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(54) **Title**: AN ORALLY DISINTEGRATING TABLET

(57) **Abstract**: The present invention relates to an orally disintegrating tablet comprising cilostazol, mannitol, saccharide other than mannitol, inorganic substance, and disintegrating agent, as well as organic excipient and glidant, which is possible to be taken with easy handling for many patients to whom cilostazol tablets are applied, especially aged patients and patients suffering from dysphagia.

DESCRIPTION

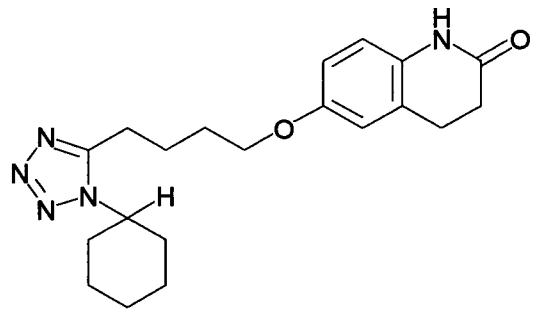
AN ORALLY DISINTEGRATING TABLET

TECHNICAL FIELD

[0001] The present invention relates to an oral tablet comprising cilostazol which can be disintegrated in oral cavity.

BACKGROUND ART

[0002] Cilostazol is 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril as shown in the following formula (1), which exhibits high inhibitory action for platelet aggregation as well as inhibitory action for phosphodiesterase, antiulcer activity, hypotensive action, antiphlogistic action, etc. and thereby is widely used in clinical use as a drug for treating various ischemic symptoms caused by chronic arterial occlusion. And, cilostazol has been additionally approved as a medicament having an indication which prevents the relapse after treatment of cerebral infarction (except cardiogenic cerebral infarction) (JP-A-56(1981)-49378). The cilostazol tablets which are called Pletaal tablet 50®, Pletaal tablet 100®, Pletaal powder 20 % (OTSUKA PHARMACEUTICAL CO., LTD.) have already been on sale.



(1)

[0003] Amongst the patients using cilostazol, elderly people occupy a major share because of the character of the applied disease. In general, it is thought that the function of feeding/swallowing is dropping down with age. In addition, it is known that some patients of cerebral infarction which has been approved as a new applied disease of cilostazol since 2003 have a mild to moderate dysphagia as an aftereffect of cerebral infarction. When administering a drug to such patients, in case of mild to moderate disorder (aspiration of water, occasional aspiration), actually the drug is orally given with some ideas, for example, given together with jelly, pudding, or rice porridge, etc., or administered using thick liquid instead of water. It is known that patients suffering from aspiration of water or occasional aspiration can swallow salivary though it is difficult for the patients to drink water.

[0004] The present inventors had extensively studied a variety of formulations of cilostazol preparations which are possible to be taken without water previously, and have

found that a powder formulation thereof wherein mannitol is formulated could be an orally disintegrable formulation (WO 2007/001086).

[0005] However, a powder formulation or a particle formulation has some problems such as a difficult handling at the administration and an adhesion in oral cavity, and thus such formulation does not always satisfy elderly patients or patient suffering from swallowing disorder. In order to solve such problems, it has been desired to develop an orally disintegrating tablet of cilostazol which is possible to be taken without water and easily at any time.

[0006] JP-B-3841804, WO 2005/037254, and WO 2005/037319 disclose compositions comprising saccharide(s), disintegrating agent(s) and inorganic excipient(s) in a certain proportion, which are suitable for the manufacture of orally disintegrable tablets. In addition, WO 2007/029376 discloses that such compositions can be improved by further adding lubricant(s), disintegrating agent(s), and binder(s) to prepare more useful orally-disintegrable tablets. However, it was only limited compounds to be used as an active ingredient at the evaluation of these disclosed orally disintegrable tablets. In addition, each excipient contained in vehicle compositions of these orally disintegrable tablets had a

widely broad range of choices and further the contents thereof were defined only by means of a certain range. It was unclear if a useful orally-disintegrable tablet of cilostazol could be prepared using the disclosed compositions, or if it was possible to select excipients suitable for an orally-disintegrable tablet of cilostazol from a widely broad range of excipients. Therefore, it was necessary for a skilled person to do extremely many experiments to find a useful orally-disintegrable tablet of cilostazol, and thus it was not thought that it was so easy to find a composition suitable for such tablet from the broad range. In particular, it was thought to be more difficult to prepare such tablet of cilostazol compared with the actual examples disclosed in these references, because (a) cilostazol is insoluble in water, (b) it is necessary to produce a tablet having high dose or a big tablet since the single dosage unit of cilostazol is high, and (c) it has a sandy feeling or a bad feeling in oral cavity when administered because of its hard-disintegrability.

DISCLOSURE OF INVENTION

[0007] As mentioned above, it has been desired to develop an orally disintegrating tablet of cilostazol which is possible to be taken with easy handling without water

and rapidly disintegrated in oral cavity; and especially is easy to handle for many patients to whom cilostazol tablets are applied, especially aged patients and patients suffering from dysphagia.

