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(54) Title: TABLET COMPRISING DABIGATRAN ETEXILATE OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF AND METHOD OF PRODUCING SAME

(57) Abstract: [Problem to be Solved] To provide a preparation of dabigatran etexilate or a pharmaceutically acceptable salt thereof that is easy even for a person with dysphagia to be swallowed and that demonstrates superior stability. [Solution] A method of producing a tablet comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof, and an excipient, comprising the step of making dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof be present in substantially close proximity; and a tablet obtained by the method.

DESCRIPTION

TABLET COMPRISING DABIGATRAN ETEXILATE OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF AND METHOD OF PRODUCING SAME

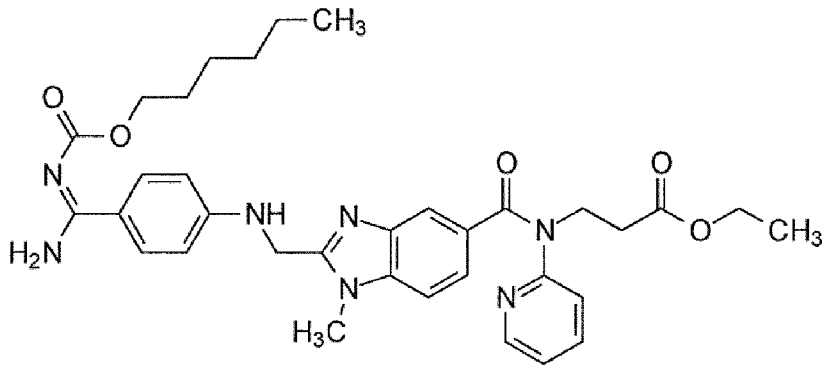
TECHNICAL FIELD

[0001] The present invention relates to a tablet comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof and a method of producing the same.

BACKGROUND ART

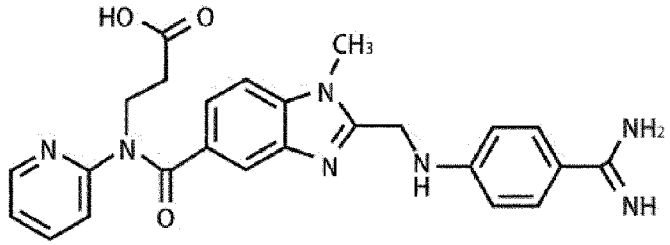
[0002] Dabigatran etexilate (chemical name: 3-({[2-({[4-(amino{[(hexyloxy)carbonyl]imino}methyl)phenyl]amino}methyl)-1-methyl-1H-benzoimidazol-5-yl]carbonyl} (pyridin-2-yl)amino) propionic acid ethyl ester) is a compound having the structure indicated below.

[Chemical Formula 1]



[0003] Dabigatran etexilate is described in Patent Document 1 under the name 1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzoimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, along with the synthesis method thereof. Dabigatran etexilate is a double prodrug of dabigatran, and dabigatran etexilate per se does not have anti-thrombin activity. However, when administered orally and absorbed from the digestive tract, it is converted to the active metabolite dabigatran having the structure indicated below via an intermediate metabolite.

[Chemical Formula 2]



[0004] Capsules of a pharmaceutically acceptable salt of dabigatran etexilate in the form of dabigatran etexilate methanesulfonate are commercially available as Prazaxa® capsules.

[0005] Patent Document 2 discloses a pharmaceutical composition for oral administration of dabigatran etexilate. Specifically, Patent Document 2 discloses a pharmaceutical composition that comprises a substantially spherical core material containing a pharmaceutically acceptable organic acid, a separation layer and an active ingredient, and that is optionally coated with a coating that enhances impact resistance of pellet and shelf life. Also, it is disclosed that the composition is produced by coating the separation layer, a layer comprising the active ingredient, and the like, on the substantially spherical core material comprising the organic acid.

[0006] Patent Document 3 discloses a tablet comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof and an organic acid such as tartaric acid, fumaric acid, succinic acid, citric acid, or malic acid, together with a conventional excipient and filler.

[Prior Art Documents]

[Patent Documents]

[0007] [Patent Document 1] Japanese Unexamined Patent Application Publication (Translation of PCT Application) No. 2001-509815

[Patent Document 2] Japanese Unexamined Patent Application Publication (Translation of PCT Application) No. 2005-519099

[Patent Document 3] Japanese Unexamined Patent Application Publication (Translation of PCT Application) No. 2007-502788

SUMMARY OF THE INVENTION

[Problem to be Solved by Invention]

[0008] Prazaxa® capsules are large hard capsule preparations that use a No. 2 capsule (approx. 18 mm length × approx. 6 mm diameter) or No. 1 capsule (approx. 19 mm length × approx. 7 mm diameter). When considering that persons having difficulty swallowing such as elderly persons and persons with dysphagia are exist and that there

are many persons having a small physique and a relatively narrow esophagus in Japan and other parts of Asia, a preparation is desirable that has a size easier to swallow than Prazaxa® capsules. A tablet, particularly a small tablet, is contemplated as one of such possible drug forms.

