich von 40-60°C in Wasser gelöst. Pro eingesetztes Kilogramm Weinsäure werden bevorzugt 0,1-0,3 kg, besonders bevorzugt 0,15-0,25 kg, insbesondere etwa 0,2 kg Acacia verwendet. Die Menge an Wasser beträgt vorzugsweise 0,6-1,0 kg, bevorzugt 0,7-0,9 kg,
25 insbesondere etwa 0,8 kg pro eingesetztes Kilogramm Weinsäure.

- Erfindungsgemäß bevorzugt wird bei der vorstehend genannten Temperatur zunächst eine klare Lösung aus Acacia in Wasser hergestellt. Liegt diese vor, erfolgt anschließend die Zugabe der Weinsäure bei vorzugsweise konstanter Temperatur und unter fortgesetztem Rühren. Nach
30 beendeter Zugabe wird wenigstens 1 Stunde, vorzugsweise zwischen 3 und 10, besonders bevorzugt 4 - 8, besonders bevorzugt 5 - 6 Stunden nachgerührt.

- Die so erhaltene Lösung wird auf Weinsäurepartikel mit einer Partikelgröße von 0,2-0,8 mm, bevorzugt 0,3-0,7 mm, besonders bevorzugt 0,4-0,6 mm aufgesprüht. Der Anteil der Partikel mit
35 der vorstehend genannten Partikelgröße sollte wenigstens 90%, vorzugsweise wenigstens 95%, besonders bevorzugt wenigstens bei 97% liegen. Hierzu werden die Weinsäurepartikel in einem geeigneten Kessel vorgelegt. Bei dem Kessel handelt es sich vorzugsweise um einen Kessel, bei dem das Mischen und die Bewegung der Partikel durch die Drehung des Kessels erfolgt. Solche Kessel sind in unterschiedlichen Ausführungen im Stand der Technik bekannt und werden

gegebenenfalls auch als Trommelcoater bezeichnet. Diesbezüglich sei beispielsweise auf die Offenbarungen der EP 80199, WO 83/03052, WO 95/19713 oder auch WO 06/134133 verwiesen. Im Rahmen der vorliegenden Erfindung werden im erfindungsgemäßen Verfahren einsetzbare Kessel gegebenenfalls auch als Horizontalkessel bezeichnet.

5

Auf die durch Rotation in Bewegung gehaltenen Partikel wird dann die nach vorstehend beschriebener Vorgehensweise hergestellte Säuregummilösung aufgesprüht.

Im Rahmen der vorliegenden Erfindung wird das vorgelegte Sprühgut gegebenenfalls auch als Pelletbett bezeichnet. Der Begriff Pellet ist im Rahmen der vorliegenden Erfindung als gleichbedeutend mit dem Begriff Partikel oder Kern anzusehen.

Pro vorgelegtes Kilogramm Weinsäurepartikel werden erfindungsgemäß bevorzugt 0,8 - 1,6 kg, besonders bevorzugt 1,0 - 1,4 kg, besonders bevorzugt 1,2 kg der vorstehend genannten Säuregummilösung aufgesprüht.

Die Zuluftmenge ist im erfindungsgemäßen Verfahren abhängig von der Chargengröße. Pro Kilogramm vorgelegte Weinsäurekerne liegt die normierte Zuluftmenge erfindungsgemäß bevorzugt in einem Bereich von 0,5 - 2 (m³/h)/kg, bevorzugt 0,75 - 1,5 (m³/h)/kg, besonders bevorzugt 0,9 - 1,1 (m³/h)/kg. Unter Zuluftmenge wird die Menge an Trockenluft verstanden, die pro Stunde in das rotierende Pelletbett eingebracht wird.

Werden in einem Ansatz beispielsweise 1000 kg Weinsäurekerne vorgelegt, entspricht eine normierte Zuluftmenge von 1,0 (m³/h)/kg einer faktischen Zuluftmenge von 1000 m³/h. Die Temperatur der zur Trocknung zugeführten Zuluft liegt erfindungsgemäß bevorzugt unterhalb von 90°C, besonders bevorzugt unterhalb von 80°C. Idealerweise sollte die Temperatur der Zuluft in einem Bereich von 35°-75°C liegen.

Die Pellettemperatur (die Temperatur des vorliegenden Pelletbetts) liegt erfindungsgemäß bevorzugt in einem Bereich von 30 - 50°C, besonders bevorzugt bei 36 - 44°C, idealerweise liegt sie bei 38 - 42°C.

Der Differenzdruck beträgt bevorzugt 1 - 3 mbar, besonders bevorzugt 1,5 - 2,5 mbar, besonders bevorzugt 1,8 - 2,2 mbar. Der Differenzdruck ist der Druckunterschied zwischen Kesseldruck und Umgebungsdruck. Der Kessel soll vorzugsweise Unterdruck haben damit kein Säurestaub austritt.

Das Aufsprühen erfolgt bei definierter Sprütrate. Unter Sprütrate wird die Menge an Säuregummilösung verstanden, die pro Stunde auf das rotierende Pelletbett aufgesprüht wird. Die Sprütrate ist im erfindungsgemäßen Verfahren abhängig von der Chargengröße. Pro

- Kilogramm vorgelegte Weinsäurekristalle liegt die normierte Sprütrate erfindungsgemäß bevorzugt in einem Bereich von 0,2 - 0,4 (kg/h)/kg, bevorzugt 0,25 - 0,35 (kg/h)/kg, besonders bevorzugt 0,28 - 0,32 (kg/h)/kg. Werden in einem Ansatz beispielsweise 1000 kg Weinsäurekristalle vorgelegt, entspricht eine normierte Sprütrate von 0,3 (kg/h)/kg einer
- 5 faktischen Sprütrate von 300 kg/h.
- Nach Aufsprühen eines ersten Teils der Säuregummilösung auf die Weinsäurepartikel der Partikelgröße 0,2-0,8 mm und Verteilen der Lösung durch Rotation des Kessels wird feines Weinsäurepulver auf die feuchten Weinsäurepartikel aufgedudert. Bei genanntem
- 10 Weinsäurepulver handelt es sich um feine Weinsäurepartikel mit einer Partikelgröße von < 100 , bevorzugt < 75, besonders bevorzugt < 50 Mikrometern (bestimmt durch Luftstrahlsiebung). Der Anteil der Partikel mit der vorstehend genannten Partikelgröße sollte wenigstens bei 85%, bevorzugt wenigstens bei 90%, besonders bevorzugt bei wenigstens 94% liegen. Pro vorgelegtes Kilogramm Weinsäurepartikel werden erfindungsgemäß bevorzugt 0,4 - 1,2 kg, besonders
- 15 bevorzugt 0,6 - 1,0 kg, besonders bevorzugt 0,8 kg des vorstehend genannten Weinsäurepulvers verwendet. Nach Aufpudern mit genanntem Weinsäurepulver wird das Sprühgut getrocknet, bis eine Guttemperatur von etwa 30-50°C, bevorzugt etwa 40°C erreicht ist. Hieran schließt sich erneut das Aufsprühen der Säuregummilösung an.
- 20 Um die gleichmäßige Bildung kugelförmiger Partikel zu gewährleisten erfolgt das Aufsprühen der Säuregummilösung und das Aufpudern mit Weinsäurepulver im Wechsel. Hierbei werden die Gesamtmengen der Säuregummilösung und des Weinsäurepuders in wenigstens 100, bevorzugt 150 bis 350, besonders bevorzugt 200 bis 300, besonders bevorzugt etwa 250 ähnlich großen Portionen zugeführt und die vorstehend beschriebenen Prozessschritte entsprechend oft
- 25 wiederholt.
- Nach beendetem Prozess werden die erhaltenen Kerne 1 getrocknet. Die Trocknung erfolgt bevorzugt bei einer Temperatur von 50-70°C, bevorzugt 55-65°C über einen Zeitraum von 24 - 72 Stunden, bevorzugt 36 - 60 Stunden.
- 30 Nach Herstellung der Weinsäurekerne 1 ist eine so genannte Isolierung des Kernmaterials erforderlich. Hierbei wird eine Isolierschicht um den Weinsäurekern aufgebracht, die eine Wechselwirkung von Wirkstoff mit Weinsäurekern im späteren Produkt verhindert.
- 35 Die Isolierung des Kernmaterials erfolgt durch Aufsprühen einer Isoliersuspension 2 auf die gemäß vorstehend beschriebener Vorgehensweise erhaltenen Weinsäurekerne 1. Zur Herstellung der Isoliersuspension 2 wird Ethanol im Ansatzbehälter vorgelegt und unter Rühren Hydroxypropylmethylcellulose und Dimethylpolysiloxan eingetragen und gelöst, danach wird Talkum zugegeben und suspendiert.

Die Verwendung von Hydroxypropylmethylcellulose und Talkum hat sich gegenüber der Verwendung von beispielsweise Gummi Arabicum und Talkum als überlegen herausgestellt. Durch die Verwendung von Hydroxypropylmethylcellulose neben Talkum ist es möglich in

5 reproduzierbarer Art und Weise eine Isolierschicht gleichbleibender Qualität herzustellen. Diese Qualität und Reproduzierbarkeit wurde im großtechnischen Maßstab erprobt.

Zur Darstellung der Isoliersuspension 2 werden pro Kilogramm Ethanol bevorzugt 0,04 - 0,06 kg, besonders bevorzugt 0,046 - 0,05 kg Hydroxypropylmethylcellulose verwendet. Neben der Verwendung von Hydroxypropylmethylcellulose hat es sich als erfindungsgemäß besonders

10 bevorzugt erwiesen, der Isoliersuspension 2 Dimethylpolysiloxan zu zusetzen, um Schaumbildung zu vermeiden. Die Menge an Dimethylpolysiloxan, die zur Herstellung der Isoliersuspension 2 unter Rühren zugesetzt wird, beträgt pro Kilogramm Ethanol bevorzugt 0,6 - 1,2 g, besonders bevorzugt 0,8 - 0,9 g. Schließlich wird Talkum unter Rühren zugesetzt und suspendiert. Pro Kilogramm Ethanol gelangen bevorzugt 0,04 - 0,06 kg, besonders bevorzugt

15 0,046 - 0,05 kg Talkum zum Einsatz.

Ein Aspekt der vorliegenden Erfindung betrifft eine ethanolische Isoliersuspension 2, die Hydroxypropylmethylcellulose, vorzugsweise in den vorstehend genannten Mengen enthält. Ein weiterer Aspekt der vorliegenden Erfindung betrifft eine ethanolische Isoliersuspension 2, die

20 neben Hydroxypropylmethylcellulose Dimethylpolysiloxan, vorzugsweise in den vorstehend genannten Mengen, enthält. Ein weiterer Aspekt der vorliegenden Erfindung betrifft eine ethanolische Isoliersuspension 2, die neben Hydroxypropylmethylcellulose und Dimethylpolysiloxan ferner Talkum, vorzugsweise in den vorstehend genannten Mengen, enthält. Ein weiterer Aspekt der vorliegenden Erfindung betrifft eine ethanolische

25 Isoliersuspension 2, die gemäß der vorstehend beschriebenen Vorgehensweise erhältlich ist.

Ein weiterer Aspekt der vorliegenden Erfindung betrifft die Verwendung der ethanolischen Isoliersuspension 2, zur Isolierung von Weinsäurekernen 1. Ein weiterer Aspekt der vorliegenden Erfindung betrifft die Verwendung der ethanolischen Isoliersuspension 2, als

30 Ausgangsmaterial zur Herstellung einer Arzneimittelformulierung des Dabigtranetexilat-methansulfonats.

Die so hergestellte Isoliersuspension 2 wird in einem kontinuierlichen Sprühprozess in einem konventionellen Horizontalcoater auf die zuvor hergestellten Weinsäurepellets 1 aufgesprüht.

35 Pro Kilogramm vorgelegter Weinsäurekerne 1 werden 0,5 - 0,8 kg, bevorzugt 0,55 - 0,75 kg, besonders bevorzugt 0,6 - 0,7 kg Isoliersuspension aufgesprüht.

Das Aufsprühen erfolgt bei definierter Sprütrate. Unter Sprütrate wird die Menge an Isoliersuspension 2 verstanden, die pro Stunde auf die Pellets 1 aufgesprüht wird. Die Sprütrate

ist im erfindungsgemäßen Verfahren abhängig von der Chargengröße. Pro Kilogramm vorgelegte Weinsäurepellets 1 liegt die normierte Sprütrate erfindungsgemäß bevorzugt in einem Bereich von 0,01 - 0,1 (kg/h)/kg, bevorzugt 0,02 - 0,04 (kg/h)/kg, besonders bevorzugt 0,025 - 0,035 (kg/h)/kg. Werden in einem Ansatz beispielsweise 1200 kg Weinsäurekerne
5 vorgelegt, entspricht eine normierte Sprütrate von 0,027 (kg/h)/kg einer faktischen Sprütrate von 32 kg/h. Werden in einem Ansatz beispielsweise 600 kg Weinsäurekerne vorgelegt, entspricht eine normierte Sprütrate von 0,035 (kg/h)/kg einer faktischen Sprütrate von 21 kg/h.

10 Während dieses kontinuierlichen Prozesses werden die Kerne kontinuierlich mit einer Zuluft von bis zu 70°C, vorzugsweise von 25 - 70°C getrocknet.

Unter Zuluftmenge wird die Menge an Trockenluft verstanden, die pro Stunde in das rotierende Pelletbett eingebracht wird. Die Zuluftmenge ist im erfindungsgemäßen Verfahren abhängig von der Chargengröße. Pro Kilogramm ursprünglich vorgelegte Weinsäurekerne 2 liegt die normierte
15 Zuluftmenge erfindungsgemäß bevorzugt in einem Bereich von 1,0 - 2,5 (m³/h)/kg, bevorzugt 1,2 - 2,0 (m³/h)/kg, besonders bevorzugt 1,40 - 1,85 (m³/h)/kg. Werden in einem Ansatz beispielsweise 600 kg Weinsäurekerne 2 vorgelegt, entspricht eine normierte Zuluftmenge von 1,83 (m³/h)/kg einer faktischen Zuluftmenge von 1100 m³/h. Werden in einem Ansatz beispielsweise 1200 kg Weinsäurekerne 3 vorgelegt, entspricht eine normierte
20 Zuluftmenge von 1,42 (m³/h)/kg einer faktischen Zuluftmenge von 1700 m³/h.

Ein weiterer Aspekt der vorliegenden Erfindung betrifft die gemäß des vorstehenden Verfahrens erhaltenen isolierten Weinsäurekerne 3 als solche.

Die erfindungsgemäß erhältlichen isolierten Weinsäurekerne 3 weisen eine gleichmäßige,
25 kugelhähnliche Geometrie auf, die die weitere Verarbeitung deutlich erleichtert. Darüber hinaus weisen die erfindungsgemäßen Pellets 3 nur geringfügige Fehlstellen durch so genannte Satelliten auf. Bei so genannten Satelliten handelten es sich um kleine, außen auf den ansonsten rundlichen Pellets anhaftenden Partikel, die die ansonsten kugelhähnliche Geometrie der Pellets nachteilig beeinflussen. Von besonderer Bedeutung ist die möglichst ideale Kugelform und eine
30 geringe Oberflächenrauigkeit der Pellets 3 für säureempfindliche Wirkstoffe, bei denen Fehlstellen der Isolierung durch Satelliten oder zu rauher Oberfläche durch zu große Weinsäurepulverpartikel zu deutlich verschlechterten Lagerstabilitäten und damit Haltbarkeiten des fertigen Produkts führen kann.

35 Die Herstellung wirkstoffhaltiger Pellets aus den erfindungsgemäßen Pellets 3 kann gemäß im Stand der Technik beschriebener Verfahren erfolgen.
Ein weiterer Aspekt der vorliegenden Erfindung betrifft die Verwendung der erfindungsgemäßen Pellets 3 als Ausgangsmaterial zur Herstellung wirkstoffhaltiger Arzneimittelformulierungen.

Beispiele für die Herstellung von Pelletformulierungen des Dipyridamols ausgehend von Starterpellets finden sich in der EP32562 (insbesondere Beispiele 1 und 2). Beispiele für die Herstellung von Pelletformulierungen des Dipyridamols in Kombination mit Acetylsalicylsäure finden sich in der EP257344 (dort insbesondere Beispiel 2). Zur Herstellung von Dabigatran-haltigen Formulierungen wird beispielsweise auf die Offenbarung der WO 03/074056 verwiesen.