[0008] The present inventors have extensively studied in order to solve the above-mentioned problems, and have found that it is possible to prepare a useful orally-disintegrating tablet of cilostazol using the composition described in WO 2007/029376; and furthermore a specifically limited range selected from the range of the excipients and the content proportions thereof described in 2007/029376 makes it possible to prepare an orally disintegrating tablet of cilostazol having more useful advantages about the disintegrability in oral cavity, formulating property and manufacturing process. Based upon the new findings, the present invention has been completed.

[0009] The present invention relates to the following inventions.

[0010] The present invention provides an orally disintegrating tablet comprising cilostazol and granulated particles which are prepared by uniformly dispersing an inorganic substance and a disintegrating agent into complex particles comprising two or more kinds of saccharides, which exhibits a good disintegrability in the oral cavity and a pleasant feeling in a mouth when administered and

also has a sufficient hardness.

[0011] And, the present invention provides an orally disintegrating tablet comprising cilostazol, granulated particles which are prepared by uniformly dispersing an inorganic substance and a disintegrating agent into complex particles comprising two or more kinds of saccharides, and a glidant. Additionally, the present invention provides the orally disintegrating tablet which further comprises an organic excipient.

[0012] In addition, the present invention provides an orally disintegrating tablet comprising cilostazol, granulated particles which are prepared by uniformly dispersing an inorganic substance and a disintegrating agent into complex particles comprising two or more kinds of saccharides, a glidant, and an organic excipient, which may further optionally comprise one or more kinds of additives selected from the group consisting of lubricants, sweeteners, flavoring substances, flavors, binders and colorants.

[0013] Furthermore, the present invention provides an orally disintegrating tablet prepared by

(1) fully mixing a glidant in cilostazol, then

(2) adding to said mixture (i) granulated particles which are prepared by uniformly dispersing an inorganic substance and a disintegrating agent into complex particles

comprising two or more kinds of saccharides, (ii) an organic excipient, (iii) a lubricant, and (iv) a sweetener,

(3) mixing the resulting mixture, and

(4) compression-molding it by an external lubricating compression.

[0014] A preferable composition of the orally disintegrating agent comprises

(1) cilostazol,

(2) a composition which is prepared by uniformly dispersing an inorganic substance and a disintegrating agent into complex particles of saccharides formed with mannitol and xylitol through a spray drying method, wherein (a) the saccharides comprising the combination of mannitol and xylitol are contained in 40 - 90 parts by weight; (b) the inorganic excipient is contained in 1 - 30 parts by weight; (c) the disintegrating agent is contained in 5 - 40 parts by weight, provided that the total amount of ingredients (a), (b) and (c) is contained in 100 parts by weight, and the ratio of mannitol and xylitol by weight is 98 : 2 - 67 : 33, and

(3) at least one ingredients selected from the group consisting (i) one or more kinds of organic excipients selected from the group consisting of starches and celluloses, and (ii) one or more kinds of glidants selected from the group consisting of hydrous silicon dioxide, light

anhydrous silicic acid, and heavy anhydrous silicic acid. More preferably in the above composition, as organic excipients, the starches are one or more kinds of starches selected from the group consisting of corn starch, rice starch, potato starch, partial pregelatinized starch, and hydroxypropyl starch; the celluloses are one or more kinds of celluloses selected from the group consisting of crystalline cellulose, and carboxymethylcellulose. Most preferably, the starches are corn starch, and the celluloses are crystalline cellulose.

In addition, more preferable glidant is one or more selected from the group consisting of hydrous silicon dioxide, light anhydrous silicic acid, and heavy anhydrous silicic acid, and the most preferably, hydrous silicon dioxide, and/or light anhydrous silicic acid.

[0015] The present invention provides an orally disintegrating tablet which is possible to be rapidly disintegrated in oral cavity, exhibits a pleasant feeling in a mouth when administered and also has a sufficient hardness, to many patients to whom cilostazol tablets are applied, especially aged patients and patients suffering from dysphagia. The present invention provides an orally disintegrating tablet of cilostazol, which is possible to be rapidly disintegrated in oral cavity, and exhibits a pleasant feeling in a mouth when administered and also an

identical dissolution property with the commercial cilostazol tablet.

BEST MODE FOR CARRYING OUT THE INVENTION

[0016] The orally disintegrating tablet means a tablet prepared by adding particles which are prepared by uniformly dispersing an inorganic substance and a disintegrating agent into complex particles comprising two or more kinds of saccharides, to cilostazol; especially, an orally disintegrating tablet prepared by adding to cilostazol, (i) particles which are prepared by uniformly dispersing an inorganic substance and a disintegrating agent into complex particles comprising two or more kinds of saccharides, (ii) a glidant and (iii) an organic excipient.

[0017] Cilostazol can be prepared, for example, by the method described in JP-A-56(1981)-49378.