Since Prazaxa® capsules are a direct thrombin inhibitor that demonstrates efficacy in inhibiting the occurrence of ischemic stroke and systemic embolisms, it is essential that the tablet demonstrate efficacy equivalent to that of the existing capsule preparations when converting the drug form of dabigatran etexilate or a pharmaceutically acceptable salt thereof to a tablet. However, dabigatran etexilate or a pharmaceutically acceptable salt thereof is poorly soluble and the solubility decreases considerably particularly in the range of weakly acidic to neutral, and therefore, means are required that minimize variations in absorption under environments having different pH as small as possible (for example, an acid needs to be contained). However, it is found that dabigatran etexilate or a pharmaceutically acceptable salt thereof has poor stability per se and hydrolysates thereof are considerably increased under highly humid conditions or acidic conditions. These factors also make it difficult to obtain a stable tablet comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof.

[0009] As was described above, the composition for oral administration disclosed in Patent Document 2 is a composition characterize by its layer structure. Such structure will be collapsed when this composition is molded into a tablet, and therefore, this composition is not suitable to produce a tablet.

[0010] Patent Document 3 describes a tablet of dabigatran etexilate or a pharmaceutically acceptable salt thereof. However, there are no specific examples that describe the production of the tablet, and it only describes that the tablet can be produced by directly mixing all of the materials and compressing into a tablet, as one possible method. In addition, there are also no specific studies about stability when dabigatran etexilate or a pharmaceutically acceptable salt thereof is molded into a tablet.

[0011] Thus, there still exists a need for a drug form of dabigatran etexilate or a pharmaceutically acceptable salt thereof that can be swallowed easily even by persons with dysphagia and that demonstrates superior stability.

[Means for Solving Problem]

[0012] The present inventors have faced with the above-mentioned problem and conducted extensive studies. Surprisingly, we have found that, differing from the conventional understanding, a tablet having superior stability can be obtained even in a state in which a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof and dabigatran etexilate or a pharmaceutically acceptable salt thereof are present

in substantially close proximity, without employing a drug form in which dabigatran etexilate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof are completely separated, such as a layered drug form as in Patent Document 2, and we have accomplished the present invention.

[0013] In summary, the present invention provides the followings.

[1] A method of producing a tablet comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof, and an excipient, comprising the step of:
making dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof be present in substantially close proximity.

[2] The method described in [1] above, wherein said step comprises the steps of:
(1) preparing granules comprising dabigatran etexilate or the pharmaceutically acceptable salt thereof and the excipient by dry granulation, and
(2) preparing granules comprising the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof.

[3] The method described in [1] above, wherein said step comprises the step of mixing dabigatran etexilate or the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof, and the excipient, and dry-granulating the mixture.

[4] The method described in any of [1] to [3] above, wherein dabigatran etexilate or the pharmaceutically acceptable salt thereof is dabigatran etexilate methanesulfonate.

[5] The method described in any of [1] to [4] above, wherein the pharmaceutically acceptable organic acid is an organic acid having solubility higher than 0.98 g/250 mL in water at 20°C.

[6] The method described in any of [1] to [5] above, wherein the pharmaceutically acceptable organic acid is at least one selected from the group consisting of fumaric acid, glutamic acid, aspartic acid, succinic acid, and tartaric acid.

[7] The method described in [6] above, wherein the pharmaceutically acceptable organic acid is fumaric acid.

[8] The method described in any of [1] to [7] above, wherein the excipient is an excipient having low hygroscopicity.

[9] The method described in [8] above, wherein the excipient having low hygroscopicity is D-mannitol and/or erythritol.

[10] The method described in any of [1] to [9] above, wherein the method further

comprises the step of coating the surface of the tablet in which dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof are present in substantially close proximity, with a water-swellable polymer.

[11] The method described in [10] above, wherein the water-swellable polymer is polyvinyl alcohol.

[12] The method described in any of [1] to [11] above, wherein the tablet comprises 15% by weight to 65% by weight of dabigatran etexilate or the pharmaceutically acceptable salt thereof when converted by calculation into dabigatran etexilate methanesulfonate, and 1% by weight to 20% by weight of the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof.

[13] A method of producing a tablet in which dabigatran etexilate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof are present in substantially close proximity, comprising the steps of:

(1) mixing dabigatran etexilate methanesulfonate with D-mannitol, a binder, and a lubricant, and dry-granulating the mixture to prepare granules;

(2) mixing fumaric acid with D-mannitol and a binder, and granulating the mixture to prepare granules; and

(3) mixing the granules of step (1) and the granules of (2), and compressing the mixture into the tablet to prepare the tablet.

[14] A method of producing a tablet in which dabigatran etexilate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof are present in substantially close proximity, comprising the step of

mixing dabigatran etexilate methanesulfonate, fumaric acid, D-mannitol, and a binder, and dry-granulating the mixture.

[15] A tablet obtained by the method described in any of [1] to [14] above.

[16] A tablet comprising, as separate granules:

(1) dry-granulated granules comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof and an excipient, and

(2) granules comprising a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof,

wherein dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof are present in substantially close proximity.

[17] A tablet comprising dry-granulated granules of a mixture of dabigatran etexilate or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof, and an excipient,
wherein dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof are present in substantially close proximity.

[18] The tablet described in [16] or [17] above, wherein dabigatran etexilate or the pharmaceutically acceptable salt thereof is dabigatran etexilate methanesulfonate.

