DESCRIPTION

Title of the Invention: ORALLY DISINTEGRATING TABLET

Technical Field

[0001]

The present invention relates to an orally disintegrating tablet comprising a proton pump inhibitor (hereinafter sometimes referred to as PPI) and acetylsalicylic acid ~~(hereinafter sometimes referred to as aspirin)~~. More particularly, the present invention relates to an orally disintegrating tablet superior in the stability of the active ingredient, which expresses a pharmacological effect stably and rapidly after the administration.

[0002]

(Background of the Invention)

Low-dose acetylsalicylic acid~~aspirin~~ administered for the purpose of suppressing formation of thrombus and embolus (antiplatelet therapy) in the diseases of the brain blood vessel and circulatory organ region sometimes causes gastric ulcer or duodenal ulcer. Since discontinuation of acetylsalicylic acid~~aspirin~~ administration may cause formation of thrombus or embolus, it is considered important to continue administration of low-dose acetylsalicylic acid~~aspirin~~ while suppressing the onset of ulcer. Acetylsalicylic acid~~Aspirin~~ is also known as a non-steroidal anti-inflammatory drug (NSAIDs), and mainly used for the treatment of pain, fever and inflammation. However, NSAIDs may cause gastric ulcer or duodenal ulcer. Particularly, in the treatment of rheumatoid arthritis, osteoarthritis and the like, since QOL decreases markedly, discontinuation of NSAIDs administration is sometimes difficult. Therefore, it is considered important to continue NSAIDs administration while suppressing the onset of ulcer.

On the other hand, PPIs of benzimidazole compounds such as lansoprazole, omeprazole and the like are widely used as therapeutic agents for peptic ulcer and the like, since they have a strong gastric acid secretion-inhibitory action, a gastric mucosa protecting action and the like. Particularly, a

lansoprazole preparation has been approved to show the efficacy of "suppression of the onset of gastric ulcer or duodenal ulcer in administration of low-dose acetylsalicylic acid~~aspirin~~" and "suppression of the onset of gastric ulcer or duodenal ulcer in administration of non-steroidal anti-inflammatory drug" also in Japan in recent years, and the clinical effect of the suppression of the onset of gastric ulcer or duodenal ulcer caused by acetylsalicylic acid~~aspirin~~ medication has been verified.

Patent document 1 discloses a pharmaceutical composition containing (a) a therapeutically effective amount of at least one proton pump inhibitor unstable to acid; (b) a sufficient amount of at least one buffering agent to increase pH of the gastric fluid to a pH that prevents acid decomposition of at least some proton pump inhibitors in the gastric fluid; and (c) a therapeutically effective amount of at least one non-steroidal anti-inflammatory drug.

Patent document 2 discloses an oral dosage form containing an acid sensitive proton pump inhibitor together with at least one kind of a non-steroidal anti-inflammatory drug (NSAID) and, when desired, a pharmaceutically acceptable excipient.

Patent document 3 discloses a drug composition in a unit dosage form suitable for oral administration to patients, (a) an acid suppressant present in an amount effective for increasing the gastric pH of the aforementioned patients to at least 3.5 after administration of one kind or a plurality of the aforementioned unit dosage form, and (b) a non-steroidal anti-inflammatory drug in an amount effective for decreasing or removing a pain or inflammation in the aforementioned patients after administration of one kind or a plurality of the aforementioned unit dosage form, wherein the aforementioned unit dosage form cooperatively releases the aforementioned NSAID after the aforementioned acid suppressant.

Furthermore, while PPI such as lansoprazole and the like or acetylsalicylic acid~~aspirin~~ is already commercially available each other as

cardiovascular sequelae due to Kawasaki disease), the orally disintegrating tablet of the present invention can be administered for the purpose of treating or suppressing the onset of gastric ulcer or duodenal ulcer while continuing the administration of acetylsalicylic acid~~aspirin~~.

In addition, since acetylsalicylic acid can be used mainly for the treatment of pain, fever and inflammation as one kind of a non-steroidal anti-inflammatory drug (NSAIDs), the orally disintegrating tablet of the present invention can also be administered for the purpose of treating or suppressing the onset of gastric ulcer or duodenal ulcer while continuing the administration of NSAIDs.