[0018] The "granulated particles which are prepared by uniformly dispersing an inorganic substance and a disintegrating agent into complex particles comprising two or more kinds of saccharides" (hereinafter referred to "granulated particles") used herein can be prepared by dispersing mannitol and a saccharide other than mannitol, a disintegrating agent, an inorganic substance in water and then spray-drying it. For example, it is a composition for

the orally disintegrating tablet which can be prepared by the method described in WO 2005/037254 or WO 2005/037319. The "two or more kinds of saccharides" contained in the granulated particles are a combination of mannitol and a saccharide which is not mannitol. The saccharide means a sugar or a sugar alcohol.

The saccharide other than mannitol includes, for example, one or more selected from the group consisting of xylitol, sorbitol, erythritol, maltitol, lactose, sucrose, glucose, fructose, maltose, trehalose, Palatinit®, Palatinose® and the like. Preferably the saccharide is a combination of mannitol and xylitol. The ratio by weight of mannitol and the saccharide other than mannitol is mannitol : saccharide other than mannitol = 98 : 2 - 67 : 33, preferably 97 : 3 - 87 : 13, and more preferably 96 : 4 - 89 : 11.

[0019] The "inorganic substance" contained in the granulated particles is preferred to be a pharmaceutically acceptable inorganic acid compound comprising any one or more of aluminum, magnesium and calcium. It includes at least one ingredients selected from, for example, magnesium aluminometasilicate, magnesium aluminosilicate, calcium hydrogenphosphate, calcium hydrogenphosphate anhydride, calcium hydrogenphosphate anhydride granule, hydrotalcite, aluminum silicate, calcium phosphate, calcium carbonate, calcium silicate, magnesium silicate, magnesium oxide,

magnesium hydroxide, alumina-magnesium hydroxide, dry aluminum hydroxide gel, magnesium carbonate, etc. It is more preferably at least one selected from magnesium aluminometasilicate, magnesium aluminosilicate, calcium hydrogen phosphate, calcium hydrogenphosphate anhydride, calcium hydrogenphosphate anhydride granule, hydrotalcite, calcium carbonate, calcium silicate, and dry aluminum hydroxide gel. It is still more preferably at least one selected from magnesium aluminometasilicate, hydrotalcite, calcium hydrogen phosphate anhydride and calcium carbonate. The mean particle size of the inorganic substance is 0.1 - 100 μm, preferably 1 - 60 μm, and more preferably 1 - 40 μm. It is possible to use an inorganic substance milled by a conventional method in order to obtain the desired mean particle size.

[0020] The "disintegrating agent" contained in the granulated particles is preferably at least one ingredients selected from crospovidone, croscarmellose sodium, low-substituted hydroxypropyl cellulose, and crystalline cellulose and, although any of them may be used as a single, it is preferred to use as a mixture of two or more thereof. Amongst them, it is more preferred to use crospovidone and crystalline cellulose. When using crospovidone and crystalline cellulose, the ratio by weight of crospovidone and crystalline cellulose is 5 : 8 - 15 : 22, preferably

5 : 10 - 14 : 22, and more preferably 6 : 12 - 13 : 21. The above disintegrating agent preferably has a mean particle size of 0.1 - 100 μm, more preferably 1 - 60 μm, and even more preferably 1 - 40 μm, in order to make a uniform dispersibility in the present composition and prevent a sandy feeling in oral cavity. The desired mean particle size can be obtained by using a disintegrating agent micronized via a conventional method.

[0021] With regard to the amount of each ingredient contained in the granulated particles, per 100 parts (total amount) by weight of the granulated particles, the saccharides are contained in 40 - 90 parts by weight, the inorganic substance is contained in 1 - 30 parts by weight, the disintegrating agent is contained in 5 - 40 parts by weight, and preferably the saccharides are contained in 50 - 80 parts by weight, the inorganic substance is contained in 2 - 15 parts by weight, the disintegrating agent is contained in 10 - 36 parts by weight. More preferably, per 100 parts (total amount) by weight of the granulated particles, the saccharides are contained in 62 - 78 parts by weight, the inorganic substance is contained in 3 - 8 parts by weight, the disintegrating agent is contained in 18 - 34 parts by weight. The granulated particles can be prepared by a conventional method such as spray-drying method, fluid-bed granulation, agitation granulation and

wet granulation (e.g. wet extrusion granulation), and also by the method described in WO 2007/029376. Such granulated particles are available, for example, as a commercially available F-MELT® (FUJI CHEMICAL INDUSTRY CO.,LTD.).

[0022] The blending quantity of the granulated particles is generally about 10 - 60 % (w/w), preferably about 20 - 40 % (w/w) per 100 % (w/w) of the orally disintegrating tablet.

[0023] The "glidant" used herein includes hydrous silicon dioxide, light anhydrous silicic acid, heavy anhydrous silicic acid and the like; preferably, light anhydrous silicic acid, or hydrous silicon dioxide; and more preferably light anhydrous silicic acid. The glidant may comprise one or more of the above ingredients. The blending quantity of the glidant is about 0.2 - 2 (w/w), preferably about 0.5 - 1.5 % (w/w) per 100 % (w/w) of the orally disintegrating tablet.