[19] The tablet described in any of [16] to [18] above, wherein the pharmaceutically acceptable organic acid is an organic acid having solubility higher than 0.98 g/250 mL in water at 20°C.

[20] The tablet described in any of [16] to [19] above, wherein the pharmaceutically acceptable organic acid is at least one selected from the group consisting of fumaric acid, glutamic acid, aspartic acid, succinic acid, and tartaric acid.

[21] The tablet described in [20] above, wherein the pharmaceutically acceptable organic acid is fumaric acid.

[22] The tablet described in any of [16] to [21] above, wherein the excipient is an excipient having low hygroscopicity.

[23] The tablet described in [22] above, wherein the excipient having low hygroscopicity is D-mannitol and/or erythritol.

[24] The tablet described in any of [16] to [23] above, wherein the surface of the tablet is coated with a water-swellable polymer.

[25] The tablet described in [24] above, wherein the water-swellable polymer is polyvinyl alcohol.

[26] The tablet described in any of [16] to [25] above, wherein the tablet comprises 15% by weight to 65% by weight of dabigatran etexilate or the pharmaceutically acceptable salt thereof when converted by calculation into dabigatran etexilate methanesulfonate, and 1% by weight to 20% by weight of the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof.

[Effect of the Invention]

[0014] According to the present invention, a stable tablet comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof can be obtained. In addition, according to the method of a tablet production according to the present invention, the formation of decomposition products and hydrolysates of dabigatran etexilate or a pharmaceutically acceptable salt thereof can be effectively inhibited.

MODE FOR CARRYING OUT THE INVENTION

[0015] The present invention is explained in detail in the followings.

[0016] In one embodiment of the present invention, a method of producing a tablet comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof, and an excipient, comprising the step of making dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof be present in substantially close proximity, is provided.

[0017] Making dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof "be present in substantially close proximity" or being "present in substantially close proximity" means that, as long as the desired effects of the present invention can be achieved, at least a portion of the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof is made to be present in substantially close proximity to dabigatran etexilate or the pharmaceutically acceptable salt thereof, or at least a portion of the pharmaceutically acceptable organic acid or the hydrate or the acidic acid thereof is present in substantially close proximity to dabigatran etexilate or the pharmaceutically acceptable salt thereof; or at least a portion of dabigatran etexilate or the pharmaceutically acceptable salt thereof is made to be be present in substantially close proximity to the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof, or at least a portion of dabigatran etexilate or the pharmaceutically acceptable salt thereof is present in substantially close proximity to the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof. For example, this means, as long as the desired effects of the present invention can be achieved, a state in which granules comprising dabigatran etexilate or the pharmaceutically acceptable salt thereof, and as desired, an excipient, and granules comprising the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof, are present as a mixture, or a state in which dabigatran etexilate or the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof, and as desired, an excipient, are present as a mixture (and the resulting mixture is granulated, where necessary).

[0018] In another embodiment of the present invention, a tablet comprising, as separate granules, (1) dry-granulated granules comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof and an excipient, and (2) granules comprising a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof, wherein

dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof are present in substantially close proximity, is provided.

In still another embodiment of the present invention, a tablet comprising dry-granulated granules of a mixture of dabigatran etexilate or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof, and an excipient, wherein dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof are present in substantially close proximity, is provided.

[0019] The "dabigatran etexilate" used in the present invention is a known compound. There are no particular limitations on the production method thereof, and it can be synthesized according to, for example, the production method described in Japanese Unexamined Patent Application Publication (Translation of PCT Application) No. 2001-509815.

[0020] There are no particular limitations on the "pharmaceutically acceptable salt" of dabigatran etexilate as long as it is a salt of dabigatran etexilate that can be used as a pharmaceutical, and examples thereof include salts and addition salts with organic or inorganic acids or bases. Preferable examples of the salts include acid addition salts with hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, maleic acid, and methanesulfonic acid. Dabigatran etexilate methanesulfonate is particularly preferable.

[0021] There are no particular limitations on the "pharmaceutically acceptable organic acid" in the phrase "a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof" used in the present invention as long as it can be used as a pharmaceutical and the desired object of the present invention can be achieved. Examples of such organic acids include pharmaceutically acceptable organic acids having solubility higher than 0.98 g/250 mL in water at 20°C, and more specifically, at least one selected from the group consisting of fumaric acid, glutamic acid, aspartic acid, succinic acid, tartaric acid, and malic acid can be used. From the viewpoint of stability of dabigatran etexilate or the pharmaceutically acceptable salt thereof used in the present invention, at least one can be selected from the group consisting of fumaric acid, glutamic acid, aspartic acid, and succinic acid. In addition, from the viewpoint of solubility of dabigatran etexilate or the pharmaceutically acceptable salt thereof in the present invention, tartaric acid or fumaric acid can be selected. Fumaric acid is preferably selected when considering stability and solubility.

Examples of the hydrates of the pharmaceutically acceptable organic acid

include monohydrates, dihydrates, and trihydrates. In addition, examples of the acidic salts of the pharmaceutically acceptable organic acid include sodium fumarate, sodium tartrate, and sodium citrate.