The orally disintegrating tablet of the present invention shows high stability of the active ingredient, and expresses the pharmacological effect of the active ingredient stably and rapidly after administration.

The orally disintegrating tablet of the present invention can be administered easily while maintaining the convenience for handling, and can be administered on demand easily, anytime and anywhere, without water.

[0007]

(Detailed Description of the Invention)

The present invention is explained in detail in the following.

The solid preparation of the present invention comprises (1) an enteric fine granule-containing layer comprising a proton pump inhibitor and (2) an acetylsalicylic acid-containing layer in combination, and is particularly a multi-layer orally disintegrating tablet.

[0008]

(1) "enteric fine granule-containing layer comprising PPI"

(1)-1: PPI

Examples of the PPI is preferably a compound represented by the following formula (I) [hereinafter sometimes simply referred to as compound (I)].

the like, each for medicament. Particularly, magnesium carbonate is preferable.

[0039]

The above-mentioned metal oxide, metal hydroxide, alkaline earth metal carbonate and aluminum glycinate may be used alone or two or more kinds (preferably, 2 - 3 kinds) thereof may be combined.

As the antacid, a mixture of alkaline earth metal carbonate and aluminum glycinate is preferable, and a mixture of magnesium carbonate and aluminum glycinate is particularly preferable.

Some of metal oxide and metal hydroxide polish the surface of a formulating device during production to entirely or partially darken the surface of a tablet, form a dark spot, line or plane or attach to a punch during tableting. Since such property markedly impairs producibility, when metal oxide or metal hydroxide having abradability or punch-sticking property is to be selected, the polishing action and punch-sticking property can be suppressed by using a combination of metal oxide and metal hydroxide free of such property, or performing wet or dry granulation together with an additive (e.g., the below-mentioned excipient, binder, disintegrant and the like) usable as a pharmaceutical product.

In addition, antacid can contribute to the stabilization of acetylsalicylic acid~~aspirin~~ by decreasing the contact with acetylsalicylic acid~~aspirin~~, by performing, in advance, wet or dry granulation together with an additive (e.g., the below-mentioned excipient, binder and the like).

[0040]

The content of the above-mentioned antacid varies depending on the gastric acid neutralizing potency of each antacid, and is 0 mg - about 200 mg, preferably about 10 mg - about 100 mg, in the orally disintegrating tablet of the present invention.

In addition, the antacid is generally added at 0 - 50

then be administered.

[0060]

Since the orally disintegrating tablet of the present invention comprises PPI, it shows superior antiulcer activity, gastric acid secretion-inhibitory action, mucosa-protecting action, anti-Helicobacter pylori action and the like.

On the other hand, since the orally disintegrating tablet of the present invention contains acetylsalicylic acid, it is useful as an agent for the suppression of thrombus or embolus formation in the diseases of brain blood vessel and circulatory organ region, for example, angina pectoris (chronic stable angina pectoris, unstable angina pectoris) and myocardial infarction; the prophylaxis or treatment of ischemic cerebrovascular disorders (transient cerebral ischemic attack (TIA), cerebral infarction); suppression of thrombus or embolus formation after operation of coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA); and an agent for the prophylaxis or treatment of Kawasaki disease (including cardiovascular sequelae due to Kawasaki disease). Therefore, the orally disintegrating tablet of the present invention can be administered for the purpose of the treatment or suppression of the onset of gastric ulcer or duodenal ulcer, while continuing acetylsalicylic acid~~aspirin~~ medication. When the prophylaxis or treatment of such diseases is desired, PPI is administered at about 10 mg - about 40 mg per day, and acetylsalicylic acid is administered at (a low dose of) about 70 mg - about 120 mg per day.

In addition, acetylsalicylic acid can also be used as one kind of non-steroidal anti-inflammatory drugs (NSAIDs) mainly for the treatment of pain, fever and inflammation. NSAIDs sometimes cause gastric ulcer or duodenal ulcer. However, particularly, in the treatment of rheumatoid arthritis, osteoarthritis and the like, since QOL decreases markedly, discontinuation of NSAIDs administration is sometimes difficult. In such cases, the orally disintegrating tablet of the present

(53.7 kg) (liquid amount)

[0067]

[over-coating solution]

mannitol 4.200 kg

(purified water) (25.2 L)

[0068]