[0024] The "organic excipient" blended in the present solid formulation includes, for example, celluloses and starches. The celluloses include, for example, crystalline cellulose, carboxymethylcellulose, ethylcellulose, carboxymethylethyl cellulose, carmellose sodium, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and the like. Preferably, it is crystalline cellulose or

carboxymethylcellulose, and more preferably crystalline cellulose. The starches include corn starch, rice starch, potato starch, flour starch, partial pregelatinized starch, hydroxypropyl starch, and the like. Preferably, it is corn starch, rice starch, potato starch, partial pregelatinized starch, or hydroxypropyl starch, and more preferably corn starch. The organic excipient may comprise one or more of the above ingredients. Preferably, crystalline cellulose and corn starch are used. The blending quantity of the organic excipient is about 5 - 60 % (w/w), preferably about 10 - 30 % (w/w) per 100 % (w/w) of the orally disintegrating tablet.

[0025] The present invention can include a variety of additives which are generally used in the preparation of tablets as long as the additives do not negatively affect its disintegrability and formability. The additives include, for example, lubricants, sweeteners, flavoring substances, flavors, binders, and colorants.

[0026] The lubricant includes, for example, stearic acid, metal stearate (e.g. magnesium stearate, and calcium stearate), stearyl fumarate sodium, talc, colloidal silica, sucrose fatty acid ester, hydrogenated oil, and polyethylene glycol. Amongst them, stearic acid and metal stearate are preferable, and magnesium stearate is more preferable. The blending quantity of the lubricant is

generally about 0.01 - 1 % (w/w), preferably 0.1 - 0.6 % (w/w) per 100 % (w/w) of the orally disintegrating tablet.

[0027] The sweetener includes, for example, acesulfame potassium, aspartame, saccharin or a salt thereof, glycyrrhizinic acid or a salt thereof, stevia or a salt thereof, sucralose, and thaumatin.

[0028] The flavoring substance includes, for example, ascorbic acid or a salt thereof, glycine, sodium chloride, magnesium chloride, hydrochloric acid, diluted hydrochloric acid, citric acid or a salt thereof, anhydrous citric acid, L-glutamic acid or a salt thereof, succinic acid or a salt thereof, acetic acid, tartaric acid or a salt thereof, sodium hydrogen carbonate, fumaric acid or a salt thereof, malic acid or a salt thereof, glacial acetic acid, disodium inosinate, and honey.

[0029] The flavor includes a favoring agent, for example, orange essence , orange oil, caramel, camphor, cinnamon oil, spearmint oil, strawberry essence, chocolate essence, cherry flavor, spruce oil, pine oil, mint oil, vanilla flavor, bitter essence, fruit flavor, peppermint essence, mixed flavor, mint flavor, menthol, lemon powder, lemon oil, and rose oil.

[0030] The binder includes, for example, gum arabic, powdered acacia, gelatin, agar, dextrin, pullulan, povidone, and polyvinyl alcohol.

[0031] The colorant includes, for example, food colorant such as food dye Red No. 3, food dye Yellow No. 5, and food dye blue No. 1; yellow ferric oxide, red ferric oxide, brown iron oxide, black iron oxide, copper chlorophyll, sodium copper chlorophyllin, riboflavin, powdered green tea.

[0032] These additive ingredients can be generally used in any amount, and as a single or a mixture. The exemplified process of the present orally disintegrating tablet includes a method comprising (1) weighing cilostazol and the other materials for formulation, (2) mixing the ingredients in a mixer such as a V-blender to prepare a mixed powder for tablet, and (3) directly compressing the powder.

[0033] In order to prepare the mixed powder for tablet, a method of strongly mixing with an agitation granulation machine or a method of mixing and milling with a mill may be used. In addition, a compaction-granulation method with a dry granulator; a wet granulation method with water, acetone, ethyl alcohol, propyl alcohol or a mixture thereof wherein optionally a binder may be dispersed or dissolved; or a method of preparing the mixed powder for tablet via separating it into two or more groups may be used. A lubricant, a sweetener, a flavoring substance, a flavor, binder, a colorant, etc. may be optionally added thereto in preparing the mixed powder for tablet.

[0034] It is preferable to sufficiently mix cilostazol and a glidant firstly, and then to add an organic excipient, granulated particles, a sweetener and a lubricant thereto and sufficiently mix the mixture again.

[0035] The resulting mixed powder for tablet is compressed at a pressure of 200 kg - 600 kg/punch with for example a single tableting machine or a rotary tableting machine. When the pressure is lower than the above-mentioned range, the tablet hardness can be shortened and thus does not arrive at a sufficient hardness to be handled. While, when the pressure is higher than the above-mentioned range, the disintegration of the tablet can be disadvantageously delayed.

[0036] For the compaction-formulation, it is possible to use a conventional tableting method as well as an external lubricating compression. The external lubricating compression enables the amount of a lubricant to be decreased, the disintegration rate to be accelerated, and the tablet hardness to be enhanced.