[0022] There are no particular limitations on the excipient used in the present invention as long as the desired object of the present invention can be achieved, and examples thereof include D-mannitol, xylitol, erythritol, lactose, microcrystalline cellulose, hydroxypropyl cellulose, and pre-gelatinized starch. These excipients can be combined as long as the desired object of the present invention can be achieved. When considering stability of dabigatran etexilate or the pharmaceutically acceptable salt thereof, the excipient preferably has low hygroscopicity. The excipient having "low hygroscopicity" means that, for example, the excipient does not absorb moisture or absorbs hardly any moisture even in an atmosphere at 20°C and relative humidity of 80%. For example, the excipient having low hygroscopicity is preferably D-mannitol and/or erythritol, with D-mannitol being particularly preferable.

[0023] In further embodiment of the present invention, a method of producing a tablet, wherein the step of making dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof be present in substantially close proximity comprises the steps of (1) preparing granules comprising dabigatran etexilate or the pharmaceutically acceptable salt thereof and the excipient by dry granulation, and (2) preparing granules comprising the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof, is provided.

In still further embodiment of the present invention, a method of producing a tablet, wherein the step of making dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof be present in substantially close proximity comprises the step of mixing dabigatran etexilate or the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof, and the excipient, and dry-granulating the mixture, is provided.

[0024] There are no particular limitations on the method of preparing granules comprising dabigatran etexilate or the pharmaceutically acceptable salt thereof and the excipient as long as the desired object of the present invention can be achieved, and the method can be carried out using a known or well-known method and apparatus in the pharmaceutical field. The granules can be prepared by dry granulation or wet granulation. When considering the stability of dabigatran etexilate or the pharmaceutically acceptable salt thereof, the above granules are preferably prepared by

dry granulation.

Specifically, the granules can be prepared by, for example, mixing dabigatran etexilate or a pharmaceutically acceptable salt thereof, an excipient, and as necessary, a binder and/or a lubricant, etc., and dry-granulating the mixture.

Dry granulation can be carried out using a known or well-known method and apparatus in the pharmaceutical field. For example, dabigatran etexilate or a pharmaceutically acceptable salt thereof is mixed with an excipient, a binder, and a lubricant, and a thin compression is prepared using a roller compacter or a large-diameter pestle. After then, the compression is crushed into flakes using a crusher, a granulator, etc. followed by granulating with a granulator, etc. to obtain granules.

[0025] The method of preparing granules comprising the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof can be carried out using a known or well-known method and apparatus in the pharmaceutical field, and can be carried out by dry granulation or wet granulation.

Specifically, in a preferred embodiment, the granules are prepared by mixing the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof with an excipient and a binder as necessary, and granulating the mixture.

For example, the granules can be prepared by preparing an aqueous solution containing the binder, mixing the aqueous solution with a mixture of the organic acid and the excipient in a granulator, granulating the mixture, and sieving the granulates. Examples of the granulator include a fluidized bed granulator and a stirring granulator.

[0026] The tablet according to the present invention can be prepared by mixing each granules as obtained above with an excipient, a binder, etc., and compressing the mixture into a tablet.

[0027] In another embodiment of the present invention, a method of producing a tablet in which dabigatran etexilate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof are present in substantially close proximity, comprising the steps of (1) mixing dabigatran etexilate methanesulfonate with D-mannitol, a binder, and a lubricant, and dry-granulating the mixture to prepare granules, (2) mixing fumaric acid with D-mannitol and a binder, and granulating the mixture to prepare granules, and (3) mixing the granules of step (1) and the granules of step (2), and compressing the mixture into the tablet to prepare the tablet, is provided.

[0028] In still another embodiment of the present invention, a method of producing a tablet in which dabigatran etexilate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof are present

in substantially close proximity, comprising the step of mixing dabigatran etexilate methanesulfonate, fumaric acid, D-mannitol, and a binder, and dry-granulating the mixture, is provided.

In yet still another embodiment of the present invention, a method of producing a tablet in which dabigatran etexilate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof are present in substantially close proximity, by a method comprising the step of mixing dabigatran etexilate or the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof, and an excipient, and dry-granulating the mixture, is provided.

[0029] There are no particular limitations on the binder used in the present invention as long as the desired object of the present invention can be achieved, and examples thereof include polyvinylpyrrolidone (povidone), copolymer of N-vinylpyrrolidone and vinyl acetate (copovidone), hydroxypropyl methyl cellulose, and hydroxypropyl cellulose. Among these, hydroxypropyl cellulose is particularly preferable.

[0030] There are no particular limitations on the lubricant used in the present invention as long as the desired object of the present invention can be achieved, and examples thereof include magnesium stearate, sodium stearyl fumarate, and sucrose fatty acid ester. Among these, magnesium stearate is particularly preferable.

[0031] In addition to the aforementioned components, the tablet according to the present invention may contain, as necessary, an additive known to be used in the production of tablets, and examples of such additives include disintegrating agents, flavoring agents, surfactants, dispersants, buffers, pH adjusters, preservatives, and diluents.

Examples of the disintegrating agent include crosslinked polyvinylpyrrolidone (crospovidone), sodium starch glycolate, and crosslinked cellulose carboxymethyl ether sodium salt (croscarmellose sodium). Among these, crosslinked polyvinylpyrrolidone is particularly preferable.