Example 1

An acetylsalicylic acid~~aspirin~~ premixed product (acetylsalicylic acid~~aspirin~~:cornstarch=90:10 dry granulation product, manufactured by Rhodia, Rhodine 2312, 1080 g), mannitol (manufactured by Roquette Pharma, PEARLITOL 200SD, 924 g), carmellose (240 g), citric anhydride (21.6 g), aspartame (24.0 g) and hydrogenated oil (110.4 g) were measured and mixed to give granule A. Aluminum glycinate (88.0 g), magnesium carbonate (176.0 g), mannitol (manufactured by Roquette Pharma, PEARLITOL 200SD, 403.3 g) and crystalline cellulose (47.7 g) were measured and placed in a fluidized bed dryer (POWREX CORPORATION, LAB-1), and the mixture was granulated while spraying a 5% hydroxypropylcellulose (HPC-L) solution (540.8 g) and dried to give granules. Furthermore, granules were obtained by repeating in the same manner and mixed with the granules produced earlier to give granule B. Granule B (1113.0 g), Lansoprazole enteric fine granules (1620 g), crospovidone (179.4 g), aspartame (32.4 g), crystalline cellulose (259.2 g, manufactured by Asahi Kasei, CEOLUS KG-1000), Neusilin (manufactured by Fuji Chemical Industries, trade name, 66.0 g) and magnesium stearate (30.0 g) were measured and mixed to give granule C. Granule A and granule C were tableted using a tableting machine (PICCOLA, manufactured by RIVA) at a tableting pressure of 11 kN to give a layered tablet having a diameter of 11 mm (preparation 1). The composition per tablet of this preparation 1 is shown in Table 1.

[0069]

Table 1

Blending composition of preparation 1

Component	preparation 1
acetylsalicylic acidaspirin	81
cornstarch	9.00
mannitol	77.0
carmellose	20.0
citric anhydride	1.8
aspartame	2.0
hydrogenated oil	9.2
Granule A subtotal (mg)	200.0
aluminum glycinate	11.0
magnesium carbonate	22.0
mannitol	50.41
crystalline cellulose	5.96
HPC-L	3.38
Lansoprazole fine granules	135
crospovidone	14.95
aspartame	2.70
crystalline cellulose	21.60
Neusilin	5.50
magnesium stearate	2.50
Granule C subtotal (mg)	275.00
total (mg)	475.00

[0070]

Example 2

An acetylsalicylic acidaspirin premixed product (acetylsalicylic acidaspirin:cornstarch=90:10 dry granulation product, manufactured by Rhodia, Rhodine 2312, 1800 g), mannitol (manufactured by Roquette Pharma, PEARLITOL 200SD, 1540 g), carmellose (400 g), citric anhydride (36.0 g), aspartame (40.0 g) and hydrogenated oil (184.0 g) were measured and mixed to give granule D. Mannitol (manufactured by Roquette Pharma, PEARLITOL 200SD, 604.9 g) and crystalline

cellulose (71.5 g) were measured and placed in a fluidized bed dryer (POWREX CORPORATION, MP-01), and the mixture was granulated while spraying a 5% hydroxypropylcellulose solution (811.2 g) and dried to give granule E. Granule E (298.9 g), Lansoprazole enteric fine granules (675 g), crospovidone (74.75 g), aspartame (13.52 g), crystalline cellulose (108 g, manufactured by Asahi Kasei, CEOLUS KG-1000), Neusilin (manufactured by Fuji Chemical Industries, trade name, 27.48 g) and magnesium stearate (12.5 g) were measured and mixed to give granule F. Granule D and granule F were tableted using a tableting machine (PICCOLA, manufactured by RIVA) at a tableting pressure of 15 kN to give a layered tablet having a diameter of 11 mm (preparation 2). The composition per tablet of preparation 2 is shown in Table 2.