Die in den vorstehend genannten Dokumenten Verfahren zur Beschichtung von Starterpellets mit Wirkstoff können auch ausgehend von den erfindungsgemäßen Pellets 3 zur Anwendung gelangen.

Ein weiterer Aspekt der vorliegenden Erfindung betrifft daher die Verwendung der erfindungsgemäßen Pellets 3 als Ausgangsmaterial zur Herstellung wirkstoffhaltiger Arzneimittelformulierungen bei denen der Wirkstoff ausgewählt ist aus der Gruppe bestehend aus Dipyridamol, Dabigatran und Acetylsalicylsäure oder Kombinationen davon.

Ein bevorzugter Aspekt der vorliegenden Erfindung betrifft die Verwendung der erfindungsgemäßen Pellets 3 als Ausgangsmaterial zur Herstellung einer Dipyridamol-haltigen Formulierung. Ein weiterer bevorzugter Aspekt der vorliegenden Erfindung betrifft die Verwendung der erfindungsgemäßen Pellets 3 als Ausgangsmaterial zur Herstellung einer Dabigatran-haltigen Formulierung.

Die nachstehenden Beispiele dienen der weitergehenden Erläuterung der vorliegenden Erfindung.

Bestimmung der Partikelgrößen der Weinsäure über Luftstrahlsiebung

Meßgerät und Einstellungen:

Meßgerät: Luftstrahlsieb, z.B. Alpine A 200 LS
Siebe: Je nach Bedarf
Einwaage: 10g/Sieb
Dauer: 1 min/Sieb, danach je 1 min bis zur maximalen Gewichtsabnahme von 0,1g

Probenvorbereitung / Produktzufuhr:

Die Substanz wird in einen Mörser überführt und vorhandene Agglomerate durch intensives Mörsern zerstört. Das Sieb mit Gummidichtung und Deckel wird auf eine Waage gestellt, tariert und 10,0 g der gemörserten Substanz auf das Sieb eingewogen. Das Sieb wird inklusive Inhalt, Gummidichtung und Deckel auf das Gerät gesetzt. Die Zeitschaltuhr wird auf 1 Minute eingestellt und das Material für diese Zeit per Luftstrahlsiebung

behandelt. Anschließend wird der Rückstand ausgewogen und dokumentiert. Dieser Vorgang wird solange wiederholt, bis die Gewichtsabnahme des Rückstandes nach Luftstrahlsiebung < 0,1 g beträgt.

5 **Beispiel 1 - Herstellung der Starter Pellets**

480kg Wasser werden auf 50°C erwärmt und unter Rühren mit 120 kg Acacia (Gummi Arabicum) in einem konventionellen Ansatzbehälter mit Klöpperboden und Rührorgan versetzt. Bei konstanter Temperatur wird solange gerührt, bis eine klare Lösung erhalten wird. Liegt eine klare Lösung vor (üblicherweise nach 1 bis 2 Stunden) werden unter Rühren 600 kg Weinsäure
10 zugesetzt. Die Zugabe der Weinsäure erfolgt bei konstanter Temperatur und unter fortgesetztem Rühren. Nach beendeter Zugabe wird noch etwas 5 bis 6 Stunden nachgerührt.

1000 kg Weinsäure werden in einen langsam rotierenden (3 Umdrehungen pro Minute) nicht perforierten Horizontalkessel mit Sprüh- und Pulverauftragungseinheit (z.B. Driamat 2000/2.5)
15 eingefüllt. Vor dem Sprühstart wird ein Muster der Säure gezogen, um sie einer Siebanalyse zu unterziehen. Bei der vorgelegten Säure handelt es sich um Weinsäurepartikel mit einer Partikelgröße im Bereich von 0,4-0,6 mm.

Auf die so vorgelegten Weinsäurepartikel wird die nach vorstehender Vorgehensweise erhaltene Säuregummilösung aufgesprüht. Beim Sprühen wird die Zuluftmenge auf 1000m³/h und 35°-
20 75°C eingestellt. Der Differenzdruck beträgt 2mbar und die Umdrehungsgeschwindigkeit des Kessels 9 Umdrehungen pro Minute. Die Düsen werden sollten in einem Abstand von 350 – 450mm zum Füllgut angebracht sein.

Das Aufsprühen der Säuregummilösung erfolgt im Wechsel mit den folgenden Prozessschritten.
25 Nach Aufsprühen von etwa 4,8 kg der Säuregummilösung auf die Weinsäurepartikel der Partikelgröße 0,4-0,6 mm und Verteilen der Lösung werden etwa 3,2 kg Weinsäurepulver auf die feuchten Weinsäurepartikel aufgedeut. Bei genanntem Weinsäurepulver handelt es sich um feine Weinsäurepartikel mit einer Partikelgröße von < 50 Mikrometern. Insgesamt werden 800 kg Weinsäurepulver benötigt. Nach Aufputern mit genanntem Weinsäurepulver und weiterem
30 Verteilen wird das Sprühgut getrocknet, bis eine Guttemperatur von etwa 40°C erreicht ist. Hieran schließt sich wieder das Aufsprühen der Säuregummilösung an.

Diese Zyklen werden so oft durchlaufen, bis die Säuregummilösung aufgebraucht ist. Nach beendetem Prozess werden die Säurepellets im Kessel bei 3 U/Min 240 Minuten lang
35 nachgetrocknet. Um eine Verklumpung nach der Nachtrocknung zu vermeiden, erfolgt stündlich eine Intervallschaltung für 3 Minuten bei 3 U/Min. Im vorliegenden Fall bedeutet dies, dass der Kessel im Intervall von 1 Stunde 3 Minuten mit 3 U/min dreht um anschließend zu ruhen. Danach werden die Säurepellets in eine Trocknungsanlage umgefüllt. Es folgt die anschließende Trocknung bei 60°C über einen Zeitraum von 48 Stunden. Zum Schluss wird die Kornverteilung

über eine Siebanalyse bestimmt. Die Korngröße mit dem Durchmesser 0,6 – 0,8mm entspricht der Gutware. Dieser Anteil sollte >85% sein.

Beispiel 2 - Isolierung der Starter Pellets

- 5 Zur Herstellung der Isoliersuspension werden 666,1 (347,5) kg Ethanol im Ansatzbehälter vorgelegt und die Hydroxypropylmethylcellulose 33,1 (17,3) kg unter Rühren mit ca. 600 U/Min zugegeben und gelöst. Danach wird unter den gleichen Bedingungen 0,6 (0,3) kg Dimeticon zugegeben. Kurz vor Gebrauch wird Talkum 33,1 (17,3) kg, ebenfalls unter Rühren, zugegeben und suspendiert.

10

Die Säurepellets 1200 (600) kg werden in den Coatinganlage (z.B. GS- Coater Mod. 600/Mod. 1200) eingefüllt und dort im rotierenden Kessel in einem mehrstündigen kontinuierlichen Sprühprozess mit einer Sprütrate von 32 kg/h im 1200 kg Ansatz bzw. 21 kg/h im 600 kg Ansatz mit der oben beschriebenen Isoliersuspension besprüht. Dabei werden die Pellets

- 15 kontinuierlich mit einer Zuluft von bis zu 70°C getrocknet.

Nach der Entleerung des GS-Coaters werden die isolierten Starter Pellets durch Sieben fraktioniert. Die Gutfraktion mit einem Durchmesser $\leq 1,0$ mm wird gelagert und weiter verwendet

Patentansprüche

- 5 1) Verfahren zur Herstellung isolierter Weinsäurepellets 3, dadurch gekennzeichnet, dass in einem ersten Schritt Weinsäurepellets 1 hergestellt werden, auf die in einem zweiten Schritt eine ethanolische Isoliersuspension 2 aufgesprüht wird, die Hydroxypropylmethylcellulose enthält.
- 2) Verfahren zur Herstellung von isolierten Weinsäurepellets 3 nach Anspruch 1, dadurch
10 gekennzeichnet, dass zur Herstellung der Weinsäurepellets 1 Weinsäurepartikeln mit einer Partikelgröße im Bereich von 0,2-0,8 mm im Wechsel mit einer Lösung aus Weinsäure und Bindemittel, bevorzugt mit Gummi Arabicum besprüht und anschließend mit feinem Weinsäurepulver mit einer Partikelgröße von < 100 Mikrometern bedudert werden.
- 15 3) Verfahren zur Herstellung von isolierten Weinsäurepellets 3 nach Anspruch 2, wobei wenigstens 90% der vorgelegten Weinsäurepartikel eine Partikelgröße im Bereich von 0,2-0,8 mm aufweisen.
- 4) Verfahren zur Herstellung von isolierten Weinsäurepellets 3 nach Anspruch 2 oder 3,
20 wobei wenigstens 85% des Weinsäurepulvers eine Partikelgröße von < 100 Mikrometern aufweisen.
- 5) Verfahren zur Herstellung von isolierten Weinsäurepellets 3 nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, dass die verwendete ethanolische Isoliersuspension 2 neben
25 Hydroxypropylmethylcellulose ferner Talkum enthält.
- 6) Verfahren zur Herstellung von isolierten Weinsäurepellets 3 nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, dass die verwendete ethanolische Isoliersuspension 2 neben Hydroxypropylmethylcellulose und Talkum ferner Dimethylpolysiloxan enthält.
30
- 7) Isolierte Weinsäurepellets 3 erhältlich nach einem der Ansprüche 1 bis 6.
- 8) Verwendung Isolierter Weinsäurepellets 3 nach Anspruch 7 als Ausgangsmaterial zur
Herstellung wirkstoffhaltiger Arzneimittelformulierungen.
35
- 9) Verwendung nach Anspruch 8, wobei es sich um wirkstoffhaltige Arzneimittelformulierungen handelt, bei denen der Wirkstoff ausgewählt ist aus der Gruppe bestehend aus Dipyridamol, Dabigatran und Acetylsalicylsäure oder Kombinationen davon.

- 10) Ethanolische Isoliersuspension 2, die Hydroxypropylmethylcellulose enthält.
- 11) Ethanolische Isoliersuspension 2 nach Anspruch 10, die ferner Dimethylpolysiloxan enthält.
- 5 12) Ethanolische Isoliersuspension 2 nach Anspruch 10 oder 11, die ferner Talkum enthält.

10

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/053468

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/16 A61K9/50 A61K31/4184 A61K31/4439 A61K31/519
A61K31/60

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 practical, 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 2008/022932 A (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; PEARN) 28 February 2008 (2008-02-28) pages 54-60; example 1 claims -----	1-8, 10-12
X	EP 1 894 561 A (REDDYS LAB LTD DR [IN]; REDDYS LAB INC DR [US]) 5 March 2008 (2008-03-05) examples 1-5 page 2, paragraph 9 - page 3, paragraph 16 -----	7-9
Y	-----	1-12
X	EP 0 257 344 A (THOMAE GMBH DR K [DE]) 2 March 1988 (1988-03-02) cited in the application page 4, lines 18-26 example 2 -----	7-9
-/--		

☒ 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 document 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.

G document member of the same patent family

Date of the actual completion of the international search

15 Mai 2009

Date of mailing of the international search report

25/05/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

van de Wetering, P

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/053468

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/074056 A (BOEHRINGER INGELHEIM PHARMA [DE]; BRAUNS ULRICH [DE]) 12 September 2003 (2003-09-12) cited in the application page 2, lines 24-30 page 3, line 4 - page 4, line 3 example 1 claims 10,11	1-12

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2009/053468

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2008022932	A	28-02-2008	AR 062321 A1	29-10-2008
			AU 2007287639 A1	28-02-2008
			CL 23582007 A1	18-04-2008
			EP 2056797 A2	13-05-2009
			US 2008069873 A1	20-03-2008
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EP 0257344	A	02-03-1988	AU 603146 B2	08-11-1990
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			BR 0306559 A	30-11-2004
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			EP 1485094 A1	15-12-2004
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			NZ 535663 A	30-06-2006
			NZ 546367 A	29-08-2008
			SG 146435 A1	30-10-2008

Form PCT/ISA/210 (patent family annex) (April 2005)

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP2009/053468

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

INV. A61K9/16 A61K9/50 A61K31/4184 A61K31/4439 A61K31/519
A61K31/60

Nach der Internationalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)

A61K

Recherchierte, aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	WO 2008/022932 A (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; PEARN) 28. Februar 2008 (2008-02-28) Seiten 54-60; Beispiel 1 Ansprüche -----	1-8, 10-12
X	EP 1 894 561 A (REDDYS LAB LTD DR [IN]; REDDYS LAB INC DR [US]) 5. März 2008 (2008-03-05) Beispiele 1-5 Seite 2, Absatz 9 - Seite 3, Absatz 16 -----	7-9
Y	-----	1-12
X	EP 0 257 344 A (THOMAE GMBH DR K [DE]) 2. März 1988 (1988-03-02) in der Anmeldung erwähnt Seite 4, Zeilen 18-26 Beispiel 2 -----	7-9
-/--		

☒ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen ☒ Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :

A Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

E älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

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Z Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche

15. Mai 2009

Absendedatum des internationalen Recherchenberichts

25/05/2009

Name und Postanschrift der Internationalen Recherchenbehörde

Europäisches Patentamt, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Bevollmächtigter Bediensteter

van de Wetering, P

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP2009/053468

C. (Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN		
Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	WO 03/074056 A (BOEHRINGER INGELHEIM PHARMA [DE]; BRAUNS ULRICH [DE]) 12. September 2003 (2003-09-12) in der Anmeldung erwähnt Seite 2, Zeilen 24-30 Seite 3, Zeile 4 - Seite 4, Zeile 3 Beispiel 1 Ansprüche 10,11	1-12

Formblatt PCT/ISA/210 (Fortsetzung von Blatt 2) (April 2005)

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen

PCT/EP2009/053468

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
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EP 0257344 A	02-03-1988	AU 603146 B2	08-11-1990
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		CA 1302272 C	02-06-1992
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		FI 873492 A	14-02-1988
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		IL 83510 A	16-02-1992
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		HR 20040807 A2	28-02-2005
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		JP 2006328081 A	07-12-2006
		MX PA04008542 A	06-12-2004
		NO 326918 B1	16-03-2009
		NZ 535663 A	30-06-2006
		NZ 546367 A	29-08-2008
		SG 146435 A1	30-10-2008



United States Patent and Trademark Office

Office of the Chief Financial Officer

March 21, 2024

23552
MERCHANT & GOULD P.C.
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Dear Sir/Madam,

The United States Patent and Trademark Office (USPTO) has reviewed your refund request for Reference Number **18356642** - Refund Request ID **REFND-20240216-77550**. Below is the current status of your refund request assigned to the following processing area: Office of Patent Application Processing

Fee code	Decision	Decision Reason(s)	Refund Amount
1202	Dismissed	Other - see attached page(s)	\$0.00
1203	Dismissed	Other - see attached page(s)	\$0.00

Please refer to the following page to review the detailed dismissal reason(s).

You will receive a separate decision letter for any additional fee codes assigned to other processing areas, if applicable. Decisions may be subject to change if an error is identified.

For questions related to this refund request, contact the Office of Patent Application Processing at (703) 756-1158.

Thank you,
Refund Branch

Enclosure: Refund Dismissal Reason(s)

Refund Dismissal Reason(s) for fee code 1202:

- Other - The Office cannot refund excess claim fees that were properly paid merely because applicant cancels the excess claims prior to the first Office action. Preliminary amendments canceling or adding claims, will be taken in to account in determining the appropriate fees due. No, refund will be made for claims being canceled that have already been paid for. See MPEP § 607.02.

Refund Dismissal Reason(s) for fee code 1203:

- Other - The Office cannot refund excess claim fees that were properly paid merely because applicant cancels the excess claims prior to the first Office action. Preliminary amendments canceling or adding claims, will be taken in to account in determining the appropriate fees due. No, refund will be made for claims being canceled that have already been paid for. See MPEP § 607.02.