[0032] Although there are no particular limitations on the content of dabigatran etexilate or the pharmaceutically acceptable salt thereof contained in the tablet according to the present invention as long as the desired pharmacological activity can be demonstrated and the desired object of the present invention can be achieved, it is preferably contained at 15% by weight to 65% by weight, more preferably at 20% by weight to 60% by weight, and particularly preferably at 30% by weight to 50% by weight, when converted by calculation into dabigatran etexilate methanesulfonate.

Although there are no particular limitations on the content of the

pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof contained in the tablet according to the present invention as long as the desired object of the present invention can be achieved, it is preferably contained at 1% by weight to 20% by weight, preferably at 4% by weight to 10% by weight, and particularly preferably at 5% by weight to 7% by weight.

Each of the aforementioned preferably incorporated amounts of dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof can be suitably combined.

[0033] The methods described in each of the aforementioned embodiments are examples of a method of producing a tablet in which dabigatran etexilate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof are allowed to be present in substantially close proximity, and it is apparent that the method can be suitably modified by a person with ordinary skill in the art as long as the desired object of the present invention can be achieved.

Even though it is general understanding that there is fear of a decrease in stability by the incorporation of an organic acid, differing from the prediction from the conventional understanding, it is surprising effect that a tablet that contains dabigatran etexilate or a pharmaceutically acceptable salt thereof and is superior in hygroscopicity and stability can be obtained by a method of producing a tablet that enables dabigatran etexilate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof to be present in close proximity, such as the methods described in each of the aforementioned embodiments.

[0034] In a particularly preferable embodiment of the present invention, the surface of the tablet produced in the manner as described above is coated with a film coating, sugar coating, or the like. Although there are no particular limitations thereon, a film coating is preferable since moisture resistance is enhanced, thereby enabling the providing of a more stable tablet. The coating can be applied using a known or well-known method and apparatus in the field of pharmaceutical preparations. For example, pan coating, a method using an instrument such as Hicoater®, spray coating, and the like can be used.

Although there are no particular limitations on a base for the film coating as long as the desired object of the present invention can be achieved and a known or well-known coating base in the field of pharmaceutical preparations can be used, a water-swellable polymer is preferably used. Examples of water-swellable polymers include hydroxypropyl methyl cellulose, polyvinyl alcohol, aminoalkyl methacrylate, ethyl

cellulose, and methyl cellulose. Among these, hydroxypropyl methyl cellulose and/or polyvinyl alcohol are preferable, with polyvinyl alcohol being particularly preferable.

[0035] The ratio of coating to tablet weight is, for example, 3% by weight to 10% by weight and preferably 5% by weight to 7% by weight.

[0036] Although there are no particular limitations thereon, the tablet according to the present invention can have a smaller dosage form than existing capsules, and therefore, it is particularly suitable for being taken by persons having difficulty in swallowing, such as the elderly and persons with dysphagia, as well as persons having a small physique and a relatively narrow esophagus. There are no particular limitations on the size of the tablet as long as the desired object of the present invention can be achieved. For example, the tablet can be small tablet having a diameter of preferably about 5 mm to about 10 mm, more preferably about 6 mm to about 8 mm, and in the case of an oval tablet, about 10 mm to about 14 mm of the long axis and about 4 mm to about 8 mm of the short axis.

EXAMPLES

[0037] The present invention is explained below in more detail by use of Examples. However, the examples illustrate an embodiment of the present invention, and are not intended to be understood as limiting the present invention.

[0038] [Examples 1 and 2]

Formulations of the tablets of Examples 1 and 2 are shown in the following Table 1. Tablets were produced according to the procedure described below using the excipients and other components indicated in Table 1.

1. Sized granules of bulk drug (Granules)

An active ingredient (dabigatran etexilate methanesulfonate), D-mannitol (fine powder) (Japanese Pharmacopoeia, Mannit P, Mitsubishi Shoji Foodtech Co., Ltd.), hydroxypropyl cellulose (Japanese Pharmacopoeia, NISSO HPC-L fine, Nippon Soda Co., Ltd.), and magnesium stearate (Japanese Pharmacopoeia, Magnesium Stearate S, NOF Corp.) were mixed (using a container rotary mixer or a stirring mixer, Vertical Granulator FM-VG100, Powrex Corp.), granulated by a dry granulator (WP-160X60, Freund Turbo Corp.), and then roughly crushed and granulated by a granulator (New Speed Mill ND-50SD, Okada Seiko Co., Ltd.) to obtain granules.

2. Sized granules of acid (Granules)

Fumaric acid (Japanese Food Additive Standards, Kawasaki Kasei Chemicals Ltd.) and D-mannitol (fine powder) (Japanese Pharmacopoeia, Mannit P, Mitsubishi Shoji Foodtech Co., Ltd.) were granulated with a 5% aqueous solution of

hydroxypropyl cellulose (Japanese Pharmacopoeia, NISSO HPC-L fine, Nippon Soda Co., Ltd.) using a fluidized bed granulator (FD-GMCG-30, Powrex Corp.) and then sieved to obtain granules.