[0071]

Table 2

Blending composition of preparation 2

component	preparation 2
acetylsalicylic acid~~aspirin~~	81
cornstarch	9.00
mannitol	77.0
carmellose	20.0
citric anhydride	1.8
aspartame	2.0
hydrogenated oil	9.2
Granule D subtotal (mg)	200.0
mannitol	50.41
crystalline cellulose	5.96
HPC-L	3.38
Lansoprazole fine granules	135
crospovidone	14.95
aspartame	2.70
crystalline cellulose	21.60

Neusilin	5.50
magnesium stearate	2.50
Granule F subtotal (mg)	242.00
total (mg)	442.00

[0072]

Example 3

An acetylsalicylic acid~~aspirin~~ premixed product (acetylsalicylic acid~~aspirin~~:cornstarch=90:10 dry granulation product, manufactured by Rhodia, Rhodine 2312, 900 g), mannitol (manufactured by Roquette Pharma, PEARLITOL 200SD, 760 g), carmellose (200 g), citric anhydride (17.93 g), aspartame (20.0 g), light anhydrous silicic acid (10.0 g) and hydrogenated oil (91.99 g) were measured and mixed to give granule G. Aluminum glycinate (550.3 g), magnesium carbonate (1100.2 g), mannitol (manufactured by Roquette Pharma, PEARLITOL 200SD, 2545.5 g) and crystalline cellulose (298.0 g) were measured and placed in a fluidized bed dryer (Freund Corporation, FLO-5M), and the mixture was granulated while spraying a 7% hydroxypropylcellulose solution (2414 g) and dried to give granules. Furthermore, granules were obtained by repeating in the same manner and mixed with the granules produced earlier to give granule H. Granule H (1091.7 g), Lansoprazole enteric fine granules (2025.2 g), crospovidone (224.3 g), aspartame (40.5 g), crystalline cellulose (323.8 g, manufactured by Asahi Kasei, CEOLUS KG-1000), Neusilin (manufactured by Fuji Chemical Industries, trade name, 82.5 g) and magnesium stearate (37.5 g) were measured and mixed to give granule I. Granule G and granule I were tableted using a tableting machine (PICCOLA, manufactured by RIVA) at a tableting pressure of 8.6 kN to give a layered tablet having a diameter of 10 mm (preparation 3). The composition per tablet of preparation 3 is shown in Table 3.

[0073]

Table 3

Blending composition of preparation 3

Component	preparation 3
acetylsalicylic acid~~aspirin~~	81
cornstarch	9.00
mannitol	76.0
carmellose	20.0
citric anhydride	1.8
aspartame	2.0
light anhydrous silicic acid	1.0
hydrogenated oil	9.2
Granule G subtotal (mg)	200.0
aluminum glycinate	11.0
magnesium carbonate	22.0
mannitol	50.41
crystalline cellulose	5.96
HPC-L	3.38
Lansoprazole fine granules	135
crospovidone	14.95
aspartame	2.70
crystalline cellulose	21.60
Neusilin	5.50
magnesium stearate	2.50
Granule I subtotal (mg)	275.00
total (mg)	475.00

[0074]

Example 4

Acetylsalicylic acid~~Aspirin~~ (1214.6 g), cornstarch (135.0 g), mannitol (manufactured by Roquette Pharma, PEARLITOL 200SD, 1140.2 g), carmellose (300.0 g), citric anhydride (27.0 g), aspartame (30.0 g), light anhydrous silicic acid (14.93 g) and hydrogenated oil (138.2 g) were measured and mixed to give granule J. Granule J and the above-mentioned granule I were

tableted using a tableting machine (PICCOLA, manufactured by RIVA) at a tableting pressure of 10 kN to give a layered tablet having a diameter of 10.5 mm (form: 2 step R) (preparation 4). The composition per tablet of preparation 4 is shown in Table 4.

[0075]

[Table 4]

Blending composition of preparation 4

component	preparation 4
acetylsalicylic ~~aspirin~~	81
cornstarch	9.00
mannitol	76.0
carmellose	20.0
citric anhydride	1.8
aspartame	2.0
light anhydrous silicic acid	1.0
hydrogenated oil	9.2
Granule J subtotal (mg)	200.0
aluminum glycinate	11.0
magnesium carbonate	22.0
mannitol	50.41
crystalline cellulose	5.96
HPC-L	3.38
Lansoprazole fine granules	135
crospovidone	14.95
aspartame	2.70
crystalline cellulose	21.60
Neusilin	5.50
magnesium stearate	2.50
Granule I subtotal (mg)	275.00
total (mg)	475.00

[0076]