[0037] With regard to the shape of the orally disintegrating tablet, it is possible to form any shape such as circular form, oval figure, globular shape, rod shape, and doughnut shape, as well as a lamination layer tablet, a dry-coated tablet, etc. In addition, the tablet may be coated by a conventional coating method used in the

field of formulation. Furthermore, it is possible to affix an engraved mark such as a symbol and letters, and a cleavage line on the tablet.

[0038] The orally disintegrating tablet can rapidly disintegrate in oral cavity with saliva, and hence it is possible to take a medicine smoothly. Typically, the hardness which is measured with a tablet hardness tester is 30 N or more. The disintegration time in oral cavity is generally within 90 seconds, preferably within 60 seconds, and more preferably within 40 seconds.

[0039] Any additives defined herein such as inorganic substance, disintegrating agent, saccharide, glidant, organic excipient, starch, cellulose, additive, lubricant, sweetener, flavoring substance, flavor, binder and colorant which are expressed as a single or a plural form may include one kind of ingredient, plural kinds of ingredients and a mixture of plural kinds of ingredients.

EXAMPLE

[0040] Hereinafter, the present invention is explained showing Examples and Reference Examples, but should not be construed to be limited thereto.

[0041] (Example 1)

To 40 parts by weight of cilostazol powder were added 39.2 parts by weight of granulated particles (F-MELT, FUJI

CHEMICAL INDUSTRY CO.,LTD.), 20 parts by weight of carmellose (NS-300, GOTOKU CHEMICAL COMPANY LTD.), 0.2 parts by weight of menthol (Takasago International Corporation), 0.2 parts by weight of aspartame (AJINOMOTO CO.,INC.) and 0.4 parts by weight of magnesium stearate (TAIHEI CHEMICAL INDUSTRIAL CO.,LTD.). After mixing, the mixture was compression-molded with a rotary tableting machine (HT-AP18SSII type, HATA IRON WORKS CO.,LTD., 9 mmφ, a flat punch) to provide 250 mg tablets having a tablet hardness of 50 N.

[0042] (Example 2)

To 40 parts by weight of cilostazol powder were added 39.2 parts by weight of granulated particles (F-MELT, FUJI CHEMICAL INDUSTRY CO.,LTD.), 10 parts by weight of crystalline cellulose (Ceolus PH-101, Asahi Kasei Chemicals Corporation), 10 parts by weight of corn starch (Nisshoku corn starch (XX16)W, Nihon Shokuhin Kako Co., Ltd.), 0.2 parts by weight of menthol (Takasago International Corporation), 0.2 parts by weight of aspartame (AJINOMOTO CO.,INC.) and 0.4 parts by weight of magnesium stearate (TAIHEI CHEMICAL INDUSTRIAL CO.,LTD.). After mixing, the mixture was compression-molded with a rotary tableting machine (HT-AP18SSII type, HATA IRON WORKS CO.,LTD., 9 mmφ, a flat punch) to provide 250 mg tablets having a tablet hardness of 50 N.

[0043] (Example 3)

To 40 parts by weight of cilostazol powder were added 39.2 parts by weight of granulated particles (F-MELT, FUJI CHEMICAL INDUSTRY CO.,LTD.), 20 parts by weight of rice starch (Micropearl, Shimada Chemical Company), 0.2 parts by weight of menthol (Takasago International Corporation), 0.2 parts by weight of aspartame (AJINOMOTO CO.,INC.) and 0.4 parts by weight of magnesium stearate (TAIHEI CHEMICAL INDUSTRIAL CO.,LTD.). After mixing, the mixture was compression-molded with a rotary tableting machine (HT-AP18SSII type, HATA IRON WORKS CO.,LTD., 9 mmφ, a flat punch) to provide 250 mg tablets having a tablet hardness of 50 N.

[0044] (Example 4)

40 parts by weight of cilostazol powder and 0.5 parts by weight of hydrous silicon dioxide (Adsolider-102, Freund Corporation) were mixed. And then, 33.7 parts by weight of granulated particles (F-MELT, FUJI CHEMICAL INDUSTRY CO.,LTD.), 15 parts by weight of crystalline cellulose (Ceolus PH-101, Asahi Kasei Chemicals Corporation), 10 parts by weight of corn starch (Nisshoku corn starch (XX16)W, Nihon Shokuhin Kako Co., Ltd.), 0.2 parts by weight of menthol (Takasago International Corporation), 0.2 parts by weight of aspartame (AJINOMOTO CO.,INC.) and 0.4 parts by weight of magnesium stearate (TAIHEI CHEMICAL

INDUSTRIAL CO.,LTD.) were added thereto, and mixed. The resulting mixture was compression-molded with a rotary tableting machine (HT-AP18SSII type, HATA IRON WORKS CO.,LTD., 9 mmφ, a flat punch) to provide 250 mg tablets having a tablet hardness of 50 N.