USSN: 18/356,642

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor:	Pratibha S. PILGAONKAR	Examiner:	Not yet assigned
Serial No.:	18/356,642	Group Art Unit:	Not yet assigned
Filed:	July 21, 2023	Docket No.:	70204.0018USC2
Title:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

SECOND PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Attention: Commissioner for Patents

Prior to examination on the merits, Applicant requests entry of the following amendments.

Amendments to the Claims are reflected in the Listing of Claims that begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. – 20. (Cancelled)
21. (New) A composition comprising: a mixture of at least two distinct types of particles wherein:
- a) the first type of particles comprise dabigatran etexilate mesylate, wherein the first type of particles is free from tartaric acid; and
 - b) the second type of particles comprise tartaric acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate mesylate.
22. (New) The composition of claim 21, wherein the first type of particles is coated with a protective coating layer.
23. (New) The composition according to claim 21, further comprising at least one pharmaceutically acceptable excipient.
24. (New) The composition according to claim 23, wherein the pharmaceutically acceptable excipient is selected from the group consisting of binders, diluents, lubricants, and mixtures thereof.
25. (New) The composition according to claim 24, wherein the binder comprises microcrystalline cellulose; the disintegrant comprises sodium croscarmellose, crospovidone, or mixtures thereof; and the diluent comprises mannitol, lactose, or mixtures thereof.

26. (New) The composition according to claim 21, wherein the particles are powder, granules, pellets, beads, or minitabets.
27. (New) The composition according to claim 21, wherein the second type of particles has a particle size between 100 microns and 900 microns
28. (New) The composition according to claim 27, wherein the second type of particles has a particle size between 400 microns and 700 microns.
29. (New) The composition of claim 27, wherein the first type of particles has a particle size comprised between 100 microns and 1000 microns.
30. (New) The composition according to claim 21, wherein the protective coating comprises talc, hydroxypropyl cellulose, or mixtures thereof.
31. (New) The composition according to claim 24, wherein the binder is selected from the group consisting of microcrystalline cellulose, low substituted hydroxypropyl cellulose, hydroxypropyl cellulose, hypromellose, hydroxyethylcellulose, hydroxyethyl methylcellulose, ethyl cellulose, cellulose gum, xanthan gum, and mixtures thereof.
32. (New) The composition of claim 21, wherein the protective coating layer is seal coated with a pharmaceutically acceptable film forming agent.
33. (New) The composition of claim 32, wherein the film forming agent is selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, acrylic acid polymers, methacrylic acid polymers, and mixtures thereof.
34. (New) The composition according to claim 21, comprising from 0.01 wt % to 90 wt % of dabigatran etexilate as dabigatran etexilate mesylate.

35. (New) The composition according to claim 21, comprising from 2 wt % to 95 wt % of the tartaric acid.

36. (New) A unit dosage form prepared from the composition according to claim 21, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

37. (New) The unit dosage form according to claim 36, wherein the unit dosage form is a capsule or a tablet.

38. (New) A capsule composition comprising: a mixture of at least two distinct types of particles wherein

a) the first type of particles comprise dabigatran etexilate mesylate, wherein the first type of particles is free from tartaric acid; and

b) the second type of particles comprise tartaric acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate mesylate, wherein the two types of particles are within the capsule.

39. (New) The capsule according to claim 38, wherein the capsule is a hard capsule comprising gelatine or hydroxypropyl methylcellulose.

40. A capsule containing a pharmaceutical composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein

a) the first type of particles comprise dabigatran etexilate mesylate, wherein the first type of particles is free from tartaric acid; and

b) the second type of particles comprise tartaric acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate mesylate.

REMARKS

Claims 21-40 are pending, with claims 21, 38, and 40 being independent. In the Preliminary Amendment, original claims 1-20 are cancelled without prejudice to or disclaimer of the subject matter. Support for the amendments may be found throughout the specification, including for example, in the original claims; page 7, lines 11-14 and 25-27; page 8, lines 18-24; page 11, lines 6-7; page 12, lines 21-26; page 14, lines 19-21 and lines 4-7; page 15, lines 8-14; and the Examples.

Applicants respectfully request that this Preliminary Amendment be entered into the record prior to examination and consideration of the above-identified application. If a telephone conference would be helpful in resolving any issues concerning this application, please contact the undersigned Applicant's attorney-of record.

Please charge any additional fees or credit any overpayment to Deposit Account No. 13-2725 (Docket No.: 70204.0018USC2).

Respectfully submitted,

March 18, 2024

/Melissa M. Hayworth/

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UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/356,642

RECEIPT DATE / TIME
03/18/2024 05:26:07 PM Z ET

ATTORNEY DOCKET #
70204.0018USC2

Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 4286

FILED BY Keyla Clements

PATENT CENTER # 64732338

FILING DATE 07/21/2023

CUSTOMER # 23552

FIRST NAMED INVENTOR Pratibha S. PILGAONKAR

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Melissa Hayworth

Documents

TOTAL DOCUMENTS: 3

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
702040018USC22ndPreliminaryAmendment.pdf		5	-	88 KB
702040018USC22ndPreliminaryAmendment-A.PE.pdf	(1-1)	1	Preliminary Amendment	75 KB
702040018USC22ndPreliminaryAmendment-CLM.pdf	(2-4)	3	Claims	79 KB
702040018USC22ndPreliminaryAmendment-REM.pdf	(5-5)	1	Applicant Arguments/Remarks Made in an Amendment	78 KB

Digest

DOCUMENT MESSAGE DIGEST(SHA-512)

702040018USC22ndPreliminaryAmendment.pdf	CA012E4BB55A0B01C4123D063612DC0D274E4F7A7EF5ADF8 BA30FFF5DE73D39C39F44F5A0B42715B06F196E68F08F15B7 589CA73C4B7BB39E45DA541C03EC32A
702040018USC22ndPreliminaryAmendment-A.PE.pdf	C92D0E8CEFC1A9E3BCCB7D6E45448DC3C57F8A475624289E 5F238FBD5FAB3BA27A391BBD4D237F3C039C32E736047DDF 5E7A2603F7345598E28E16B22E32DA5D
702040018USC22ndPreliminaryAmendment-CLM.pdf	E1C1FD3F882F9BD8AAD2F353DEA6DC1C53519540BE81DF38 74102D4F62C2597147A118FA8B88EA530C19C6FCD2E6D71C1 12D6875E3995AF04D8E846BE9F9CC8A
702040018USC22ndPreliminaryAmendment-REM.pdf	0834B1A40700B78639F6D7F1132931EA26AA3352DCD66E55E 9D330378F53165D90049848127929EB3D54AFDF04BF5EFC646 0AEFB894890D7433C80322A1E8F03

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



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APPLICATION # 18/356,642	RECEIPT DATE / TIME 02/15/2024 04:21:40 PM Z ET	ATTORNEY DOCKET # 70204.0018USC2
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Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4286	FILED BY	Keyla Clements
PATENT CENTER #	64339617	FILING DATE	07/21/2023
CUSTOMER #	23552	FIRST NAMED INVENTOR	Pratibha S. PILGAONKAR
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Melissa Hayworth

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
702040018USC2Requestfor Refund.pdf	1	Refund Request	740 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
702040018USC2RequestforRef und.pdf	C4F1C6E15C37533369F83B2240400034C243C7C83A884E2949 15D0CCE8313985A19E233EAD361A259943C2F959001973CC1 5D027ABCDF48BE882D5E01F225F97

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REQUEST FOR REFUND

Reference # <i>(Patent #, Application #, Trademark Serial #, Registration #, etc.)</i>		Title of Invention or Mark Information	
18/356642		ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	
Attorney Docket # <i>(if applicable)</i>	Payment Date <i>(mm/dd/yyyy)</i>	Refund Request Amount	
70204.0018USC2	02/15/2024	\$ 960.00	
Refund Option <i>(Select one)</i>			
☒ If approved, issue the refund to the account associated with the original payment.			
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☐ If approved, and the original payment was a check, issue the refund as a U.S. Treasury check.			
Reason for Refund Request <i>Refund requests must generally be filed within 2 years of payment date (37 CFR 1.26 and 2.209)</i>			
☐ Duplicate Payment ☒ No Fee Due ☐ Office Error ☐ Other:			
☐ Small Entity Later Established* <i>*(Must be filed within 3 months of payment date, 37 CFR 1.28. There is no refund when micro entity is later established.)</i>			
Rationale <i>(Supporting documentation may be submitted with this form)</i>			
Applicants filed the application with no fees on July 21, 2023. A Notice to File Missing Parts (NTFMP) issued on August 14, 2023. A response to the NTFMP and a Preliminary Amendment removing multiple dependencies and any additional claims were filed on February 14, 2024. The total claim count is 20 dependent and 1 independent claim. Thus, the deposit account should not have been charged pending a Response to NTFMP. A refund of \$960.00 is requested.			

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APPLICATION #
18/356,642

RECEIPT DATE / TIME
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Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 4286

FILED BY Keyla Clements

PATENT CENTER # 64326239

FILING DATE 07/21/2023

CUSTOMER # 23552

FIRST NAMED INVENTOR Pratikha S. PILGAONKAR

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Melissa Hayworth

Documents

TOTAL DOCUMENTS: 7

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
702040018USC2EOT.pdf	2	Extension of Time	284 KB
702040018USC2Declarations.pdf	4	Oath or Declaration filed	1275 KB
702040018USC2IDSTransmittal.pdf	1	Transmittal Letter	90 KB
702040018USC2IDS.pdf	7	Information Disclosure Statement (IDS) Form (SB08)	1013 KB
702040018USC2PreliminaryAmendmentResponse.pdf	7	-	158 KB
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702040018USC2PrelimAm endandResponse-CLM.pdf	(2-5)	4	Claims	145 KB
702040018USC2PrelimAm endandResponse-REM.pdf	(6-7)	2	Applicant Arguments/Remarks Made in an Amendment	91 KB

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702040018USC2PrelimAmenda ndResponse.pdf	95450846857A73CE3030DD7AF7B94562E8B125AC3C4B53CA1 816BB75F2466B1302B4B75820974D41473F3C3C421CD38869E E6AD4D512B066D88EA68857699614
702040018USC2PrelimAmenda ndResponse-PEFR.pdf	037665D37335495347AF8EC9C7C81F31C8189250DF2FC8AAC 8A3CC48C72643365616D2E32D5F6AC53523CC434C1EB0098A 28496CAA6C2140142B22CA525BDD1B
702040018USC2PrelimAmenda ndResponse-CLM.pdf	3ED62F6BF229A940C143FE49969918BB897D7DF29D185C55B EDB07B7693970F410E1467F2C3DFE4712DAB7AEDF91345582 71654D7353341EA8B2844EF9E8AB90
702040018USC2PrelimAmenda ndResponse-REM.pdf	FFF152E9E38E61C486B94209DE59E0290FD0B23F5BEC8CA60 DA4F792FB8B8276D8B8B2C60733E143479F4DE606853A38CE 1CB037A6EC166ED85984EFB21974BF

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18356642
	Filing Date		2023-07-21
	First Named Inventor	Pratibha S. PILGAONKAR	
	Art Unit		
	Examiner Name		
	Attorney Docket Number	70204.0018USC2	

U.S.PATENTS Remove						
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	1	20050234104		2005-10-20	Schmid, et al.	
	2	20110129538		2011-06-02	Landerer, et al.	
	3	20040109890		2004-06-10	Sugimoto	
	4	20050123606		2005-06-09	Kidane	
	5	20060183779		2006-08-17	Brauns	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18356642	
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	Art Unit			
	Examiner Name			
	Attorney Docket Number		70204.0018USC2	

	6	20060074056		2006-04-06	Vaisburg, et al.	
	7	20050038077		2005-02-17	Kohlrausch	
	8	20080069891		2008-03-20	Habib	

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	1	2005028468	WO		2005-03-31	Boehringer Ingelheim PH		☐
	2	2012001156	WO		2012-01-05	Krka Tovarna Zdravil		☐
	3	9837075	WO		1998-08-27	Boehringer Ingelheim PH		☐
	4	0012064	WO		2000-03-09	Chen		☐
	5	101632668	CN		1020-01-27	Brauns		☐
	6	1366760	EP		2002-02-12	Sugimoto		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18356642	
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	First Named Inventor		Pratibha S. PILGAONKAR	
	Art Unit			
	Examiner Name			
	Attorney Docket Number		70204.0018USC2	

	7	2001524131	JP		2001-11-27	Chen		☐
	8	2002316923	JP		2002-10-31	Sugimoto		☐
	9	2002523443	JP		2002-07-30	Chen		☐
	10	2005046663	WO		2005-05-26	Kidane		☐
	11	2005121102	WO		2005-12-22	Torkelson		☐
	12	2005519099	JP		2005-06-30	Brauns		☐
	13	2007092026	WO		2007-08-16	Leibovici		☐
	14	2007510655	JP		2007-04-26	Kidane		☐
	15	2008501702	JP		2008-01-24	Torkelson		☐
	16	2008534681	JP		2008-08-28	Leibovici		☐
	17	2476054	CA		2003-09-12	Brauns		☐

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	Art Unit			
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	18	9850019	WO		1998-11-12	Chen		☐
	19	H04103525	JP		1992-04-06	Masatsune		☐
	20	03074056	WO		2003-09-12	Boehringer Ingelheim		☐

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	1	Declaration under 37 C.F.R. 1.132 of Dr. Ulrich Brauns filed in U.S. Application No. 11/381890 dated 11 March 2014.	☐
	2	Australian Public Assessment Report for Dabigatran Etxilate Mesylate, May 2011	☐
	3	Belousov, Yu B., et al., Rational Pharmacotherapy in Cardiology, Vol. 8, No. 1, pp. 37-44, 2012, English Abstract	☐
	4	Bozhkova, S.A., Traumatology and Orthopedics, Vol, 1, No. 59, pp 138-143, 2011, English Abstract	☐
	5	Stangier, Clin Pharmacokinet 2008: 47 (5) 285-295	☐
	6	International Search Report for PCT/EP2013/053426 dated 16 April 2013	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18356642
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	Art Unit		
	Examiner Name		
	Attorney Docket Number		70204.0018USC2

7	PubChem, Dabigatran Etexilate (accessed 03/21/2016), pp. 1-25	☐
8	Vippagunta et al., "Crystalline Solids," Advanced Drug Delivery Reviews, (2001), 48, pp. 3-26	☐
9	Muller, Inorganic Chemistry (1993) pp 14-15	☐
10	Wikipedia, Dabigatran (09/25/2015) pp. 1-4	☐
11	European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), European Public Assessment Report for Pradaxa (dabigatran etexilate), published 23 April 2008, pp. 1-36	☐
12	European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), Post Authorisation Summary of Positive Opinion for Pradaxa (dabigatran etexilate mesilate), published 14 April 2011, pp. 1-2	☐
13	Loke, Y. K., et al., Journal of Clinical Pharmacy and Therapeutics, (2011), 36, 111-124.	☐
14	Huisman, Menno V., et al., Thromb Haemost, (2012); 107: 838-847.	☐

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	Filing Date		2023-07-21
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	Art Unit		
	Examiner Name		
	Attorney Docket Number	70204.0018USC2	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Melissa M. Hayworth/	Date (YYYY-MM-DD)	2024-02-14
Name/Print	Melissa M. Hayworth	Registration Number	45774

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
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Approved for use through 01/31/2014. OMB 0661-0032

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)	Attorney Docket Number	ESTEVE 6 PCT US
	First Named Inventor	Pratibha PILGADKAR, et al
	COMPLETE IF KNOWN	
	Application Number	
	Filing Date	21 August 2014
	Art Unit	
	Examiner Name	

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

(Title of the invention)

As a below named inventor, I hereby declare that:

This declaration is directed to:

☒ The attached application,

OR

☐ United States Application Number or PCT International application number _____
filed on _____

Statement under 35 USC § 115

The above-identified application was made or authorized to be made by me.

I (we) believe I (we) am (are) the original inventor or an original joint inventor of a claimed invention in the application.

I (we) hereby acknowledge that any willful false statement made in this declaration is punishable under 18 USC § 1001 by fine or imprisonment of not more than five (5) years, or both.

And I (we) further authorize any member of The Firm of Hueschen and Saga, PLLC to insert or complete any information in this document to effect its submission in the United States Patent and Trademark Office, and countries foreign thereto.