Example 5

An acetylsalicylic acid~~aspirin~~ premixed product (acetylsalicylic acid~~aspirin~~: cornstarch=90:10 dry granulation product, manufactured by Rhodia, Rhodine 2312, 31500 g), mannitol (manufactured by Roquette Pharma, PEARLITOL 200SD, 28420 g), carmellose (7000 g), citric anhydride (630 g), aspartame (700 g), light anhydrous silicic acid (manufactured by NIPPON AEROSIL, AEROSIL, 350 g) and hydrogenated oil (1400 g) were measured and mixed by a tumbler mixer to give granule K. Aluminum glycinate (4840 g), magnesium carbonate (9680 g), mannitol (manufactured by Roquette Pharma, PEARLITOL 200SD, 22180 g), crystalline cellulose (manufactured by Asahi Kasei, CEOLUS PH-101, 2622 g), crospovidone (6578 g), aspartame (1188 g), crystalline cellulose (9504 g, manufactured by Asahi Kasei, CEOLUS KG-1000) and Neusilin (manufactured by Fuji Chemical Industries, trade name, 2420 g) were measured and placed in a fluidized bed dryer (POWREX CORPORATION, WSG-60 type), and the mixture was granulated while spraying a 6% hydroxypropylcellulose solution (24785 g) and dried to give granule L. Granule L was sieved by a power mill, 34380 g thereof was measured and mixed with Lansoprazole enteric fine granules (33750 g) and magnesium stearate (625 g) by a tumbler mixer to give granule M. Granule K and granule M were tableted using a tableting machine (manufactured by HATA IRON WORKS CO., LTD., HT-CVX54LS-UW/C&3L) at a tableting pressure of 11 kN to give a layered tablet having a diameter of 10.5 mm. This layered tablet was vacuum-dried to give preparation 5. The composition per tablet of preparation 5 is shown in Table 5.

[0077]

[Table 5]

Blending composition of preparation 5

Component	preparation 5
acetylsalicylic acid~~aspirin~~	81
cornstarch	9.00

mannitol	81.2
carmellose	20.0
citric anhydride	1.8
aspartame	2.0
light anhydrous silicic acid	1.0
hydrogenated oil	4.0
Granule K subtotal (mg)	200.0
aluminum glycinate	11.0
magnesium carbonate	22.0
mannitol	50.41
crystalline cellulose (PH101)	5.96
HPC-L	3.38
crospovidone	14.95
aspartame	2.70
crystalline cellulose (KG1000)	21.6
Neusilin	5.50
Lansoprazole fine granules	135
magnesium stearate	2.50
Granule M subtotal (mg)	275.00
total (mg)	475.00

[0078]

Evaluation

Experimental Example 1

The tablets obtained in Example 1 and Example 5, after storage in the closed bottle with a desiccant at 40°C for 1 month, were quantified for the content of acetylsalicylic acid~~aspirin~~ in the preparation by high performance liquid chromatography. The residual ratio (%) of acetylsalicylic acid~~aspirin~~ (=acetylsalicylic acid~~aspirin~~ content after storage/initial acetylsalicylic acid~~aspirin~~ content×100) was calculated from the quantified value. For evaluation, an acetylsalicylic acid~~aspirin~~ residual ratio of not less than 95% and not more than 100% was marked with O, not less than 90% and less than 95% with Δ, and less than 90%

with ×. The evaluation results are shown in Table 6.

[0079]

[Table 6]

Acetylsalicylic acid~~Aspirin~~ stability test results

Example 1	○
Example 5	○

[0080]

Experimental Example 2

The tablets obtained in Example 1 and Example 5 were measured for the oral disintegration time. The time from placing the tablet in the mouth of a healthy individual to the dissolution thereof without biting at all was taken as the oral disintegration time (average of n=2). The results are shown in Table 7.

[0081]

[Table 7]

Oral disintegration time measurement results

Example 1	37 seconds
Example 5	43 seconds

[0082]

Experimental Example 3

Using a tablet measurement apparatus (manufactured by PHARMA TEST), the tablets obtained in Example 1 and Example 5 were measured for the initial tablet hardness. The test was performed 5 times for Example 1 and 10 times for Example 5 and the average values thereof are shown in Table 8.