[0045] (Example 5)

40 parts by weight of cilostazol powder and 0.5 parts by weight of light anhydrous silicic acid (Adsolider-101, Freund Corporation) were mixed. And then, 33.7 parts by weight of granulated particles (F-MELT, FUJI CHEMICAL INDUSTRY CO.,LTD.), 15 parts by weight of crystalline cellulose (Ceolus PH-101, Asahi Kasei Chemicals Corporation), 10 parts by weight of corn starch (Nisshoku corn starch (XX16)W, Nihon Shokuhin Kako Co., Ltd.), 0.2 parts by weight of menthol (Takasago International Corporation), 0.2 parts by weight of aspartame (AJINOMOTO CO.,INC.) and 0.4 parts by weight of magnesium stearate (TAIHEI CHEMICAL INDUSTRIAL CO.,LTD.) were added thereto, and mixed. The resulting mixture was compression-molded with a rotary tableting machine (HT-AP18SSII type, HATA IRON WORKS CO.,LTD., 9 mmφ, a flat punch) to provide 250 mg tablets having a tablet hardness of 50 N.

[0046] (Example 6)

40 parts by weight of cilostazol powder and 0.5 parts by weight of light anhydrous silicic acid (AEROSIL 380,

NIPPON AEROSIL CO., LTD.) were mixed. And then, 33.7 parts by weight of granulated particles (F-MELT, FUJI CHEMICAL INDUSTRY CO.,LTD.), 15 parts by weight of crystalline cellulose (Ceolus PH-101, Asahi Kasei Chemicals Corporation), 10 parts by weight of corn starch (Nisshoku corn starch (XX16)W, Nihon Shokuhin Kako Co., Ltd.), 0.2 parts by weight of menthol (Takasago International Corporation), 0.2 parts by weight of aspartame (AJINOMOTO CO.,INC.) and 0.4 parts by weight of magnesium stearate (TAIHEI CHEMICAL INDUSTRIAL CO.,LTD.) were added thereto, and mixed. The resulting mixture was compression-molded with a rotary tableting machine (HT-AP18SSII type, HATA IRON WORKS CO.,LTD., 9 mmφ, a flat punch) to provide 250 mg tablets having a tablet hardness of 50 N.

[0047] (Example 7)

40 parts by weight of cilostazol powder and 0.5 parts by weight of hydrous silicon dioxide (Adsolider-102, Freund Corporation) were mixed. And then, 33.7 parts by weight of granulated particles (F-MELT, FUJI CHEMICAL INDUSTRY CO.,LTD.), 10 parts by weight of crystalline cellulose (Ceolus PH-101, Asahi Kasei Chemicals Corporation), 15 parts by weight of corn starch (Nisshoku corn starch (XX16)W, Nihon Shokuhin Kako Co., Ltd.), 0.2 parts by weight of menthol (Takasago International Corporation), 0.2 parts by weight of aspartame (AJINOMOTO CO.,INC.) and 0.4

parts by weight of magnesium stearate (TAIHEI CHEMICAL INDUSTRIAL CO.,LTD.) were added thereto, and mixed. The resulting mixture was compression-molded with a rotary tableting machine (HT-AP18SSII type, HATA IRON WORKS CO.,LTD., 9 mmφ, a flat punch) to provide 250 mg tablets having a tablet hardness of 50 N.

[0048] (Reference Example 1)

192 g of erythritol (Nikken Chemicals Co., Ltd) and 100 g of corn starch (Nisshoku corn starch (XX16)W, Nihon Shokuhin Kako Co., Ltd.), 8 g of hydroxypropyl cellulose (HPC-L, NIPPON SODA CO., LTD.) and 100 g of cilostazol powder were introduced into a granulation drying machine for fluidizing (Multiplex MP-1 model, POWREX CORPORATION), and sprayed with purified water as a binding liquid to be granulated. And the granules were directly dried to provide Granule A. 40 g of PVP-XL (ISP company) as a disintegrating agent and 2 g of magnesium stearate as a lubricant were added thereto per 400 g of Granule A. The mixture was compression-molded with a continuous tableting machine (812HUK, Kikusui Seisakusho Ltd.) to provide tablets containing 100 mg of cilostazol (the weight of a tablet is 442 mg and a diameter of 12 mm).

[0049] (Reference Example 2)

94 g of corn starch (Nisshoku corn starch (XX16)W, Nihon Shokuhin Kako Co., Ltd.), 6 g of hydroxypropyl

cellulose (HPC-L, NIPPON SODA CO., LTD.) and 100 g of cilostazol powder were introduced into a granulation drying machine for fluidizing (Multiplex MP-1 model, POWREX CORPORATION), and sprayed with purified water as a binding liquid to be granulated. And the granules were directly dried to provide Granule B. Magnesium stearate as a lubricant was added thereto in a ratio of 0.5 % (w/w) of Granule B. The mixture was compression-molded with a continuous tableting machine (812HUK, Kikusui Seisakusho Ltd.) to provide tablets containing 100 mg of cilostazol (the weight of a tablet is 201 mg and a diameter of 9 mm).