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In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the above-identified patent application with respect to: 1) the above-identified patent application-as-filed; 2) any foreign application to which the above-identified patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified patent application; and 3) any U.S. application-as-filed from which benefit is sought in the above-identified patent application.

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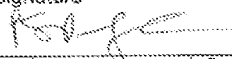
[Page 1 of 2]

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(P151 - rev. 11/2012)

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WARNING: Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available. Petitioner/applicant is advised that documents which form the record of a patent application (such as the PTO/SB/01) are placed into the Privacy Act system of records DEPARTMENT OF COMMERCE, COMMERCE-PAT-7, System name: <i>Patent Application Files</i>. Documents not retained in an application file (such as the PTO-2038) are placed into the Privacy Act system of COMMERCE/PAT-TM-10, System name: <i>Deposit Accounts and Electronic Funds Transfer Profiles</i>.						
LEGAL NAME OF SOLE OR FIRST INVENTOR:						
(E.g., Given Name (first and middle (if any)) and Family Name or Surname)						
Pratibha S. PILGAONKAR						
Inventor's Signature				Date		
				31 st July 2014		
Residence: City		State		Country		
Mumbai				INDIA		
Mailing Address						
221 Annexe Bldg. Goregaon-Mulund Link Road						
City		State		Zip		Country
Mumbai				400 078		INDIA
☒ Additional inventors are being named on the <u>2</u> supplemental sheet(s) PTO/AIA/10 attached hereto						

[Page 2 of 2]

SUPPLEMENTAL SHEET FOR DECLARATION	ADDITIONAL INVENTOR(S)
	Supplemental Sheet (for PTO/AIA/08.09)

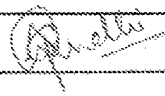
Page 1 of 2

Legal Name of Additional Joint Inventor:			
(E.g., Given Name (first and middle (if any)) and Family Name or Surname)			
Maharukh T. RUSTOMJEE			
Inventor's Signature	<i>M.T. Rustomjee</i>		Date <i>31/7/2014</i>
Residence, City	Mumbai	State	INDIA
221 Annexe Bldg, Goregaon-Mulund Link Road			
Mailing Address			
City	Mumbai	State	INDIA
Zip	400 078	Country	

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

SUPPLEMENTAL SHEET FOR DECLARATION	ADDITIONAL INVENTOR(S) Supplemental Sheet (for PTO/AIA/08,09) Page <u>2</u> of <u>2</u>
---	---

Legal Name of Additional Joint Inventor: (E.g., Given Name (first and middle (if any)) and Family Name or Surname) Anilkumar S. GANDHI			
Inventor's Signature 		Date <u>31st July 2014</u>	
Residence City <u>Mumbai</u>	State _____	Country <u>INDIA</u>	
Mailing Address <u>221 Annexe Bldg, Goregaon-Mulund Link Road</u>			
City <u>Mumbai</u>	State _____	Zip <u>400 078</u>	Country <u>INDIA</u>

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-756-9199) and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor:	Pratibha S. PILGAONKAR	Examiner:	Not yet assigned
Serial No.:	18/356,642	Group Art Unit:	Not yet assigned
Filed:	July 21, 2023	Docket No.:	70204.0018USC2
Title:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

**PRELIMINARY AMENDMENT AND
RESPONSE TO NOTICE TO FILE MISSING PARTS**

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Attention: Commissioner for Patents

In complete response to the Notice to File Missing Parts of NonProvisional Application, dated August 14, 2023, Applicant submits herewith the following amendment and a four-month extension of time.

Amendments to the Claims are reflected in the Listing of Claims that begins on page 2 of this paper.

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Original) A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid.
2. (Original) A composition according to claim 1 wherein at least one type of particles are coated with a protective coating layer.
3. (Currently Amended) A composition according to ~~any one of claims 1 and 2~~claim 1 additionally comprising at least one pharmaceutically acceptable excipient.
4. (Currently Amended) A composition according to ~~any preceding claim 1~~ wherein said first type of particles is free from acids.
5. (Currently Amended) A composition according to ~~any preceding claim 1~~ wherein said second type of particles is free from dabigatran etexilate.
6. (Currently Amended) A composition according to ~~any preceding claim 1~~ comprising from 0.01 wt % to 90 wt % of dabigatran etexilate (expressed as dabigatran etexilate mesylate).
7. (Currently Amended) A composition according to ~~any preceding claim 1~~ wherein at least 90% by weight of the organic acid present in the composition is contained in said second type of

particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients.

8. (Currently Amended) A composition according to ~~any preceding~~ claim 1 wherein said first type of particles is coated with a protective coating layer.

9. (Currently Amended) A composition according to ~~any preceding~~ claim 1 wherein said second type of particles is coated with a protective coating layer.

10. (Currently Amended) A composition according to ~~any preceding~~ claim 1 comprising from 2 wt % to 95 wt % of said at least one pharmaceutically acceptable organic acid.

11. (Currently Amended) A composition according to ~~any preceding~~ claim 1 wherein at least 90% by weight, of the organic acid present in the composition is contained in said second type of particles, the rest (if any) of the organic acid forming part of said excipients.

12. (Currently Amended) A unit dosage form prepared from a composition according to ~~any preceding~~ claim 1 which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

13. (Currently Amended) Composition according to ~~any one of claims 1 to 11~~ claim 1 or a unit dose ~~according to claim 12~~ for use in the reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or in the prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

14. (Currently Amended) Use of a composition according to ~~any one of claims 1 to 11~~ claim 1 or a unit dose ~~according to claim 12~~ for the preparation of a medicament to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or to prevent venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery

15. (Currently Amended) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the subject in need thereof a composition according to ~~any one of claims 1 to 11~~claim 1 or a unit dose ~~according to claim 12~~.

16. (Currently Amended) A process for the preparation of a composition according to ~~any one of claims 3 to 11~~claim 3 comprising the step of mixing said first type of particles and said second type of particles with a at least one at least one pharmaceutically acceptable excipient.

17. (Original) The process of claim 16 wherein said first type of particles are prepared by granulation.

18. (Original) The process according to claim 17 comprising the steps of:

- (i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;
- (ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;
- (iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;
- (iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;
- (v) coating the organic acid granules with a protective coating layer;
- (vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;
- (vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;
- (viii) adding a lubricant to the blend of step (vii); and
- (ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

19. (Original) The process according to claim 17 comprising the steps of:

- (i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;
- (ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;
- (iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;
- (iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;
- (v) coating the granules of dabigatran etexilate with a protective coating layer;
- (vi) blending the granules of step (iv) with the coated granules of step (v) to form a mixture of at least two types of granules;
- (vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;
- (viii) adding a lubricant to the blend of step (vii); and
- (ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

20. (Original) A process according to claim 17 comprising the steps of:

- (i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;
- (ii) granulating the blend of step (i) with a binder solution to form granules of the dabigatran etexilate;
- (iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;
- (iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;
- (v) coating the organic acid pellets of step (iv) with a protective coating layer;
- (vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;
- (vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;
- (viii) adding a lubricant to the blend of step (vii); and
- (ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

REMARKS

Claims 1-20 are pending, with claim 2 being independent. In the Preliminary Amendment, the claims have been amended to remove multiple dependencies without prejudice to or disclaimer of the subject matter. Applicants expressly reserve the right to add additional new claims directed to the subject matter of the multiple dependencies, original claims, and/or subject matter as disclosed in the specification. Applicants further expressly reserve the right to file one or more divisional and/or continuation applications directed to this subject matter.

In the Preliminary Amendment, claims 3-16 also have been amended to improve their form in accordance with U.S. patent practice. Support for the amendments may be found throughout the specification, including in the original claims. Therefore, no new matter has been added.

The Preliminary Amendment filed herewith cancels all multiple dependent claims and no further fees are believed to be due in response to the Notice to File Missing Parts.

Applicant submit the following filing fees: Application fee \$320; Search Fee \$700; Examination Fee \$800; Late Surcharge \$160. Prior to examination of the above-identified application, please enter the following amendments.

Applicants respectfully request that this Preliminary Amendment be entered into the record prior to examination and consideration of the above-identified application. If a telephone conference would be helpful in resolving any issues concerning this application, please contact the undersigned Applicant's attorney-of record.

70204.0018USC2
18/356,642
Preliminary Amendment

Please charge any additional fees or credit any overpayment to Deposit Account
No. 13-2725 (Docket No.: 70204.0018USC2).

Respectfully submitted,

February 14, 2024

/Melissa M. Hayworth/

Melissa M. Hayworth
Registration No. 45,774

MERCHANT & GOULD PC
P.O. Box 2903
Minneapolis, MN 55402
Telephone No. 703.684.2522



PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) 70204.0018USC2																																		
Application Number 18/356,642	Filed July 21, 2023																																			
For ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE																																				
Art Unit	Examiner																																			
This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application. The requested extension and fee are as follows (check time period desired and enter the appropriate fee below): <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 10px;"><thead><tr><th></th><th style="text-align: center;">Fee</th><th style="text-align: center;">Small Entity Fee</th><th style="text-align: center;">Micro Entity Fee</th><th></th></tr></thead><tbody><tr><td>☐ One month (37 CFR 1.17(a)(1))</td><td style="text-align: center;">\$220</td><td style="text-align: center;">\$88</td><td style="text-align: center;">\$44</td><td>\$ _____</td></tr><tr><td>☐ Two months (37 CFR 1.17(a)(2))</td><td style="text-align: center;">\$640</td><td style="text-align: center;">\$256</td><td style="text-align: center;">\$128</td><td>\$ _____</td></tr><tr><td>☐ Three months (37 CFR 1.17(a)(3))</td><td style="text-align: center;">\$1,480</td><td style="text-align: center;">\$592</td><td style="text-align: center;">\$296</td><td>\$ _____</td></tr><tr><td>☒ Four months (37 CFR 1.17(a)(4))</td><td style="text-align: center;">\$2,320</td><td style="text-align: center;">\$928</td><td style="text-align: center;">\$464</td><td>\$ 2,320.00</td></tr><tr><td>☐ Five months (37 CFR 1.17(a)(5))</td><td style="text-align: center;">\$3,160</td><td style="text-align: center;">\$1,264</td><td style="text-align: center;">\$632</td><td>\$ _____</td></tr></tbody></table> ☐ Applicant asserts small entity status. See 37 CFR 1.27. ☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously. ☐ A check in the amount of the fee is enclosed. ☒ Payment by credit card. Form PTO-2038 is attached. ☐ The Director has already been authorized to charge fees in this application to a Deposit Account. ☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number <u>13-2725</u>. ☒ Payment made via USPTO patent electronic filing system. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. I am the ☐ applicant. ☒ attorney or agent of record. Registration number <u>45,774</u>. ☐ attorney or agent acting under 37 CFR 1.34. Registration number _____. <table style="width: 100%; margin-top: 10px;"><tr><td style="width: 50%;"><u>/Melissa M. Hayworth/</u> Signature</td><td style="width: 50%;"><u>February 14, 2024</u> Date</td></tr><tr><td><u>Melissa M. Hayworth</u> Typed or printed name</td><td><u>703-684-2522</u> Telephone Number</td></tr></table> NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.				Fee	Small Entity Fee	Micro Entity Fee		☐ One month (37 CFR 1.17(a)(1))	\$220	\$88	\$44	\$ _____	☐ Two months (37 CFR 1.17(a)(2))	\$640	\$256	\$128	\$ _____	☐ Three months (37 CFR 1.17(a)(3))	\$1,480	\$592	\$296	\$ _____	☒ Four months (37 CFR 1.17(a)(4))	\$2,320	\$928	\$464	\$ 2,320.00	☐ Five months (37 CFR 1.17(a)(5))	\$3,160	\$1,264	\$632	\$ _____	<u>/Melissa M. Hayworth/</u> Signature	<u>February 14, 2024</u> Date	<u>Melissa M. Hayworth</u> Typed or printed name	<u>703-684-2522</u> Telephone Number
	Fee	Small Entity Fee	Micro Entity Fee																																	
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<u>Melissa M. Hayworth</u> Typed or printed name	<u>703-684-2522</u> Telephone Number																																			

☐ * Total of _____ forms are submitted.

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013). <https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013). <https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

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- 2) a federal, state, local, or international agency, in response to its request;
- 3) a contractor of the USPTO having need for the information in order to perform a contract;
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- 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
- 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
- 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
- 8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
- 9) the Office of Personnel Management (OPM) for personnel research purposes; and
- 10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.



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PATENT AND TRADEMARK OFFICE

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ELECTRONIC PAYMENT RECEIPT

APPLICATION # 18/356,642	RECEIPT DATE / TIME 02/14/2024 06:25:57 PM Z ET	ATTORNEY DOCKET # 70204.0018USC2
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Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4286	FILED BY	Keyla Clements
PATENT CENTER #	64326239	AUTHORIZED BY	Melissa Hayworth
CUSTOMER #	23552	FILING DATE	07/21/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Pratibha S. PILGAONKAR

Payment Information

PAYMENT METHOD CARD / 0677	PAYMENT TRANSACTION ID E20242DI28429905	PAYMENT AUTHORIZED BY Keyla Clements
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FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1254	EXTENSION FOR RESPONSE WITHIN FOURTH MONTH	2320.00	1	2320.00
TOTAL AMOUNT:				\$2,320.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage

submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	Pratibha S. PILGAONKAR	Examiner:	
	et al.		
Serial No.:	18/356,642	Group Art Unit:	
Filed:	July 21, 2023	Docket No.:	70204.0018USC2
Customer No.:	23552	Confirmation No.:	1465
Title:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

INFORMATION DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b))

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Attention: Commissioner for Patents

The items of information listed on the enclosed Form SB08 are brought to the attention of the Examiner as a formality in the above-referenced application. Applicant notes that all of the items listed on the submitted Form SB08 were cited in the parent applications U.S. Application Nos. 17/241,793 and 14/379,613.

In accordance with 37 C.F.R. §1.98(d), copies of the documents listed on the enclosed Form SB08 are not provided because these documents were previously cited by or submitted to the U.S. Patent and Trademark Office in parent application U.S. Application Nos. 17/241,793 and 14/379,613 to which the present application claims priority.

Pursuant to the provisions of M.P.E.P. 609, it is requested that the Examiner return a copy of the attached Form SB08, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

Respectfully submitted,

February 14, 2024

/Melissa M. Hayworth/

Melissa M. Hayworth
Registration No. 45,774

MERCHANT & GOULD PC
PO Box 2903
Minneapolis, MN 55402
Telephone No. 703.684.2522
Facsimile No. 612.332.9081





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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
18/356,642	07/21/2023		2940	70204.0018USC2	20	1

23552
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

CONFIRMATION NO. 4286
UPDATED FILING RECEIPT



0000000067426624

Date Mailed: 01/26/2024

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Pratibha S. PILGAONKAR, Mumbai, INDIA;
Maharukh T. RUSTOMJEE, Mumbai, INDIA;
Anilkumar S. GANDHI, Mumbai, INDIA;

Applicant(s)

Breckenridge Pharmaceutical, Inc., Berkeley Heights, NJ;

Assignment For Published Patent Application

Breckenridge Pharmaceutical, Inc., Berkeley Heights, NJ

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 17/241,793 04/27/2021 PAT 11,752,142
which is a CON of 14/379,613 08/19/2014 PAT 11,013,729
which is a 371 of PCT/EP2013/053426 02/21/2013

Foreign Applications (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see <http://www.uspto.gov> for more information.)
INDIA 461/MUM/2012 02/21/2012 No Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 08/11/2023

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/356,642**

Projected Publication Date: 05/02/2024

Non-Publication Request: No

Early Publication Request: No

Title

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)							Application Number 18/356,642		Filing Date		
							Applicant(s) Pratibha S. PILGAONKAR				
							* May be used for additional claims or amendments				
CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT			*		*	
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/356,642	07/21/2023	Pratibha S. PILGAONKAR	70204.0018USC2

CONFIRMATION NO. 4286

23552
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

INFORMAL NOTICE



OC000000067426683

Date Mailed: 01/26/2024

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
Pratibha S. PILGAONKAR
Maharukh T. RUSTOMJEE
Anilkumar S. GANDHI

An inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to each inventor must be submitted no later than the date on which the issue fee is paid in response to a notice requiring such fee. See 37 CFR 1.53(f).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/ygizaw/



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
18/356,642	07/21/2023		0	70204.0018USC2	20	1

23552
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

CONFIRMATION NO. 4286
CORRECTED FILING RECEIPT



0000000067352027

Date Mailed: 01/25/2024

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Pratibha S. PILGAONKAR, Mumbai, INDIA;
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Applicant(s)

Breckenridge Pharmaceutical, Inc., Berkeley Heights, NJ;

Assignment For Published Patent Application

Breckenridge Pharmaceutical, Inc., Berkeley Heights, NJ

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 17/241,793 04/27/2021 PAT 11,752,142
which is a CON of 14/379,613 08/19/2014 PAT 11,013,729
which is a 371 of PCT/EP2013/053426 02/21/2013

Foreign Applications (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see <http://www.uspto.gov> for more information.)