3. Tablets

The granules produced in 1 and 2 above were mixed (using Volley Container Mixer, Matsubo Corp.) with Crospovidone Type A (Japanese Pharmacopoeia, Kollidon CL, BASF Corp.) and magnesium stearate (Japanese Pharmacopoeia, Magnesium Stearate S, NOF Corp.), and compressed into tablets (using HT-CVX-MS-II, Hata Tekkosho Co, Ltd.) to obtain tablets.

4. Film Coating

An aqueous solution of polyvinyl alcohol (partially saponified) (Japanese Pharmaceutical Excipients, Gohsenol EG-05P, Nippon Synthetic Chemical Industry Co., Ltd.) was prepared and mixed with a dispersion of sucrose fatty acid ester (Japanese Pharmaceutical Excipients, Surfhope SE J-1803F, Mitsubishi Chemical Foods Corp.), titanium oxide (Japanese Pharmacopoeia, Tipaque A-100, Ishihara Sangyo Kaisha, Ltd.), and Polysorbate 80 (Japanese Pharmacopoeia, Polysorbate 80 (GS), NOF Corp.) in water, and the mixture was passed through a sieve to prepare a coating solution. The tablets produced in 3 above were coated (using HCFS-130N, Freund Corp.) with this coating solution to obtain the tablets of Examples 1 and 2.

[0039] [Table 1]

Intermediate product		Components	Grade	Example 1 amount (mg)	Example 2 amount (mg)
Tablet Molded Products	Sized granules of bulk drug	Active ingredient	---	126.83	126.83
		D-mannitol (fine powder)	Mannit P	42.68	44.11
		Hydroxypropyl cellulose	NISSO HPC-L fine	5.94	5.94
		Magnesium stearate	Magnesium Stearate S	2.97	2.97
	Sized granules of acid	Fumaric acid	Fumaric acid	18.26	18.26
		D-mannitol (fine powder)	Mannit P	77.77	77.77
		Hydroxypropyl cellulose	NISSO HPC-L fine	2.97	2.97
		Purified water	---	(volatile component)	(volatile component)
		Crospovidone Type A	Kollidon CL	4.29	2.86
		Magnesium stearate	Magnesium Stearate S	4.29	4.29
Subtotal					
Coating Solution		Polyvinyl alcohol	Gohsenol EG-05P	8.00	8.00
		Sucrose fatty acid ester	Surfhope SE J-1803F	8.00	8.00
		Titanium oxide	Tipaque A-100	3.60	3.60
		Polysorbate 80	Polysorbate 80 (GS)	0.40	0.40
		Purified water	---	(volatile component)	(volatile component)
Subtotal					20.00
					306.00

[0040] [Example 3]

Tablets were produced according to the procedure described below.

1. Sized granules of bulk drug (Granules)

126.83 mg (weight per tablet, to apply similarly hereinafter) of active ingredient (dabigatran etexilate methanesulfonate), 18.26 mg of fumaric acid (Japanese Food Additive Standards, Kawasaki Kasei Chemicals Ltd.), 75.13 mg of D-mannitol (fine powder) (Japanese Pharmacopoeia, Mannit P, Mitsubishi Shoji Foodtech Co., Ltd.), 5.72 mg of hydroxypropyl cellulose (Japanese Pharmacopoeia, NISSO HPC-L fine, Nippon Soda Co., Ltd.), and 2.86 mg of magnesium stearate (Japanese Pharmacopoeia, Magnesium Stearate S, NOF Corp.) were mixed (using a container rotary mixer or a stirring mixer, Vertical Granulator FM-VG100, Powrex Corp.), granulated by a dry granulator (WP-160X60, Freund Turbo Corp.), and then roughly crushed and granulated by a granulator (New Speed Mill ND-50SD, Okada Seiko Co., Ltd.) to obtain granules.

2. Tablets

228.8 mg of the granules produced in 1 above were mixed (using Volley Container Mixer, Matsubo Corp.) with 38.61 mg of D-mannitol (fine powder) (Japanese Pharmacopoeia, Mannit P, Mitsubishi Shoji Foodtech Co., Ltd.), 14.30 mg of crospovidone Type A (Japanese Pharmacopoeia, Kollidon CL, BASF Corp.), and 4.29 mg of magnesium stearate (Japanese Pharmacopoeia, Magnesium Stearate S, NOF Corp.), and compressed into tablets (using HT-CVX-MS-II, Hata Tekkosho Co, Ltd.) to obtain tablets.

3. Film Coating

An aqueous solution of polyvinyl alcohol (partially saponified) (Japanese Pharmaceutical Excipients, Gohsenol EG-05P, Nippon Synthetic Chemical Industry Co., Ltd.) was prepared and mixed with a dispersion of sucrose fatty acid ester (Japanese Pharmaceutical Excipients, Surfhope SE J-1803F, Mitsubishi Chemical Foods Corp.), titanium oxide (Japanese Pharmacopoeia, Tipaque A-100, Ishihara Sangyo Kaisha, Ltd.), and Polysorbate 80 (Japanese Pharmacopoeia, Polysorbate 80 (GS), NOF Corp.) in water, and the mixture was passed through a sieve to prepare a coating solution. The tablets produced in 2 above were coated (using HCFS-130N, Freund Corp.) with this coating solution to obtain the tablets of Example 3.