[0083]

[Table 8]

Tablet hardness measurement results

Example 1	61N
Example 5	56N

Industrial Applicability

CLAIMS

1. A multi-layer orally disintegrating tablet comprising (1) an enteric fine granule-containing layer comprising a proton pump inhibitor, ~~and~~ (2) an acetylsalicylic acid-containing layer and (3) an antacid in a part other than the enteric fine granules in the said enteric fine granule-containing layer.

~~2. The orally disintegrating tablet according to claim 1, wherein the enteric fine granule-containing layer comprises an antacid in a part other than the enteric fine granules.~~

~~3~~2. The orally disintegrating tablet according to claim ~~2~~1, wherein the antacid is at least one kind of component selected from the group consisting of metal oxide, metal hydroxide, alkaline earth metal carbonate and aluminum glycinate.

~~4~~3. The orally disintegrating tablet according to claim ~~3~~2, wherein the metal oxide is at least one kind selected from the group consisting of magnesium oxide, magnesium silicate, dried aluminum hydroxide gel and magnesium aluminometasilicate.

~~5~~4. The orally disintegrating tablet according to claim ~~3~~2, wherein the metal hydroxide is at least one kind selected from the group consisting of magnesium hydroxide, aluminum hydroxide, synthetic hydrotalcite, coprecipitate of aluminum hydroxide and magnesium hydroxide, coprecipitate of aluminum hydroxide, magnesium carbonate and calcium carbonate and coprecipitate of aluminum hydroxide and sodium hydrogen carbonate.

~~6~~5. The orally disintegrating tablet according to claim ~~3~~2, wherein the alkaline earth metal carbonate is calcium carbonate or magnesium carbonate.

~~7~~6. The orally disintegrating tablet according to claim ~~2~~1, wherein the antacid is a mixture of magnesium carbonate and aluminum glycinate.

~~8~~7. The orally disintegrating tablet according to claim ~~2~~1, wherein the content of the antacid is about 10 mg - about 100 mg.

~~9~~8. The orally disintegrating tablet according to claim 1, wherein the proton pump inhibitor is lansoprazole, omeprazole, rabeprazole, pantoprazole or an optically active form thereof or a salt thereof.

~~10~~9. The orally disintegrating tablet according to claim 1, wherein the content of the acetylsalicylic acid is about 70 mg - about 120 mg per tablet.

~~11~~10. The orally disintegrating tablet according to claim 1, wherein the acetylsalicylic acid-containing layer comprises carboxymethylcellulose.

~~12~~11. The orally disintegrating tablet according to claim 1, wherein the enteric fine granule-containing layer comprising a proton pump inhibitor comprises at least one kind of a disintegrant selected from crospovidone and magnesium aluminometasilicate in a part other than the enteric fine granules.

~~13~~12. The orally disintegrating tablet according to claim 1, wherein the acetylsalicylic acid-containing layer comprises a lubricant.

~~14~~13. The orally disintegrating tablet according to claim ~~13~~12, wherein the lubricant is hydrogenated oil.

~~15~~14. The orally disintegrating tablet according to claim 1, which is a bi-layer tablet.

~~16~~15. The orally disintegrating tablet according to claim 1, comprising an intermediate layer between (1) the enteric fine granule-containing layer comprising a proton pump inhibitor and (2) the acetylsalicylic acid-containing layer.

~~17~~16. The orally disintegrating tablet according to claim 1, wherein the acetylsalicylic acid is not enteric-coated.

~~18~~17. The orally disintegrating tablet according to claim 1, wherein the tablet weight is about 300 mg - about 800 mg, and the weight ratio of (1) the enteric fine granule-containing layer comprising a proton pump inhibitor and (2) the acetylsalicylic acid-containing layer is about 10:1 - about 1:10.

~~19~~18. The orally disintegrating tablet according to claim 1, having a curved surface on a tablet surface.

~~20~~19. The orally disintegrating tablet according to claim 1, having an oral disintegration time of within about 60 seconds.

~~21~~20. The orally disintegrating tablet according to claim 1, having a tablet hardness of about 20 - about 100 N.

ABSTRACT

The present invention relates to a multi-layer orally disintegrating tablet having (1) an enteric fine granule-containing layer containing a proton pump inhibitor and (2) an acetylsalicylic acid-containing layer, which shows high stability of the active ingredients (proton pump inhibitor, acetylsalicylic acid~~aspirin~~) and expresses the pharmacological effects of the active ingredients stably and rapidly after administration.