INDIA 461/MUM/2012 02/21/2012 No Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 08/11/2023

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/356,642**

Projected Publication Date: To Be Determined - pending completion of Missing Parts.

Non-Publication Request: No

Early Publication Request: No

Title

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Preliminary Class

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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Office of the Chief Financial Officer

Document Code:WFEE

User :Tram Vo

Sale Accounting Date:01/24/2024

Sale Item Reference Number
18356642

Effective Date
08/25/2023

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20241NE01089731	1011	UTILITY APPLICATION FILING	\$320.00	Deposit Account
I20241NE01089731	1111	UTILITY SEARCH FEE	\$700.00	Deposit Account
I20241NE01089731	1311	UTILITY EXAMINATION FEE	\$800.00	Deposit Account
I20241NE01089731	1201	INDEPENDENT CLAIMS IN EXCESS OF 3	\$480.00	Deposit Account
I20241NE01089731	1203	MULTIPLE DEPENDENT CLAIMS	\$860.00	Deposit Account



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Document Code:WFEE

User :Tram Vo

Sale Adjustment Accounting Date:01/24/2024

Effective Date	Sale Accounting Date	Sale Item Reference Number
08/25/2023	01/24/2024	18356642

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20241NF38087900	1201	INDEPENDENT CLAIMS IN EXCESS OF 3	\$480.00	DA



United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Tram Vo

Refund Accounting Date:01/24/2024

Effective Date	Sale Item Reference Number	Refund Total
08/25/2023	18356642	\$480.00

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method	Account Number
I20241NF38087900	1201	INDEPENDENT CLAIMS IN EXCESS OF 3	\$480.00	DA	132725



United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Tram Vo

Sale Accounting Date:01/24/2024

Sale Item Reference Number	Effective Date
18356642	08/25/2023

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20241NF42358725	1202	CLAIMS IN EXCESS OF 20	\$100.00	Deposit Account
I20241NF42358725	1051	LATE FILING FEE FOR OATH OR DECLARATION	\$160.00	Deposit Account



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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/356,642

RECEIPT DATE / TIME
01/23/2024 07:57:58 AM Z ET

ATTORNEY DOCKET #
70204.0018USC2

Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 4286

FILED BY Lisa Kenney

PATENT CENTER # 64046700

FILING DATE 07/21/2023

CUSTOMER # 23552

FIRST NAMED INVENTOR Pratibha S. PILGAONKAR

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Melissa Hayworth

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-01-23_70204_0018USC2-Corrected_Filing_Receipt2.pdf	3	Request for Corrected Filing Receipt	1409 KB

Warning: The attached file contains comments or annotations. Comments are not recommended and may cause processing problems with the document.

2024-01-23_70204-0018USC2_SADS.pdf	9	Application Data Sheet	1955 KB
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Warning: This is not a USPTO supplied ADS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2024-01-23_70204_0018USC2-Corrected_Filing_Receipt2.pdf	6D6014C11C1485FEFDAA5E7E1AD9BE6889FC9CF9552BAD4A7C7879424AAA8D1D2D7CB2CB48D36D18E3E61DCA89EDE09D18B6023D4BF3CFC6D3198A6010AED42E
2024-01-23_70204-0018USC2_SADS.pdf	D7D8A163C2A884269763ABCC5A6BD67CC25561069BB72D7402875B172D35CD0B70D542534661A88B77143A8756EA50CC0F2DB4739F1F8ED73F908308A3E0E95E

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	18/356,642
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
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Inventor Information:

Inventor 1					Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Pratibha	S.	PILGAONKAR		
Residence Information (Select One) ☐ US Residency ☒ Non US Residency ☐ Active US Military Service					
City	Mumbai	Country of Residence ⁱ	IN		
Mailing Address of Inventor:					
Address 1	221 Annexe Bldg.				
Address 2	Goregaon-Mulund Link Road				
City	Mumbai	State/Province			
Postal Code	400 078	Country ⁱ	IN		
Inventor 2					Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Maharukh	T.	RUSTOMJEE		
Residence Information (Select One) ☐ US Residency ☒ Non US Residency ☐ Active US Military Service					
City	Mumbai	Country of Residence ⁱ	IN		
Mailing Address of Inventor:					
Address 1	221 Annexe Bldg.				
Address 2	Goregaon-Mulund Link Road				
City	Mumbai	State/Province	IN		
Postal Code	400 078	Country ⁱ	IN		
Inventor 3					Remove
Legal Name					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	18/356,642
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Prefix	Given Name	Middle Name	Family Name	Suffix
	Anilkumar	S.	GANDHI	

Residence Information (Select One) ☐ US Residence ☒ Non US Residence ☐ Active US Military Service

City	Mumbai	Country of Residence ⁱ	IN
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Mailing Address of Inventor:

Address 1	221 Annexe Bldg.		
Address 2	Goregaon-Mulund Link Road		
City	Mumbai	State/Province	
Postal Code	400 078	Country ⁱ	IN

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button.

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ An Address is being provided for the correspondence Information of this application.

Customer Number	23552		
Email Address	mhayworth@merchantgould.com	Add Email	Remove Email

Application Information:

Title of the Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		
Attorney Docket Number	70204.0018USC2	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	18/356,642
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Publication Information:
☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	23552		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status		<u>Patented</u> ~~Pending~~		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
<u>18356642</u>	Continuation of	17241793	2021-04-27	<u>11752142</u>	<u>2023-09-12</u>
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17241793	Continuation of	14379613	2014-08-19	11013729	2021-05-25
Prior Application Status		Expired		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
14379613	a 371 of international	PCT/EP2013/053426	2013-02-21		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	18/356,642
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)^j the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ^j	Filing Date (YYYY-MM-DD)	Access Code ^k (if applicable)
461/MUM/2012	IN	2012-02-21	

[Remove](#)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

- ☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
- NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	18/356,642
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	18/356,642
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.			
Applicant 1			
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.			
Clear			
☒ Assignee		☐ Legal Representative under 35 U.S.C. 117	
☐ Person to whom the inventor is obligated to assign.		☐ Person who shows sufficient proprietary interest	
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:			
Name of the Deceased or Legally Incapacitated Inventor:			
If the Applicant is an Organization check here. ☒			
Organization Name	Breckenridge Pharmaceutical, Inc.		
Mailing Address Information For Applicant:			
Address 1	~~15 Massasoit Drive~~ <u>200 Connell Drive</u>		
Address 2	~~Suite 204~~ <u>Suite 4200</u>		
City	~~Berlin~~ <u>Berkeley Heights</u>	State/Province	~~CT~~ <u>NJ</u>
Country	US	Postal Code	~~06037~~ <u>07922</u>
Phone Number		Fax Number	
Email Address			
Additional Applicant Data may be generated within this form by selecting the Add button.			

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	18/356,642
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Assignee 1			
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.			
If the Assignee or Non-Applicant Assignee is an Organization check here. ☒			
Organization Name	Breckenridge Pharmaceutical, Inc.		
Mailing Address Information For Assignee including Non-Applicant Assignee:			
Address 1	~~15 Massino Drive~~ 200 Connell Drive		
Address 2	~~Suite 204~~ Suite 4200		
City	~~Berlin~~ Berkeley Heights	State/Province	~~CT~~ NJ
Country	US	Postal Code	~~06037~~ 07922
Phone Number		Fax Number	
Email Address			
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.			

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the **INITIAL** filing of the application and either box A or B is **not** checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Melissa M. Hayworth/		Date (YYYY-MM-DD)	2024-01-29	
First Name	Melissa	Last Name	Hayworth	Registration Number	45774
Additional Signature may be generated within this form by selecting the Add button.					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	18/356,642
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.



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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
18/356,642	07/21/2023		0	70204.0018USC2	20	1

23552

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

CONFIRMATION NO. 4286
REPLACEMENT FILING RECEIPT



0000000061221671

Date Mailed: 08/30/2023

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Pratibha S. PILGAONKAR, Mumbai, INDIA;
Maharukh T. RUSTOMJEE, Mumbai, INDIA;
Anilkumar S. GANDHI, Mumbai, INDIA;

Applicant(s)

Breckenridge Pharmaceutical, Inc., ~~Berlin, CT~~, Berkeley Heights, NJ

Assignment For Published Patent Application

Breckenridge Pharmaceutical, Inc., ~~Berlin, CT~~, Berkeley Heights, NJ

Power of Attorney: None**Domestic Priority data as claimed by applicant**

This application is a CON of 17/241,793 04/27/2021 PAT 11,752,142
which is a CON of 14/379,613 08/19/2014 PAT 11,013,729
which is a 371 of PCT/EP2013/053426 02/21/2013

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.)
INDIA 461/MUM/2012 02/21/2012 No Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 08/11/2023

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/356,642**

Projected Publication Date: To Be Determined - pending completion of Missing Parts.

Non-Publication Request: No

Early Publication Request: No

Title

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.



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UNITED STATES DEPARTMENT OF COMMERCE
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
18/356,642	07/21/2023		0	70204.0018USC2	20	1

23552
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

CONFIRMATION NO. 4286
REPLACEMENT FILING RECEIPT



0000000061221671

Date Mailed: 08/30/2023

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

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Inventor(s)

Pratibha S. PILGAONKAR, Mumbai, INDIA;
Maharukh T. RUSTOMJEE, Mumbai, INDIA;
Anilkumar S. GANDHI, Mumbai, INDIA;

Applicant(s)

Breckenridge Pharmaceutical, Inc., Berlin, CT;

Assignment For Published Patent Application

Breckenridge Pharmaceutical, Inc., Berlin, CT

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 17/241,793 04/27/2021 PAT 11,752,142
which is a CON of 14/379,613 08/19/2014 PAT 11,013,729
which is a 371 of PCT/EP2013/053426 02/21/2013

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.)
INDIA 461/MUM/2012 02/21/2012 No Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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If Required, Foreign Filing License Granted: 08/11/2023

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/356,642**

Projected Publication Date: To Be Determined - pending completion of Missing Parts.

Non-Publication Request: No

Early Publication Request: No

Title

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	18/356,642
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
--------------------------	---

Inventor Information:

Inventor 1					Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Pratibha	S.	PILGAONKAR		
Residence Information (Select One) ☐ US Residency ☒ Non US Residency ☐ Active US Military Service					
City	Mumbai	Country of Residence ⁱ	IN		
Mailing Address of Inventor:					
Address 1	221 Annexe Bldg.				
Address 2	Goregaon-Mulund Link Road				
City	Mumbai	State/Province			
Postal Code	400 078	Country ⁱ	IN		
Inventor 2					Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Maharukh	T.	RUSTOMJEE		
Residence Information (Select One) ☐ US Residency ☒ Non US Residency ☐ Active US Military Service					
City	Mumbai	Country of Residence ⁱ	IN		
Mailing Address of Inventor:					
Address 1	221 Annexe Bldg.				
Address 2	Goregaon-Mulund Link Road				
City	Mumbai	State/Province	IN		
Postal Code	400 078	Country ⁱ	IN		
Inventor 3					Remove
Legal Name					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	18/356,642
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Prefix	Given Name	Middle Name	Family Name	Suffix
	Anilkumar	S.	GANDHI	

Residence Information (Select One) ☐ US Residence ☒ Non US Residence ☐ Active US Military Service

City	Mumbai	Country of Residence ⁱ	IN
------	--------	-----------------------------------	----

Mailing Address of Inventor:

Address 1	221 Annexe Bldg.		
Address 2	Goregaon-Mulund Link Road		
City	Mumbai	State/Province	
Postal Code	400 078	Country ⁱ	IN

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button.

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ An Address is being provided for the correspondence Information of this application.

Customer Number	23552		
Email Address	mhayworth@merchantgould.com	Add Email	Remove Email

Application Information:

Title of the Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		
Attorney Docket Number	70204.0018USC2	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	<u>18/356,642</u>
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.			
Please Select One:			
☒	Customer Number	☐	US Patent Practitioner
☐	Limited Recognition (37 CFR 11.9)		
Customer Number	23552		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove			
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
	Continuation of	17241793	2021-04-27		
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17241793	Continuation of	14379613	2014-08-19	11013729	2021-05-25
Prior Application Status	Expired	Remove			
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
14379613	a 371 of international	PCT/EP2013/053426	2013-02-21		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	<u>18/356,642</u>
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)^j the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ^j	Filing Date (YYYY-MM-DD)	Remove
			Access Code ^k (if applicable)
461/MUM/2012	IN	2012-02-21	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

- ☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
- NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	<u>18/356.642</u>
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	<u>18/356,642</u>
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.			
Applicant 1			
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.			
Clear			
☒ Assignee		☐ Legal Representative under 35 U.S.C. 117	
☐ Person to whom the inventor is obligated to assign.		☐ Person who shows sufficient proprietary interest	
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:			
Name of the Deceased or Legally Incapacitated Inventor:			
If the Applicant is an Organization check here. ☒			
Organization Name	Breckenridge Pharmaceutical, Inc.		
Mailing Address Information For Applicant:			
Address 1		15 Massirio Drive	
Address 2		Suite 201	
City		Berlin	State/Province CT
Country	US	Postal Code	06037
Phone Number		Fax Number	
Email Address			
Additional Applicant Data may be generated within this form by selecting the Add button.			

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	18/356,642
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Assignee 1			
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.			
If the Assignee or Non-Applicant Assignee is an Organization check here. ☒			
Organization Name	Breckenridge Pharmaceutical, Inc.		
Mailing Address Information For Assignee including Non-Applicant Assignee:			
Address 1	15 Massirio Drive		
Address 2	Suite 201		
City	Massirio- Berlin	State/Province	CT
Country	US	Postal Code	06037
Phone Number		Fax Number	
Email Address			
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.			

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the **INITIAL** filing of the application and either box A or B is **not** checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Melissa M. Hayworth/		Date (YYYY-MM-DD)	2023-08-25	
First Name	Melissa	Last Name	Hayworth	Registration Number	45774
Additional Signature may be generated within this form by selecting the Add button.					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	<u>18/356,642</u>
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt	
EFS ID:	48494588
Application Number:	18356642
International Application Number:	
Confirmation Number:	4286
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. PILGAONKAR
Customer Number:	23552
Filer:	Melissa M. Hayworth/Lisa Kenney
Filer Authorized By:	Melissa M. Hayworth
Attorney Docket Number:	70204.0018USC2
Receipt Date:	25-AUG-2023
Filing Date:	21-JUL-2023
Time Stamp:	16:20:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	2023-08-25-70204-0018USC2-Communication-Corrected-OFR.PDF	75885 8a1a3d351dbc1dc96f148768c341f27259434ff	no	1

Warnings:

Information:					
2	Request for Corrected Filing Receipt	2023-08-17_Corrected_Filing_Receipt-Marked.PDF	2836366 7ef3c06e667736b0eef5e64a1be15d7c32947ebc	no	3
Warnings:					
Information:					
3	Application Data Sheet	2023-08-25-70204-0018USC2-SADS-assignee-.PDF	1981658 28f35da6a364b66f981821ad21b4812c617eb6ba	no	9
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
Total Files Size (in bytes):			4893909		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	Pilgaonkar et al.	Examiner:	
Serial No.:	18/356,642	Group Art Unit:	
Filed:	July 21, 2023	Docket No.:	70204.0018USC2
Customer No.:	23552	Confirmation No.:	4286
Title:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

COMMUNICATION – CORRECTED OFFICIAL FILING RECEIPT

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Attention: Commissioner for Patents

Submitted herewith is a copy of the Official Filing Receipt from the United States Patent and Trademark Office in the above-identified application showing a requested correction. An updated Application Data Sheet indicating the requested correction also is being submitted herewith.