[0041] [Comparative Example]

The tablets that did not contain organic acid of Comparative Example were produced using the formulation shown in Table 2, according to the production methods of the sized granules of bulk drug in Example 3 and the tablets described in Example 3.

[0042] [Examples 4 to 6]

The tablets of Examples 4 to 6 were produced using the formulation shown in Table 2 and according to the production methods described in Examples 1 to 3.

The tablets of Example 4 were produced according to the production methods of the sized granules of bulk drug in Example 3 and the tablets described in Example 3.

The tablets of Example 5 were film-coated tablets obtained by coating the tablets of Example 4 with the the formulation shown in Table 2.

The tablets of Example 6 were film-coated tablets produced according to the production methods in Examples 1 and 2 and coated with the formulation shown in Table 2. Specifically, sized granules of the bulk drugs and sized granules of the acids were respectively prepared and molded into tablets, and then the tablets were coated with the film. The formulation of the coating solution comprised 6.72 mg of hypromellose (Japanese Pharmacopoeia, TC-5R, Shin-Etsu Chemical Co., Ltd.), 1.96 mg of Macrogol 6000 (Japanese Pharmacopoeia, Macrogol 6000P, NOF Corp.), 2.52 mg of titanium oxide (Japanese Pharmacopoeia, Tipaque A-100, Ishihara Sangyo Kaisha, Ltd.), and 2.80 mg of talc (Japanese Pharmacopoeia, Talkum, Guangxi Longguang Talc Dev. Co., Ltd.).

[0043] [Table 2]

Intermediate product		Components	Comparative Example amount (mg)	Example 4 amount (mg)	Example 5 amount (mg)	Example 6 amount (mg)
Tablet Molded Products	Sized granules of bulk drug	Active ingredient	126.83	126.83	126.83	126.83
		Fumaric acid	---	25.00	25.00	---
		D-mannitol (fine powder)	93.39	68.39	68.39	43.00
		Hydroxypropyl cellulose	5.72	5.72	5.72	5.94
		Magnesium stearate	2.86	2.86	2.86	2.97
	Sized granules of acid	Fumaric acid	---	---	---	25.00
		D-mannitol (fine powder)	---	---	---	71.03
		Hydroxypropyl cellulose	---	---	---	2.97
		Purified water	---	---	---	(volatile component)
		D-mannitol (fine powder)	38.61	38.61	38.61	---
		Crospovidone Type A	14.30	14.30	14.30	14.85
		Magnesium stearate	4.29	4.29	4.29	4.46
Coating Solution		Polyvinyl alcohol	---	---	6.30	---
		Sucrose fatty acid ester	---	---	6.72	---
		Titanium oxide	---	---	0.70	2.52
		Polysorbate 80	---	---	0.28	---
		Hypromellose	---	---	---	6.72
		Macrogol 6000	---	---	---	1.96
		Talc	---	---	---	2.80
		Purified water	---	---	(volatile component)	(volatile component)

[0044] [Experimental Example 1]

A test for variation due to mixing was carried out by mixing the active ingredient (dabigatran etexilate methanesulfonate) with each of the organic acids at a 1:1 ratio. The mixtures were stored for 6 weeks under condition at 40°C and relative humidity of 75%, and then the decomposition percentages of the active ingredient were evaluated based on a value of 100 for the initial amount of the active ingredient. The results are shown in Table 3.

From the results, it was found that the active ingredient was considerably decomposed by mixing with the organic acid and exposing to the high humidity condition. It is already known that hydrolysates are formed by such decomposition.

[0045] [Table 3]

Organic Acid	Tartaric acid	Citric acid	Fumaric acid	Succinic acid	Maleic acid
Percentage of decomposition of active ingredient (wt%)	65.5	36.0	10.1	23.9	52.9

[0046] [Experimental Example 2]

A hydrolysate and Decomposition Product A (which is a mesylate and differs from the hydrolysate) under condition at 40°C and relative humidity of 75% were evaluated for the tablets of Comparative Example and Examples 4 to 6. The results are shown in Table 4.

[0047] [Table 4]

		Before Storage	After 6 Months
Comparative Example	Hydrolysate (wt%)	0.18	0.61
	Decomposition Product A (ppm)	0.86	3.14
Example 4	Hydrolysate (wt%)	0.19	0.90
	Decomposition Product A (ppm)	0.40	0.36
Example 5	Hydrolysate (wt%)	0.22	0.80 (after 3 months)
	Decomposition Product A (ppm)	0.36	0.00 (after 3 months)
Example 6	Hydrolysate (wt%)	0.18	0.67
	Decomposition Product A (ppm)	0.48	0.71

[0048] From the results of Experimental Example 2, it is found that, in the tablets obtained according to the present invention, the formation of decomposition products of dabigatran etexilate or the pharmaceutically acceptable salt thereof was effectively inhibited and the formation of the hydrolysates thereof was effectively inhibited to the same degree as tablets that did not contain organic acid (Comparative Example) even under high humidity conditions, despite dabigatran etexilate or the pharmaceutically acceptable salt thereof and the organic acid being present in close proximity.

CLAIMS

1. A method of producing a tablet comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof, and an excipient, comprising the step of:
making dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof be present in substantially close proximity.