[0050] (Test 1)

100 mg cilostazol tablets of Examples 1 to 7 and Reference Examples 1 and 2 were put in oral cavity and disintegrated on a tongue. The time required for each tablet to be completely disintegrated was measured as an oral disintegration time and compared each other. And the pharmacopoeia disintegration time and the hardness of Examples 1 to 7 were also measured. The hardness was measured with a Monsanto hardness tester (Kayagaki Irika Kougyo), and the pharmacopoeia disintegration time was measured as time (sec.) required for each tablet to be completely disintegrated, according to the disintegration test in the Japanese pharmacopoeia 15th edition. The disintegration test was carried out with water as a test

solution and without a disk.

[Table 1]

	Oral disintegration time (sec)	Pharmacopoeia disintegration time (sec)	Hardness (N)
Example 1	49	35	55
Example 2	28	24	59
Example 3	-	34	58
Example 4	17	21	51
Example 5	28	23	63
Example 6	20	18	57
Example 7	20	26	55
Reference Example 1	>60		
Reference Example 2	>180		

[0051] As shown in Table 1, the oral disintegration time using the orally disintegrating tablets of Examples 1 to 7 of the present invention was drastically shortened, compared with those of the tablets of Reference Examples 1 and 2.

In each process in Examples 1 to 7, especially, the pre-tableted compositions in Examples 4 to 7 which comprise a glidant had a better fluidity than those of Examples 1 to 3 and could be easily compression-molded. In addition, for the tablets of Examples 4 and 7, the feeling test in oral cavity when administered was done. The feeling in oral cavity when administered was good in both the tablets, but the feeling of Example 7 was better than that of Example 4.

[0052] (Example 8)

40 parts by weight of cilostazol powder and 1.2 parts by weight of light anhydrous silicic acid (Adsolider-101, Freund Corporation) were mixed stirring in a high speed vertical granulator (VG-10, POWREX CORPORATION, main paddle: 400 rpm, granulating paddle: 1500 rpm) for 15 minutes. To the mixed powder was added 15 parts by weight of corn starch (Nisshoku corn starch (XX16)W, Nihon Shokuhin Kako Co., Ltd.), and the mixture was stirred for 15 minutes under the same condition. To the mixed powder was added 35.12 parts by weight of granulated particles (F-MELT, FUJI CHEMICAL INDUSTRY CO.,LTD.) , and the mixture was stirred for 15 minutes under the same condition. Furthermore, 8 parts by weight of crystalline cellulose (Ceolus KG802, Asahi Kasei Chemicals Corporation) and 0.2 parts by weight of aspartame (AJINOMOTO CO.,INC.) were added thereto, and stirred for 15 minutes under the same condition to provide powder for tablet. And then, using a rotary tableting machine equipped with an external lubricating device (Kikusui Seisakusho Ltd.), tablets which had a weight of 250 mg per a tablet were prepared under the condition that 1.2 mg of magnesium stearate should be adhered on a tablet. The shape of the punch was circular form, the diameter thereof was 9 mm, and the tableting pressure was 400-500 kg.

[0053] (Example 9)

40 parts by weight of cilostazol powder and 1.2 parts by weight of light anhydrous silicic acid (Adsolider-101, Freund Corporation) were mixed stirring in a high speed vertical granulator (FM-VG-120P, POWREX CORPORATION, main paddle: 240 rpm, granulating paddle: 1500 rpm) for 15 minutes. To the mixed powder was added 15 parts by weight of corn starch (Nisshoku corn starch (XX16)W, Nihon Shokuhin Kako Co., Ltd.) and 8 parts by weight of crystalline cellulose (Ceolus KG802, Asahi Kasei Chemicals Corporation) as organic excipients, and 0.2 parts by weight of aspartame (AJINOMOTO CO.,INC.) as other additive, and the mixture was stirred for 15 minutes under the same condition. To the mixed powder was added 35.12 parts by weight of granulated particles (F-MELT, FUJI CHEMICAL INDUSTRY CO.,LTD.), and the mixture was mixed in a drum type mixer (Ishitobi Manufacture, 12 rpm) for 10 minutes. 0.16 parts by weight of magnesium stearate (TAIHEI CHEMICAL INDUSTRIAL CO.,LTD.) was added to the mixed powder, and stirred for 10 minutes under the same condition to provide powder for tablet. And then, using a rotary tableting machine equipped with an external lubricating device (Kikusui Seisakusho Ltd.), tablets which had a weight of 250 mg per a tablet were prepared under the condition that 0.8 mg of magnesium stearate should be adhered on a tablet. The shape of the punch was circular form, the diameter

thereof was 9 mm, and the tableting pressure was 400-500 kg.

[0054] (Test 2)

The tablets prepared in Examples 8 and 9 were tested about some formulation properties, and the results were shown in Table 2. The hardness was measured with a tablet hardness tester (Schleuniger), and the pharmacopoeia disintegration time was measured as time (sec.) required for each tablet to be completely disintegrated, according to the disintegration test in the Japanese pharmacopoeia 15th edition. The disintegration test was carried out with water as a test solution and without a disk. The test was carried out with 6 tablets, the report was shown as an average thereof.