The requested correction addresses an obvious typographical error in the Assignee information as originally provided on the Application Data Sheet filed with the application. No new matter is being presented.

Applicant requests correction of the record and issuance of a corrected Official Filing receipt. Please charge any deficiency in fees to Deposit Account No. 13-2725 (70204.0018USC2).

Respectfully submitted,

August 25, 2023

/Melissa M. Hayworth/

Melissa M. Hayworth
Registration No. 45,774

MERCHANT & GOULD PC
PO Box 2903
Minneapolis, MN 55402
Telephone No. 703.684.2522
Facsimile No. 612.332.9081





UNITED STATES PATENT AND TRADEMARK OFFICE

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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
18/356,642	07/21/2023		0	70204.0018USC2	20	1

23552

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

CONFIRMATION NO. 4286

FILING RECEIPT



0000000060494857

Date Mailed: 08/14/2023

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Pratibha S. PILGAONKAR, Mumbai, INDIA;
Maharukh T. RUSTOMJEE, Mumbai, INDIA;
Anilkumar S. GANDHI, Mumbai, INDIA;

Applicant(s)

Breckenridge Pharmaceutical, Inc., Berlin, CT;

Assignment For Published Patent Application

Breckenridge Pharmaceutical, Inc., ~~Massire, CT~~ Berlin, CT

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 17/241,793 04/27/2021
which is a CON of 14/379,613 08/19/2014 PAT 11,013,729
which is a 371 of PCT/EP2013/053426 02/21/2013

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.)
INDIA 461/MUM/2012 02/21/2012 No Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 08/11/2023

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/356,642**

Projected Publication Date: To Be Determined - pending completion of Missing Parts.

Non-Publication Request: No

Early Publication Request: No

Title

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.



UNITED STATES PATENT AND TRADEMARK OFFICE

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NOT GRANTED

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)							Application Number 18/356,642		Filing Date		
							Applicant(s) Pratibha S. PILGAONKAR				
							* May be used for additional claims or amendments				
CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT			*		*	
	Indep	Depend	Indep	Depend	Indep	Depend		Indep	Depend	Indep	Depend
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PATENT APPLICATION FEE DETERMINATION RECORD						Application or Docket Number 18/356,642				
Substitute for Form PTO-875										
APPLICATION AS FILED - PART I										
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY				
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)			
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	320			
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	700			
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800			
TOTAL CLAIMS (37 CFR 1.16(i))	21 minus 20 =	*				x 100 =	100			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x =	0			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							860			
			TOTAL			TOTAL	2680			
* If the difference in column 1 is less than zero, enter "0" in column 2.										
APPLICATION AS AMENDED - PART II										
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OTHER THAN SMALL ENTITY		
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x =			x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =			x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE			TOTAL ADD'L FEE	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x =			x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =			x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE			TOTAL ADD'L FEE	
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.										



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/356,642	07/21/2023	Pratibha S. PILGAONKAR	70204.0018USC2

CONFIRMATION NO. 4286

23552
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

FORMALITIES LETTER



OC000000060494860

Date Mailed: 08/14/2023

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

An application number and filing date have been accorded to the above-identified nonprovisional application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee has not been received.
- The application search fee must be submitted.
- The application examination fee must be submitted.
- Additional claim fees of **\$960** as an undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- Surcharge as set forth in 37 CFR 1.16(f) has not been received.

The surcharge is due for any one of:

- late submission of the basic filing fee, search fee, or examination fee,
- late submission of inventor's oath or declaration,
- filing an application that does not contain at least one claim on filing, or
- submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required (including the fees noted above) are as follows. No entity status discount is in effect. If applicant is qualified for small entity status, a written assertion of small entity status must be submitted to establish small entity status. (See 37 CFR 1.27). If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- **\$320** basic filing fee.
- **\$160** surcharge.
- **\$700** search fee.
- **\$800** examination fee.

- **\$100** for 1 total claims over 20.
- **\$860** for multiple dependent claim surcharge.
- **\$(0) previous unapplied payment amount.**
- **\$2940** TOTAL FEE BALANCE DUE.

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this Notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

Items Required To Avoid Processing Delays:

The deficiencies indicated below should be addressed promptly to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):

Pratibha S. PILGAONKAR

Maharukh T. RUSTOMJEE

Anilkumar S. GANDHI

An inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to each inventor must be submitted no later than the date on which the issue fee is paid in response to a notice requiring such fee. See 37 CFR 1.53(f).

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be addressed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

REPLY VIA ELECTRONIC FILING

A reply may be submitted via electronic filing only by registered users of the appropriate USPTO patent electronic filing system and must include:

- A separate document having the document description, "**Applicant response to Pre-Exam Formalities Notice**"; and
- the item(s) for which a reply period is set forth above.

For more information about electronic filing, contact the Patent Electronic Business Center (EBC) 1-866-217-9197 or visit <https://www.uspto.gov/ebc>

NOTE: If the reply is not being submitted electronically, a copy of this notice must be included.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/kung/



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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/356,642

RECEIPT DATE / TIME
07/21/2023 02:49:29 PM ET

ATTORNEY DOCKET #
70204.0018USC2

Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 4286

FILED BY Lisa Kenney

PATENT CENTER # 62483810

FILING DATE -

CUSTOMER # 23552

FIRST NAMED INVENTOR Pratibha S. PILGAONKAR

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Melissa Hayworth

Documents

TOTAL DOCUMENTS: 4

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2023-07-21_70204-0018USC2_ADS_aia0014.PDF	9	Application Data Sheet	1227 KB
2023-07-21_70204-0018USC2-Application.PDF	30	-	213 KB
2023-07-21_70204-0018USC2-Application-SPEC.pdf	(1-25) 25	Specification	200 KB
2023-07-21_70204-0018USC2-Application-CLM.pdf	(26-29) 4	Claims	73 KB

2023-07-21_70204-0018USC2-Application-ABST.pdf	(30-30)	1	Abstract	50 KB
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Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-07-21_70204-0018USC2_ADS_aia0014.PDF	B97D59A8B0E516911CEB0AFD3BEAE596AFEAA468FE9002963F057B9C099128217E5AFA5B200A5E7F99E9CDF797B02ECE99706232AE97D2C028C8EB74FECAC6768
2023-07-21_70204-0018USC2-Application.PDF	3555B8509D6498F576FEBB5EB67FFFEEB869C315F30E98348A4B68BF5826231751F31BD3DC32C2656BA6B70C11178B0969069013C046DFEB71C0F889E2C16E27
2023-07-21_70204-0018USC2-Application-SPEC.pdf	59B9127E77756E7648EADA736A1AB36604E2E2735E3614535578900B6AC61368C4F9E5EAEBA4378F72AA7DCF2B61A0CC9C4825BF1657D4999EB68D3EB95BC2059
2023-07-21_70204-0018USC2-Application-CLM.pdf	55F295CF9D14535540373EA34D2265CA12E4393EF9006D37EE3E55F38E17FEFC5E96FAA1E622B18A0A444FA38055427931485F76B1F9BA01A6326EF01698E417
2023-07-21_70204-0018USC2-Application-ABST.pdf	C2D394B513C4A2DCA094E769A2575B3F10A685128C4E09FE3C38863E79C946B1E19B59A7FC54E1E3010CE2AC6012FE458E0420F1B6F4160E755062B510CF672D

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
--------------------------	---

Inventor Information:

Inventor 1					Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Pratibha	S.	PILGAONKAR		
Residence Information (Select One) ☐ US Residency ☒ Non US Residency ☐ Active US Military Service					
City	Mumbai	Country of Residence ⁱ	IN		
Mailing Address of Inventor:					
Address 1	221 Annexe Bldg.				
Address 2	Goregaon-Mulund Link Road				
City	Mumbai	State/Province			
Postal Code	400 078	Country ⁱ	IN		
Inventor 2					Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Maharukh	T.	RUSTOMJEE		
Residence Information (Select One) ☐ US Residency ☒ Non US Residency ☐ Active US Military Service					
City	Mumbai	Country of Residence ⁱ	IN		
Mailing Address of Inventor:					
Address 1	221 Annexe Bldg.				
Address 2	Goregaon-Mulund Link Road				
City	Mumbai	State/Province	IN		
Postal Code	400 078	Country ⁱ	IN		
Inventor 3					Remove
Legal Name					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Prefix	Given Name	Middle Name	Family Name	Suffix
	Anilkumar	S.	GANDHI	

Residence Information (Select One) ☐ US Residence ☒ Non US Residence ☐ Active US Military Service

City	Mumbai	Country of Residence ⁱ	IN
------	--------	-----------------------------------	----

Mailing Address of Inventor:

Address 1	221 Annexe Bldg.		
Address 2	Goregaon-Mulund Link Road		
City	Mumbai	State/Province	
Postal Code	400 078	Country ⁱ	IN

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button.

Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ An Address is being provided for the correspondence Information of this application.

Customer Number	23552		
Email Address	mhayworth@merchantgould.com	Add Email	Remove Email

Application Information:

Title of the Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		
Attorney Docket Number	70204.0018USC2	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.			
Please Select One:			
☒	Customer Number	☐	US Patent Practitioner
☐	Limited Recognition (37 CFR 11.9)		
Customer Number	23552		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove			
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
	Continuation of	17241793	2021-04-27		
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17241793	Continuation of	14379613	2014-08-19	11013729	2021-05-25
Prior Application Status	Expired	Remove			
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
14379613	a 371 of international	PCT/EP2013/053426	2013-02-21		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.					Add

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)	Remove
461/MUM/2012	IN	2012-02-21		

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

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Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

- ☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
- NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.			
Applicant 1			Remove
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.			
Clear			
☒ Assignee	☐ Legal Representative under 35 U.S.C. 117	☐ Joint Inventor	
☐ Person to whom the inventor is obligated to assign.		☐ Person who shows sufficient proprietary interest	
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:			
Name of the Deceased or Legally Incapacitated Inventor:			
If the Applicant is an Organization check here. ☒			
Organization Name	Breckenridge Pharmaceutical, Inc.		
Mailing Address Information For Applicant:			
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Address 2	Suite 201		
City	Berlin	State/Province	CT
Country	US	Postal Code	06037
Phone Number		Fax Number	
Email Address			
Additional Applicant Data may be generated within this form by selecting the Add button. Add			

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Assignee 1			
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.			
Remove			
If the Assignee or Non-Applicant Assignee is an Organization check here. ☒			
Organization Name	Breckenridge Pharmaceutical, Inc.		
Mailing Address Information For Assignee including Non-Applicant Assignee:			
Address 1	15 Massirio Drive		
Address 2	Suite 201		
City	Massirio	State/Province	CT
Country ⁱ	US	Postal Code	06037
Phone Number		Fax Number	
Email Address			
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add			

Signature: [Remove](#)

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Melissa M. Hayworth/		Date (YYYY-MM-DD)	2023-07-21
First Name	Melissa	Last Name	Hayworth	Registration Number
				45774
Additional Signature may be generated within this form by selecting the Add button. Add				

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	70204.0018USC2
		Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

**ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN
ETEXILATE**

5 This application is a continuation of U.S. Patent Application No. 17/241,793 filed April 27, 2021, which is a continuation of U.S. Patent Application No. 14/379,613 filed August 19, 2014, now U.S. Patent No. 11,013,729, issued May 25, 2021, entitled "Oral Pharmaceutical Compositions of Dabigatran Etexilate", the contents of all of which are hereby incorporated by reference in their entirety.

10 **Field of Invention**

The present invention relates to oral pharmaceutical compositions comprising dabigatran etexilate or pharmaceutically acceptable salts thereof.

Background of the Invention

15 Atrial fibrillation is the most common cardiac arrhythmia which is characterized by abnormal heart rhythm. It is considered to be a common cause of irregular heart beat and can cause stroke and other systemic embolic events, eventually leading to death. It has been seen that the incidence of atrial fibrillation increases with age and nearly 6% of individuals over the age of 65 are affected while the prevalence is about 8% in
20 individuals over the age of 80. The lack of organized cardiac contractions in atrial fibrillation generally results in some stagnant blood in the left atrium or left atrial appendage. This lack of movement of blood leads to thrombus formation or blood clotting. Patients with atrial fibrillation are therefore at greater risk of developing clots which increases the risk of stroke and other systemic embolic events. Since the
25 consequence of stroke or systemic embolism is devastating, a primary aim of therapy for atrial fibrillation is to reduce the risk of arterial thrombus formation and thromboembolism. Anticoagulants such as warfarin are mainly used in case of atrial fibrillation along with other medications such as beta blockers and calcium channel blockers or some noninvasive rhythm control methods. Though anticoagulation therapy
30 with warfarin has been shown to significantly reduce the incidence of stroke or systemic embolism, its use is found to be cumbersome due to multiple diet and drug interactions, chances of hemorrhage which are difficult to manage, requirement of frequent

laboratory monitoring etc. Use of a newer safe and effective anticoagulant is therefore necessary.

Direct thrombin inhibitors, is another class of anticoagulants that act by directly
5 inhibiting the enzyme thrombin and are expected to replace heparin (and derivatives)
and warfarin in various clinical scenarios. Thrombin, a serine protease protein formed
by proteolytic cleavage of prothrombin, converts soluble fibrinogen into insoluble
strands of fibrin and further catalyzes many other coagulation-related reactions. Direct
thrombin inhibitors inhibit thrombin including fibrin-bound thrombin, thereby
10 delimiting thrombus growth, provide predictable anticoagulant responses because they
are not bound to plasma proteins and have no drug-drug interactions. Depending on
their interaction with the thrombin molecule, there are bivalent as well as univalent
types of direct thrombin inhibitors, with some being in clinical use, while others
undergoing clinical development.

15 Dabigatran is a potent, reversible, univalent direct thrombin inhibitor. It reduces the risk
of stroke and systemic embolism in patients with non-valvular atrial fibrillation. It is
also useful in primary prevention of venous thromboembolic events in adult patients
who have undergone elective total hip replacement surgery or total knee replacement
20 surgery. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-
induced platelet aggregation. Dabigatran was first disclosed in WO98/37075, which
claimed compounds with a thrombin-inhibiting effect and the effect of prolonging the
thrombin time, under the name 1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)
phenyl] aminomethyl] benzimidazol-5-ylcarboxylic acid-N-(2-pyridyl)-N-(2
25 ethoxycarbonylethyl)amides.

Dabigatran is currently available as dabigatran etexilate mesylate (DEM) under the
brand name Pradaxa® from Boehringer Ingelheim as immediate release oral capsules of
75 mg and 110 mg (in Europe) and 75 mg and 150 mg strengths (in the United States) to
30 be administered twice daily. DEM is a salt form of the prodrug dabigatran etexilate
which after oral administration is absorbed and converted to dabigatran by esterase-
catalysed hydrolysis in the liver. DEM is a yellow-white to yellow non-hygroscopic
powder that exists in two anhydrous polymorphic forms, Form I and II, which are

described in WO 2005/028468. The aqueous solubility of DEM is strongly pH dependent with rather high solubility in acidic media and very poor solubility in neutral and basic media while solubility in water is 1.8mg/mL. The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately about 5 3-7% and elimination half life is 12-17 hours. DEM is BCS Class II drug, indicating poor aqueous solubility but good membrane permeability. DEM is stable in the solid state and not sensitive to light irradiation but it predominantly undergoes degradation by hydrolytic pathways in the presence of moisture. It is also acid sensitive.

10 Due to these physicochemical and biopharmaceutical properties of DEM, some attempts have been made to provide compositions of DEM that are stable and/or provide desirable *in vitro* release and bioavailability.

U.S Patent Application 2006/0183779A1 describes pharmaceutical compositions of 15 DEM for oral administration in the form of pellets comprising (a) substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1g/250ml at 20°C such as tartaric acid; and (b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material. The separating agent layer or insulating layer separates the 20 acid core from the active substance containing layer. The layer of active substance may in turn be enclosed in a coating which increases the abrasion resistance and shelf life of the pellets. Such layered pellets are later filled into hard capsules. However, the process of preparing layered pellets is cumbersome, time consuming and uneconomical.