2. The method according to claim 1, wherein said step comprises the steps of:
(1) preparing granules comprising dabigatran etexilate or the pharmaceutically acceptable salt thereof and the excipient by dry granulation, and
(2) preparing granules comprising the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof.

3. The method according to claim 1, wherein said step comprises the step of mixing dabigatran etexilate or the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof, and the excipient, and dry-granulating the mixture.

4. The method according to any one of claims 1 to 3, wherein dabigatran etexilate or the pharmaceutically acceptable salt thereof is dabigatran etexilate methanesulfonate.

5. The method according to any one of claims 1 to 4, wherein the pharmaceutically acceptable organic acid is an organic acid having solubility higher than 0.98 g/250 mL in water at 20°C.

6. The method according to any one of claims 1 to 5, wherein the pharmaceutically acceptable organic acid is at least one selected from the group consisting of fumaric acid, glutamic acid, aspartic acid, succinic acid, and tartaric acid.

7. The method according to claim 6, wherein the pharmaceutically acceptable organic acid is fumaric acid.

8. The method according to any one of claims 1 to 7, wherein the excipient is an excipient having low hygroscopicity.

9. The method according to claim 8, wherein the excipient having low hygroscopicity is D-mannitol and/or erythritol.

10. The method according to any one of claims 1 to 9, wherein the method further comprises the step of coating the surface of the tablet in which dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof are present in substantially close proximity, with a water-swellable polymer.

11. The method according to claim 10, wherein the water-swellable polymer is polyvinyl alcohol.

12. The method according to any one of claims 1 to 11, wherein the tablet comprises 15% by weight to 65% by weight of dabigatran etexilate or the pharmaceutically acceptable salt thereof when converted by calculation into dabigatran etexilate methanesulfonate, and 1% by weight to 20% by weight of the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof.

13. A method of producing a tablet in which dabigatran etexilate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof are present in substantially close proximity, comprising the steps of:
(1) mixing dabigatran etexilate methanesulfonate with D-mannitol, a binder, and a lubricant, and dry-granulating the mixture to prepare granules;
(2) mixing fumaric acid with D-mannitol and a binder, and granulating the mixture to prepare granules; and
(3) mixing the granules of step (1) and the granules of (2), and compressing the mixture into the tablet to prepare the tablet.

14. A method of producing a tablet in which dabigatran etexilate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof are present in substantially close proximity, comprising the step of
mixing dabigatran etexilate methanesulfonate, fumaric acid, D-mannitol, and a binder, and dry-granulating the mixture.

15. A tablet obtained by the method according to any one of claims 1 to 14.

16. A tablet comprising, as separate granules:
(1) dry-granulated granules comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof and an excipient, and
(2) granules comprising a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof,
wherein dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof are present in substantially close proximity.

17. A tablet comprising dry-granulated granules of a mixture of dabigatran etexilate or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable organic acid or a hydrate or acidic salt thereof, and an excipient,
wherein dabigatran etexilate or the pharmaceutically acceptable salt thereof and the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof are present in substantially close proximity.

18. The tablet according to claim 16 or 17, wherein dabigatran etexilate or the pharmaceutically acceptable salt thereof is dabigatran etexilate methanesulfonate.

19. The tablet according to any one of claims 16 to 18, wherein the pharmaceutically acceptable organic acid is an organic acid having solubility higher than 0.98 g/250 mL in water at 20°C.

20. The tablet according to any one of claims 16 to 19, wherein the pharmaceutically acceptable organic acid is at least one selected from the group consisting of fumaric acid, glutamic acid, aspartic acid, succinic acid, and tartaric acid.

21. The tablet according to claim 20, wherein the pharmaceutically acceptable organic acid is fumaric acid.

22. The tablet according to any one of claims 16 to 21, wherein the excipient is an excipient having low hygroscopicity.

23. The tablet according to claim 22, wherein the excipient having low hygroscopicity is D-mannitol and/or erythritol.

24. The tablet according to any one of claims 16 to 23, wherein the surface of the tablet is coated with a water-swellable polymer.

25. The tablet according to claim 24, wherein the water-swellable polymer is polyvinyl alcohol.

26. The tablet according to any one of claims 16 to 25, wherein the tablet comprises 15% by weight to 65% by weight of dabigatran etexilate or the pharmaceutically acceptable salt thereof when converted by calculation into dabigatran etexilate methanesulfonate, and 1% by weight to 20% by weight of the pharmaceutically acceptable organic acid or the hydrate or acidic salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/060731

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/28 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, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP 1 658 056 A1 (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]) 24 May 2006 (2006-05-24)	1,3-12, 14,15, 17-26
Y	the whole document	13
X	US 2015/157618 A1 (KANDI CHANDRASHEKHAR [IN] ET AL) 11 June 2015 (2015-06-11) paragraphs [0011], [0014], [0015], [0069], [0070]; examples 2,5B, 5C	1,15
X	CN 105 919 962 A (CHONGQING LIANGJIANG MEDICINE RES AND DEV CENTER CO LTD) 7 September 2016 (2016-09-07)	1,2,15, 16
Y	claim 10; examples 1-7	13

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

☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 2018	20/06/2018

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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