In addition, the tablets were orally administered to 6 healthy male adults, and the time required for each tablet to be completely disintegrated in oral cavity only with saliva was measured. The results were shown below as an average thereof.

[Table 2]

	Example 8	Example 9
Hardness (N)	53	53
Pharmacopoeia disintegration time (sec)	22	22
Oral disintegration time (sec)	29	24

[0055] (Test 3)

Using the tablets of Examples 7 and 9 and the

commercially available tablets containing 100 mg of cilostazol, the dissolution tests thereof were carried out, and the results thereof were shown in Table 3.

The dissolution test was done according to the dissolution test in the Japanese pharmacopoeia 15th edition, wherein the test solution was 900 ml of aqueous sodium lauryl sulfate (3 g in 1000 mL), the method was paddle method, and the spinning rate was 50 rpm. The content of each sample was assayed by an ultraviolet-visible spectrophotometry (257 nm).

The tests were done with 3 tablets of Example 7, 6 tablets of Example 9 and 6 of the commercially available tablets containing 100 mg of cilostazol. The results were shown below as an average thereof.

[Table 3]

Dissolution test

	Released cilostazol (%)		
Time (min)	Example 7	Example 9	100 mg cilostazol tablet
0	0	0	0
10	39	43	44
20	54	61	62
30	62	70	70
45	70	78	78
60	75	82	82

The orally disintegrating tablet prepared according to the composition and the process shown in Example 9 had an equivalent dissolution profile with the commercially available tablets containing 100 mg of cilostazol.

CLAIMS

1. An orally disintegrating tablet comprising cilostazol and granulated particles which are prepared by uniformly dispersing an inorganic substance and a disintegrating agent into complex particles comprising two or more kinds of saccharides.

2. The orally disintegrating tablet of claim 1 further comprising a glidant.

3. The orally disintegrating tablet of claim 2 wherein the amount of the glidant is 0.2 - 2 % (w/w).

4. The orally disintegrating tablet of claim 3 wherein the glidant is one or more kinds of glidants selected from the group consisting of hydrous silicon dioxide, light anhydrous silicic acid, and heavy anhydrous silicic acid.

5. The orally disintegrating tablet of claim 4 wherein the glidant is hydrous silicon dioxide and/or light anhydrous silicic acid.

6. The orally disintegrating tablet of any one of claims 1 to 5 which further comprises an organic excipient.

7. The orally disintegrating tablet of claim 6 wherein the organic excipient is one or more kinds of excipients selected from the group consisting of starches and celluloses.

8. The orally disintegrating tablet of claim 7 wherein the starches are one or more kinds of starches selected from the group consisting of corn starch, rice starch, potato starch, partial pregelatinized starch and hydroxypropyl starch.

9. The orally disintegrating tablet of claim 8 wherein the starches are corn starch.

10. The orally disintegrating tablet of claim 7 wherein the celluloses are one or two kinds of celluloses selected from the group consisting of crystalline cellulose and carboxymethylcellulose.

11. The orally disintegrating tablet of claim 10 wherein the celluloses are crystalline cellulose.

12. The orally disintegrating tablet of claim 7 wherein the organic excipient is crystalline cellulose and corn

starch.

13. The orally disintegrating tablet of any one of claims 1 to 12 which may further optionally comprise one or more kinds of additives selected from the group consisting of lubricants, sweeteners, flavoring substances, flavors, binders and colorants.

14. The orally disintegrating tablet of claim 13 wherein the sweetener is aspartame.

15. The orally disintegrating tablet of any one of claims 1 to 14 which is formulated by an external lubricating compression.

16. A method for preparing an orally disintegrating tablet comprising

(a) mixing cilostazol and a glidant,

(b) mixing an organic excipient, granulated particles and other additives in the mixed powder prepared in step (a), and

(c) compression-molding the mixture prepared in step (b).

17. The method of claim 16 wherein the compression-molding

method in step (c) is an external lubricating compression.

18. The orally disintegrating tablet of any one of claims 1 to 15 wherein the saccharides in granulated particles which are prepared by uniformly dispersing an inorganic substance and a disintegrating agent into complex particles comprising two or more kinds of saccharides are a combination of mannitol and one or more kinds of saccharides selected from the group consisting of xylitol, sorbitol, erythritol, maltitol, lactose, sucrose, glucose, fructose, maltose, trehalose, Palatinit® and Palatinose®.

19. The orally disintegrating tablet of claim 18 wherein

(a) the saccharides are contained in 40 - 90 parts by weight, (b) the inorganic substance is contained in 1 - 30 parts by weight, (c) the disintegrating agent is contained in 5 - 40 parts by weight, and the total amount of ingredients (a) , (b) and (c) is 100 parts by weight, and

the saccharides (a) consist of mannitol and saccharide(s) other than mannitol in the ratio by weight of mannitol and the saccharide(s) other than mannitol is 98 : 2 - 67 : 33.

20. The orally disintegrating tablet of claim 19 wherein the saccharides are mannitol and xylitol.