25 U.S Patent Application 2005/0038077 discloses a tablet comprising dabigatran etexilate or pharmaceutically acceptable salt thereof; one or more pharmaceutically acceptable organic acids with a solubility in water of > 1g/250ml at 20°C and a pharmaceutically acceptable excipient or filler. However due to the presence of an organic acid in close contact with the active in a tablet composition without any special steps taken to 30 separate the two from each other, can make the active highly susceptible to hydrolysis in the presence of humidity.

The above attempts only provided compositions of DEM, which are either tedious or technologically demanding to prepare or are unlikely to remain stable over the shelf life of the product. Need therefore exists to prepare alternate compositions of dabigatran etexilate that are stable, easy or convenient to prepare, provide the desired *in vitro* release and bioavailability.

The present inventors after rigorous experimentation provide oral compositions of dabigatran etexilate 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. Such compositions are chemically and polymorphically stable, provide desired in-vitro and in-vivo performance and can be prepared by simple, non-tedious and cost-effective process. In particular, the compositions of the present invention provide a quick dissolution particularly at earlier time points as compared to formulation having one type of particles/pellets. Such a faster dissolution at earlier time points can ensure availability of more amount of active especially when (a) absorption of the active is rapid with faster T_{max} (~ 45 minutes – 1 hour), (b) significant bioactivation is involved and (c) negligible and variable absorption at higher pH.

Detailed Description of the Invention

The present invention provides, in one of its aspects, pharmaceutical compositions, preferably for oral administration, 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 dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid.

In a particular embodiment, the present invention provides pharmaceutical compositions, preferably for oral administration, 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 dabigatran etexilate in the form of free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; 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.

The compositions of the present invention are stable, easy to prepare, and provide the desired in-vitro release of the active.

The first type of particles present in the composition of the present invention, comprise dabigatran etexilate. Dabigatran etexilate may be used in the compositions of the present invention as the free base (3-[(2-{4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]methyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino-propionic acid ethyl ester) or in the form of pharmaceutically acceptable salts,, polymorphs, solvates, hydrates thereof. For the sake of conciseness, the term dabigatran etexilate is employed in this specification to designate any of the above-mentioned forms except when the term is further qualified (i.e. dabigatran etexilate mesylate). Whenever it is necessary to designate the free base of dabigatran etexilate the term “dabigatran etexilate (free base)” is employed.

The term “pharmaceutically acceptable salt” refers to those salts which are, according to medical judgement, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like. Pharmaceutically acceptable salts are well known in the art.

In one embodiment the amount of dabigatran etexilate (expressed as dabigatran etexilate mesylate) in the composition can vary from about 0.01 weight % to about 90 weight %, based on the total weight of the composition. In another embodiment the amount of dabigatran etexilate in the composition can vary from about 0.02 weight % to about 85 weight %, based on the total weight of the composition. In still another embodiment, the amount of dabigatran etexilate in the composition can vary from about 0.05 weight % to about 80 weight %, based on the total weight of the composition.

In one embodiment the compositions of the present invention may be in the form of unit dose forms 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.

- 5 In one embodiment of the present invention dabigatran etexilate is used in the form of the mesylate salt, i.e. dabigatran etexilate mesylate.

In a particular embodiment of the present invention dabigatran etexilate is used in the form of polymorphic form I of dabigatran etexilate mesylate (as described in WO
10 2005/028468).

In another particular embodiment of the present invention dabigatran etexilate is used in the form of polymorphic form II of dabigatran etexilate mesylate (as described in WO
15 2005/028468).

The oral pharmaceutical composition of the present invention comprises a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, with a first type of particles comprising dabigatran etexilate and second type of particles comprising at least one pharmaceutically acceptable organic acid.
20

In a preferred embodiment of the present invention the first type of particles comprising dabigatran etexilate is free from organic and inorganic acids.

In a preferred embodiment of the present invention the first type of particles comprising
25 dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof also comprise at least one pharmaceutical excipient.

In a most preferred embodiment of the present invention, the said first type of particles
30 comprising dabigatran etexilate mesylate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof also comprise one or more excipients selected from the group consisting of binders, diluents and/or lubricants.

In a particular embodiment said first type of particles comprise at least one binder, preferably microcrystalline cellulose.

- 5 In another particular embodiment, said first type of particles comprises at least one disintegrant, preferably selected from sodium croscarmellose or crospovidone.

In another particular embodiment, said first type of particles comprise at least one diluent, preferably selected from mannitol or lactose.

10

In another particular embodiment, said first type of particles comprise at least one binder, preferably microcrystalline cellulose, a disintegrant, preferably selected from sodium croscarmellose or crospovidone and a diluent, preferably selected from mannitol or lactose.

15

In another preferred embodiment of the present invention the second type of particles comprising at least one pharmaceutically acceptable organic acid is free from dabigatran etexilate.

- 20 In a most preferred embodiment of the present invention the first type of particles comprising dabigatran etexilate is free from acids and the second type of particles comprising at least one pharmaceutically acceptable organic acid is free from dabigatran etexilate.

- 25 In another preferred embodiment of the present invention the second type of particles comprise tartaric acid, preferably in the form of pellets with a particle size between 100 and 900 microns, more preferably between 400 and 700 microns.

- 30 An acid is a substance that releases hydrogen ions and decreases the pH of an aqueous solution.

Organic acids that may be employed in the present composition include, but are not limited to, tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic

acid, aspartic acid and the like or combinations thereof including the hydrates and acid salts thereof.

In one embodiment the organic acid is present in the composition of the present invention in an amount of about 2% by weight to about 95% by weight of the composition. In another embodiment the organic acid is present in the composition of the present invention in an amount of about 5% by weight to about 90% by weight of the composition. In a further embodiment the organic acid is present in the composition of the present invention in an amount of about 10% by weight to about 85% by weight of the composition.

In one embodiment at least 90% by weight, preferably at least 95% by weight, more preferably at least 99% by weight and still more preferably 100% by weight of the organic acid present in the composition is contained in the second type of particles which comprise at least one pharmaceutically acceptable organic acid, the rest (if any) of the organic acid being added as part of the excipients.

Further the oral pharmaceutical compositions of the present invention comprise a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein optionally at least one type of particles are coated with a protective coating layer. In one embodiment, the first type of particles is coated with a protective coating layer. In another embodiment, the second type of particles is coated with a protective coating layer. In yet another embodiment, the first and the second type of particles are coated with a protective coating layer.

The term “protective coating layer” as used herein is intended to mean a layer of a polymeric or a non-polymeric material disposed on the surface of a particle core in order to avoid direct contact of the particle core with its environment.

In one embodiment, protective coating layer is formed of a polymeric or a non-polymeric pharmaceutically acceptable agent or any combination thereof.

The polymeric pharmaceutically acceptable agents used for the protective coating layer include, but are not limited to, 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

5 be employed, include, but are not limited to, methylcellulose, hydroxypropylmethylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, ethylcellulose, hydroxypropyl ethylcellulose, carboxymethylethyl cellulose, carboxy ethylcellulose, carboxymethyl hydroxyethylcellulose, hydroxyethylmethyl carboxymethyl cellulose, hydroxyethyl

10 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, but are not limited to copolymers of vinyl pyrrolidone, copolymers of polyvinyl alcohol (Kollicoat IR),

15 polyvinylpyrrolidone or combinations thereof. Gums that may be employed include, but are not limited to, 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, but are not limited to, a) copolymer formed from

20 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

25 methacrylates with/without quarternary ammonium group in combination with sodium carboxymethylcellulose, e.g. those available from Röhm GmbH under the trademark Eudragit[®] like Eudragit EPO (dimethylaminoethyl methacrylate copolymer; basic butylated methacrylate copolymer), Eudragit RL and RS (trimethylammonioethyl methacrylate copolymer), Eudragit NE30D and Eudragit NE40D (ethylacrylate

30 methymethacrylate copolymer), Eudragit RD 100 (ammoniomethacrylate copolymer with sodium carboxymethylcellulose); or the like or any combinations thereof.

The non-polymeric pharmaceutically acceptable agents used for the protective coating layer include, but are not limited to C8-C22 fatty acids, C8-C22 fatty alcohols, fats, in particular mono-, di- or triesters of glycerol and C8-C22 fatty acids, waxes, and the like, or combinations thereof. Fatty acids that may be employed include, but are not limited to, decenoic acid, docosanoic acid, stearic acid, palmitic acid, lauric acid, myristic acid, hydrogenated palm kernel oil, hydrogenated peanut oil, hydrogenated palm oil, hydrogenated rapeseed oil, hydrogenated rice bran oil, hydrogenated soybean oil, hydrogenated sunflower oil, hydrogenated castor oil, hydrogenated cottonseed oil, and the like, and mixtures thereof. Long chain monohydric alcohols that may be employed include, but are not limited to, cetyl alcohol, stearyl alcohol and mixtures thereof. Waxes that may be employed include, but are not limited to, spermaceti wax, carnauba wax, Japan wax, bayberry wax, flax wax, beeswax, Chinese wax, shellac wax, lanolin wax, sugarcane wax, candelilla wax, paraffin wax, microcrystalline wax, petrolatum wax, carbowax, glyceryl monostearate, glyceryl distearate, glyceryl tristearate, glyceryl dipalmitate, glyceryl tripalmitate, glyceryl monopalmitate, glyceryl dilaurate, glyceryl trilaurate, glyceryl monolaurate, glyceryl trimyristate, glyceryl monodecenoate, glyceryl didecenoate, glyceryl tridecenoate, glyceryl behenate and the like, or mixtures thereof.

In a further embodiment, in addition to polymeric or non-polymeric pharmaceutically acceptable agent or any combination thereof, the protective coating layer may optionally further comprise one or more pharmaceutically acceptable excipients such as, but not limited to, plasticizer, anti-tacking agent, pigment, and the like, or combinations thereof. A plasticizer that may be employed includes, but is not limited to, 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, but is not limited to, talc, or glyceryl monostearate. A pigment such as, but not limited to, titanium dioxide, iron oxide, or a mixture thereof may be employed.

The protective coating layer may be optionally applied onto at least one type of particles of the present invention. For example, the protective coating layer is applied onto the

first type of particles which comprise dabigatran etexilate in the form of free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof.

5 In a preferred embodiment of the present invention the protective coating layer is coated onto the second type of particles which comprise at least one pharmaceutically acceptable organic acid. In a particular embodiment said coating layer comprises hydroxypropylmethyl cellulose and talc.

10 In another embodiment, both particles are coated with the said protective coating layer.

The protective coating layer may be optionally applied onto at least a type of particles of the present invention in any suitable equipment where coating can be achieved, such as, but not limited to, coating pan, conventional film coating apparatus or a fluidized bed apparatus, or the like. Furthermore, in one embodiment, the protective coating layer
15 can be applied from an aqueous or organic solution or dispersion. In another embodiment, the particles being coated with the protective coating layer may be coated to a weight gain of about 2% to about 50% by weight.

In one embodiment, in order to reduce any damage to the protective coating layer
20 during transfer into capsules, the particles coated with the protective coating layer may be further seal coated with conventional pharmaceutically acceptable film forming agents which may optionally be combined with plasticizers or pigments. Suitable film forming agents include, but are not limited to, hydroxypropyl cellulose, hydroxypropyl methylcellulose, acrylic and methacrylic acid polymers, copolymers or esters, and the
25 like or combinations thereof. Plasticizers or pigments as discussed above may optionally be used with the film forming agents.

The compositions of the present invention comprise a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient. In a further
30 embodiment, the first type of particles comprising dabigatran etexilate may optionally further comprise at least one pharmaceutically acceptable excipient. In another embodiment, the second type of particles comprising at least one organic acid, may optionally further comprise at least one pharmaceutically acceptable excipient. In yet

another embodiment, at least two types of particles that are present in the pharmaceutical composition optionally further comprise at least one pharmaceutically acceptable excipient.

- 5 The pharmaceutically acceptable excipients that may be incorporated in the composition of the present invention include, but are not limited to, binders, disintegrants, diluents, surfactants, glidants, lubricants, and the like or combinations thereof.

The term "disintegrant" as used herein is intended to mean a compound used in solid
10 dosage formulations to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved. Exemplary disintegrants include, by way of example and without limitation, natural, modified or pregelatinized starch, modified starches (such as sodium starch glycolate) and partially pregelatinized starches (such as Starch 1500), polyvinylpyrrolidone, crospovidone, croscarmellose sodium, calcium
15 silicate clays, such as bentonite, microcrystalline cellulose, gums such as agar, guar, locust bean, karaya, pectin, tragacanth, alginates, ion exchange resins (such as Polacrillin potassium, Polacrilex) Neusilins, low substituted hydroxypropyl cellulose and the like, combinations thereof and other such materials known to those of ordinary skill in the art.

20

The term "binders" as used herein is intended to mean substances used to cause adhesion of powder particles in granulations. Examples of suitable binders include, but are not limited to celluloses such as microcrystalline cellulose, modified celluloses (such as low substituted hydroxypropyl cellulose, hydroxypropyl cellulose (or HPC),
25 hydroxypropyl methylcellulose (or HPMC or hypromellose), hydroxyethylcellulose, hydroxyethyl methylcellulose, ethyl cellulose, cellulose gum, xanthan gum, sugars (such as sucrose, glucose, amilose, maltodextrin, dextrose and the like), starches such as corn or potato starch partially pregelatinized starches (such as Starch 1500), polyvinyl acetate (Kollicoat SR), polyvinyl alcohol-polyethylene glycol graft copolymer
30 (Kollicoat IR), copovidone, cross-linked polyvinylpyrrolidone, acrylic acid polymer (Carbopol), poloxamer, polycarbophil, polyethylene oxide, polyethylene glycol, and the like, combinations thereof and other material known to those of ordinary skill in the art.

The term "diluent" or "filler" as used herein is intended to 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 diluents include, but are not limited to microcrystalline cellulose, coprocessed microcrystalline celluloses (such
5 as Avicel CI-611, Avicel RC-581, Avicel RC591, Avicel CE, Avicel DG, Avicel HFE), lactose, sucrose, xylitol, mannitol, maltose, polyols, fructose, guar gum, sorbitol, magnesium hydroxide, dibasic calcium phosphate, kaolin, calcium sulphate, carrageenan, chitosan, pectinic acid, sodium alginate, magnesium aluminium silicate, calcium carbonate and the like, combinations thereof and other such materials known to
10 those of ordinary skill in the art.

The term "lubricant" as used herein is intended to mean substances used in solid dosage formulations to reduce friction during compression of the solid dosage. Such compounds include, but are not limited to, magnesium stearate, calcium stearate, zinc
15 stearate, stearic acid, talc, mineral oil and sodium stearyl fumarate, combinations thereof and other such materials known to those of ordinary skill in the art.

The tablet compositions of the invention may also include a glidant. The term "glidant" as used herein is intended to mean agents used in solid dosage formulations to improve
20 flow-properties during tablet compression and to produce an anti-caking effect. Such compounds include, but not limited to, colloidal silica, silica gel, precipitated silica, calcium silicate, magnesium silicate, cornstarch, talc, combinations thereof and other such materials known to those of ordinary skill in the art.

25 The term "surfactant" as used herein is intended to mean substances used to reduce the surface tension of the aqueous solutions comprising them. Examples of surfactants include, but are not limited to, sodium docusate, glyceryl monooleate, polyethylene alkyl ether, polyoxyethylene sorbitan fatty acid ester, sodium lauryl sulfate, sorbic acid, sorbitan fatty acid ester, mixtures thereof and other such materials known to those of
30 ordinary skill in the art.

The compositions of the present invention comprise a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, with first

type of particles comprising dabigatran etexilate and second type of particles comprising at least one organic acid.

5 The term “particle” as used herein is intended to mean any solid or semi-solid portion of a substance or a composition having defined physical boundaries. Examples of particles particles include, but are not limited to, powder, granules, pellets, beads, minitables or the like. The granules may be prepared by methods such as, but not limited to, wet granulation, melt granulation, dry granulation or roll compaction or the like. In an embodiment of the present invention, pellets may be prepared using extrusion
10 spheronization. In another embodiment of the present invention, dabigatran etexilate present in the first set of particles or at least one organic acid present in the second set of particles can be loaded on an inert carrier. The inert carrier can be selected from, but not limited to, beads, pellets, spheres or similar particles that do not contain an active ingredient. Non-limiting examples of inert carrier include microcrystalline cellulose,
15 sugar or silicon dioxide. In yet another embodiment, the particles of the present invention, in the powder form, may be incorporated in the compositions of the present invention.

In an embodiment of the present invention said first type of particles has a particle size
20 comprised between 50 and 1000 microns and said second type of particles have a particle size comprised between 100 and 1000 microns.

The compositions of the present invention comprise from about 5% to about 100% by weight of the mixture of at least two types of particles. Ratio of the first and second
25 types of particles is from about 1:99 to about 99:1.

The term “composition” or “formulation” has been employed interchangeably for the purpose of the present invention.

30 The term “dosage form” is as used herein is intended to mean a pharmaceutical composition which is suitable for administration to a patient. In one embodiment the compositions of the present invention can be in the form of capsules, tablets, minitables, stick formulation, dispersible tablets, dry suspension for reconstitution,

powder or granule for solution or suspension, granules, and the like or any combinations thereof. Depending of the final dosage form the compositions of the present invention may comprise appropriate pharmaceutically acceptable excipients such as those mentioned above or some additional ones such as, but not limited to, sweeteners,
5 flavors, colorants and the like or combinations thereof. Further it is contemplated within the scope of the invention that the dosage form can be encapsulated or coated. In one embodiment, the composition of the present invention is in the form of a capsule. Capsules include, for example, hard capsules of gelatine or hydroxypropylmethylcellulose and the like. In a further embodiment, the compositions
10 of the present invention may be manufactured using conventional techniques known in the art.

The term "unit dosage form" refers to a physically discrete unit suitable as a unitary dosage for a human patient such as a capsule, a tablet or a vial.
15 In another aspect the present invention provides a unit dosage form prepared from the above mentioned compositions comprising two types of particles.

The compositions of the present invention provide flexibility of blending at least two types of particles to attain different release patterns. In one embodiment, the
20 compositions of the present invention provide tailored in-vitro profiles and corresponding in-vivo profiles. In a further embodiment, the compositions of the present invention can provide tailored profiles wherein dissolution of the compositions of the present invention can be faster at initial time points when compared to formulations having only single type of particles comprising both dabigatran etexilate or
25 pharmaceutically acceptable salts thereof and organic acid. Without being bound to any theory it is believed that such a faster dissolution at earlier time points can ensure availability of more amount of active especially when (a) absorption of the active is rapid with faster T_{max} (~ 45 minutes – 1 hour), (b) significant bioactivation is involved for action of dabigatran and (c) negligible and variable absorption is observed at higher
30 pH.

In another aspect the present invention provides a process for the preparation of a composition comprising the two types of particles described above comprising the step

of mixing said first type of particles and said second type of particles with a at least one pharmaceutically acceptable excipient. In a particular embodiment of the present invention said first type of particles are prepared by granulation.

- 5 In one embodiment the process of preparing the compositions of the present invention comprises the steps of
 - (i) blending dabigatran etexilate and at least one pharmaceutically acceptable excipient such as diluent;
 - (ii) granulating the blend of step (i) with a binder solution to form granules of the
 - 10 active agent;
 - (iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient such as diluent;
 - (iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;
 - 15 (v) coating the organic acid granules with a protective coating layer;
 - (vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;
 - (vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;
 - 20 (viii) lubricating the blend of step (vii);
 - (ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

In another embodiment the process of preparing the compositions of the present invention comprises the steps of

- 25 (i) blending dabigatran etexilate and at least one pharmaceutically acceptable excipient such as diluent;
- (ii) granulating the blend of step (i) with a binder solution to form granules of the active agent;
- (iii) blending at least one organic acid and at least one pharmaceutically acceptable
- 30 excipient such as diluent;
- (iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;
- (v) coating the granules of active agent with a protective coating layer;

- (vi) blending the granules of step (iv) with the coated granules of step (v) to form a mixture of at least two types of granules;
- (vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;
- 5 (viii) lubricating the blend of step (vii);
- (ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

In yet another embodiment the process of preparing the compositions of the present invention comprises the steps of

- 10 (i) blending dabigatran etexilate and at least one pharmaceutically acceptable excipient such as diluent;
- (ii) granulating the blend of step (i) with a binder solution to form granules of the active agent;
- (iii) blending at least one organic acid and at least one pharmaceutically acceptable
15 excipient such as diluent or binder;
- (iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;
- (v) coating the organic acid pellets of step (iv) with a protective coating layer;
- (vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;
- 20 (vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;
- (viii) lubricating the blend of step (vii);
- (ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

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

In still another aspect the present invention provides a method of for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or

preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the subject in need thereof pharmaceutical compositions of dabigatran etexilate of the present invention.

5

In another embodiment of the present invention the dabigatran etexilate may be combined with other active agents or pharmaceutically acceptable salts thereof including, but not limited to, atorvastatin, dipyridamole, mepidamol and the like or combinations thereof.

10

The invention is further illustrated by the following examples, which are for illustrative purposes and should not be construed as limiting the scope of the invention in any way.

Examples

15

Example 1: Oral capsule formulation of dabigatran etexilate mesylate

A) Preparation of coated tartaric acid pellets

20

(a) Preparation of tartaric acid pellets

Table 1: Composition of tartaric acid pellets

Ingredients	mg/unit
Tartaric acid	80
Microcrystalline cellulose	30
Hydroxypropyl cellulose	10
Isopropyl alcohol*	q.s
Total	120

*not present in the final product

25

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

pellets. These pellets were then coated with a protective coating layer as follows to give coated tartaric acid pellets.

(b) Preparation of coated tartaric acid pellets

5 Table 2: Composition of tartaric acid pellets

Ingredients	mg/unit
Tartaric acid pellets	120
Hydroxypropyl methylcellulose	10
Talc	6
Isopropyl alcohol*	q.s
Total	136

*not present in the final product

Procedure: Tartaric acid pellets prepared as above were coated with dispersion of hydroxypropyl cellulose and talc in isopropyl alcohol. The coated pellets were then
 10 dried to give coated tartaric acid pellets.

B) Preparation of dabigatran etexilate mesylate granules

Table 3: Composition of dabigatran etexilate mesylate granules

Ingredients	mg/unit
Dabigatran etexilate mesylate equivalent to 110 mg of dabigatran etexilate	126.83
Microcrystalline cellulose	40.17
Lactose anhydrous	30
Crospovidone	4
Hydroxypropyl cellulose	4
Isopropyl alcohol*	q.s
Total	205

15 *not present in the final product

Procedure: Dabigatran etexilate mesylate, microcrystalline cellulose, lactose anhydrous and crospovidone were blended. The blend was granulated using solution

of hydroxypropyl cellulose in isopropyl alcohol. The granules were sized and screened to form dabigatran etexilate mesylate granules.

C) Preparation of oral capsule formulation of dabigatran etexilate mesylate

5

Table 4: Composition of capsule formulation of dabigatran etexilate mesylate

Ingredients	mg/unit
Dabigatran etexilate mesylate granules	205
Coated tartaric acid pellets	136
Sodium stearyl fumarate	4
Total	345

Procedure: Dabigatran etexilate mesylate granules prepared as per composition of Table 3 above and coated tartaric acid pellets prepared as per Table 2 above were blended. Blend was lubricated with sodium stearyl fumarate and filled into capsules
10 by means of a capsule filling machine.

Example 2: Oral capsule formulation of dabigatran etexilate mesylate

A) Preparation of tartaric acid pellets

15

Table 5: Composition of tartaric acid pellets

Ingredients	mg/unit
Tartaric acid	60
Microcrystalline cellulose	18
Hydroxypropyl cellulose	4
Isopropyl alcohol*	q.s
Total	82

*not present in the final product

Procedure: Tartaric acid and microcrystalline cellulose were blended and to this
20 blend was added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass was extruded, spheronized, dried and screened to give

pellets. These pellets were then coated using with a protective coating layer as follows to give coated tartaric acid pellets.

B) Preparation of dabigatran etexilate mesylate coated granules

5

(a) Preparation of dabigatran etexilate mesylate granules

Table 6: Composition of dabigatran etexilate mesylate granules

Ingredients	mg/unit
Dabigatran etexilate mesylate equivalent to 110 mg of dabigatran etexilate	86.48
Microcrystalline cellulose	32.52
Lactose anhydrous	25
Crospovidone	3
Hydroxypropyl cellulose	3
Isopropyl alcohol*	q.s
Total	150

*not present in the final product

10

Procedure: Dabigatran etexilate mesylate, microcrystalline cellulose, lactose anhydrous and crospovidone were blended. The blend was granulated using solution of hydroxypropyl cellulose in isopropyl alcohol. The granules were sized and screened to form dabigatran etexilate mesylate granules.

15

(b) Preparation of dabigatran etexilate mesylate coated granules

Table 7: Composition of dabigatran etexilate mesylate coated granules

Ingredients	mg/unit
Dabigatran etexilate mesylate granules	150
Polyvinyl pyrrolidone	22
Talc	3
Isopropyl alcohol	q.s.
Total	175

*not present in the final product

Procedure: Dabigatran etexilate mesylate granules prepared as per the process mentioned above were coated with a coating dispersion of polyvinyl pyrrolidone and talc in isopropyl alcohol to form coated dabigatran etexilate mesylate granules.

C) Preparation of oral capsule formulation of dabigatran etexilate mesylate

Table 8: Composition of capsule formulation of dabigatran etexilate mesylate

Ingredients	mg/unit
Coated dabigatran etexilate mesylate granules	175
Tartaric acid pellets	82
Sodium stearyl fumarate	3
Total	260

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Procedure: Dabigatran etexilate mesylate granules prepared as per Table 7 above and coated tartaric acid pellets prepared as per table 5 above were blended. Blend was lubricated with sodium stearyl fumarate and filled into capsules by means of a capsule filling machine.

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Example 3: Comparative evaluation of two formulation approaches for dabigatran etexilate mesylate

The two formulation approaches for dabigatran etexilate mesylate as shown below were evaluated:

- (i) First approach being that of the present invention having two types of particles/pellets (one of dabigatran etexilate mesylate and the other of organic acid) and
- (ii) Second approach having one type of particles/pellets having both dabigatran etexilate mesylate and organic acid. This formulation was prepared according to the teachings of US 2006/074056 and, in particular, Example 1. Formulation (B)

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(A) Preparation of formulation A having two types of particles/pellets (i.e. Dabigatran etexilate mesylate granules and seal coated tartaric acid pellets)

Table 17: Composition of Dabigatran etexilate mesylate granules

Ingredients	mg/capsule
Intragranular	
Dabigatran etexilate mesylate equivalent to 150 mg dabigatran etexilate	172.95
IPA	q.s
Extragranular	
Microcrystalline cellulose	67.05
Croscarmellose Sodium	50
Total weight of the Dabigatran etexilate mesylate granules	290

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Table 18: Composition of seal coated tartaric acid pellets

Ingredients	mg/capsule
Tartaric acid (TAP® 600)	196.34
Seal coating of Tartaric acid pellets	
Hydroxypropylmethyl cellulose	5.62
Lactose	5.62
Talc	8.42
Isopropyl alcohol- water	q.s
Total weight of seal coated pellets	216

Procedure:

- 10 (i) Preparation of Dabigatran etexilate mesylate granules portion

Loaded weighed quantity of dabigatran etexilate mesylate in the granulator and granulated it using isopropyl alcohol. The granules were further dried in fluidized bed drier. The granules were then sized, sifted and blended with microcrystalline cellulose,

croscarmellose sodium in a suitable blender to give dabigatran etexilate mesylate granules portion.

(ii) Preparation of seal coated tartaric acid pellets

- 5 Hydroxypropyl cellulose was added to a suitable quantity of isopropyl alcohol water mixture under continuous stirring to obtain a clear solution. Lactose was added to this solution and mixed, followed by addition of talc and stirring. The suspension thus formed was filtered through a suitable sieve and sprayed under continuous stirring on tartaric acid pellets using a fluidized bed coater with Wurster column to achieve desired weight gain. The coated tartaric acid pellets were then dried.

The lubricated seal coated tartaric acid pellets and dabigatran etexilate mesylate granules were filled in capsules using the automatic capsule filling machine in HPMC size 0 capsules.

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(C) Comparative evaluation of dissolution profiles of formulation of the present invention having two types of particles/pellets (Formulation A above) and formulation having one type of particles/pellets (Formulation B above)

- 20 Dissolution profiles of the formulations in 0.01N HCl pH 2 media at 100 rpm USP type I (basket) are as depicted under A and B below:

Time (minutes)	% release	
	Formulation A (two types of particles/pellets)	Formulation B (one type of particles/pellets)
10	65.1	19.2
15	79.2	57
20	86.7	86.1
30	92	97
45	95.5	97.6
60	96.8	98.5

Comparative evaluation of dissolution profiles of formulation of the present invention having two types of particles/pellets (Formulation A above) and formulation having one type of particles/pellets (Formulation B above) indicates that formulations of the present invention having two types of particles/pellets can provide faster dissolution particularly
5 at earlier time points as compared to formulation having one type of particles/pellets. Such a faster dissolution at earlier time points can ensure availability of more amount of active especially when (a) absorption of the active is rapid with faster T_{max} (~ 45 minutes – 1 hour), (b) significant bioactivation is involved and (c) negligible and variable absorption at higher pH.

Claims

1. A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid.
2. A composition according to claim 1 wherein at least one type of particles are coated with a protective coating layer.
3. A composition according to any one of claims 1 and 2 additionally comprising at least one pharmaceutically acceptable excipient.
4. A composition according to any preceding claim wherein said first type of particles is free from acids.
5. A composition according to any preceding claim wherein said second type of particles is free from dabigatran etexilate.
6. A composition according to any preceding claim comprising from 0.01 wt % to 90 wt % of dabigatran etexilate (expressed as dabigatran etexilate mesylate).
7. A composition according to any preceding claim wherein at least 90% by weight of the organic acid present in the composition is contained in said second type of particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients.
8. A composition according to any preceding claim wherein said first type of particles is coated with a protective coating layer.
9. A composition according to any preceding claim wherein said second type of particles is coated with a protective coating layer.

10. A composition according to any preceding claim comprising from 2 wt % to 95 wt % of said at least one pharmaceutically acceptable organic acid.

11. A composition according to any preceding claim wherein at least 90% by weight, of the organic acid present in the composition is contained in said second type of particles, the rest (if any) of the organic acid forming part of said excipients.

12. A unit dosage form prepared from a composition according to any preceding claim which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

13. Composition according to any one of claims 1 to 11 or a unit dose according to claim 12 for use in the reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or in the prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

14. Use of a composition according to any one of claims 1 to 11 or a unit dose according to claim 12 for the preparation of a medicament to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or to prevent venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery

15. A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the subject in need thereof a composition according to any one of claims 1 to 11 or a unit dose according to claim 12.

16. A process for the preparation of a composition according to any one of claims 3 to 11 comprising the step of mixing said first type of particles and said second type of particles with a at least one at least one pharmaceutically acceptable excipient.

17. The process of claim 16 wherein said first type of particles are prepared by granulation.

18. The process according to claim 17 comprising the steps of:
- (i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;
 - (ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;
 - (iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;
 - (iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;
 - (v) coating the organic acid granules with a protective coating layer;
 - (vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;
 - (vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;
 - (viii) adding a lubricant to the blend of step (vii); and
 - (ix) filling the lubricated mixture of step (viii) into suitable hard capsules.
19. The process according to claim 17 comprising the steps of:
- (i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;
 - (ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;
 - (iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;
 - (iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;
 - (v) coating the granules of dabigatran etexilate with a protective coating layer;
 - (vi) blending the granules of step (iv) with the coated granules of step (v) to form a mixture of at least two types of granules;

- (vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;
- (viii) adding a lubricant to the blend of step (vii); and
- (ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

20. A process according to claim 17 comprising the steps of:

- (i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;
- (ii) granulating the blend of step (i) with a binder solution to form granules of the dabigatran etexilate;
- (iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;
- (iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;
- (v) coating the organic acid pellets of step (iv) with a protective coating layer;
- (vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;
- (vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;
- (viii) adding a lubricant to the blend of step (vii); and
- (ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

Abstract

Compositions comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, use of said compositions in the reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or in the prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery and processes for the preparation of said compositions.