

PHARMACEUTICAL COMPOSITION COMPRISING RABEPRAZOLE AND SODIUM BICARBONATE

【Technical Field】

The present invention relates to stable pharmaceutical composition for the
5 treatment of gastrointestinal diseases, comprising rabeprazole or a
pharmaceutically acceptable salt thereof and sodium bicarbonate.

Specifically, the present invention relates to a stable pharmaceutical
composition comprising a predetermined amount of sodium bicarbonate to
improve the bioavailability of the active ingredient rabeprazole in a low pH
10 environment, such as the stomach, and to achieve rapid pharmacological effect.

【Background Art】

Proton-pump inhibitors (PPIs) are active ingredients that significantly and
continuously inhibit the secretion of gastric acid and are commonly prescribed to
15 treat gastrointestinal disorders such as digestive disorders caused by excessive
stomach acid with relatively few side effects. Specifically, proton-pump inhibitors
are classified as powerful attack factor inhibitors along with H₂ receptor
antagonists as drugs for the treatment of gastrointestinal diseases.

20 Among them, rabeprazole is known as the most powerful proton pump
inhibitor, and it has the effect of inhibiting gastric acid secretion by inhibiting the
wall cell H⁺/K⁺ ATP pump, thereby relieving symptoms caused by excessive
gastric acid.

Rabeprazole is known for its ability to easily bind and dissociate from the proton pump by glutathione secreted in the secretory tubules, resulting in a faster recovery of acid secretion after discontinuation compared to other proton pump inhibitors. In addition, it has the highest pKa among proton pump inhibitors, thus
5 it has a rapid onset of action that responds much faster than other drugs, and can be activated at a higher pH level.

In addition, rabeprazole is a prodrug, which means that it is inactive in the body and needs to be activated to become the active form in order to be effective. Although this can be accomplished by gastric acid, it has been shown that
10 rabeprazole that is pre-activated prior to absorption into the wall cells does not show proton pump inhibition. In other words, rabeprazole must be activated after absorption into the wall cells to irreversibly bind to the proton pump and inhibit gastric acid secretion. Therefore, most proton pump inhibitors such as rabeprazole are designed as delayed-release formulations using enteric-coated to prevent pre-
15 activation by gastric acid.

Representatively, pariet tablets, which are enteric-coated tablets containing rabeprazole as an active ingredient, are designed to prevent contact of the active ingredient with stomach acid by an enteric coating layer after oral administration until the tablet passes through the gastrointestinal tract where
20 stomach acid is present.

However, although the enteric-coated tablets can protect proton pump inhibitors from gastric acid, they have the disadvantage that the elution of the active ingredient cannot occur for more than 4 hours until the enteric coating on the tablet surface disappears due to the high pH environment, thereby

significantly delaying the expression of pharmacological effects.

Meanwhile, sodium bicarbonate, also known as sodium bicarbonate, bicarbonate of soda, bicarbonate of soda, bicarbonate of soda, etc. is also used as an antacid in medicine because it is slightly basic and therefore neutralizes stomach acid. However, overdosing on sodium bicarbonate can cause several side effects. As a typical side effect, carbon dioxide is produced when stomach acid reacts with sodium bicarbonate and is neutralized, causing belching, which can cause reflux of stomach acid, causing discomfort and pain in patients with gastric reflux disease.

However, no pharmaceutical formulation has been developed to improve the pharmacological effect of rabeprazole active ingredient for the treatment of gastrointestinal diseases while expressing the pharmacological effect significantly faster than conventional enteric-coated tablets. In other words, due to the physicochemical properties of rabeprazole, which are unstable in a low pH environment, conventional formulations can only be manufactured as enteric-coated tablets, and inevitably, the absorption of the drug is delayed, and the effect is expressed late, thus the rapid improvement of gastrointestinal disease symptoms desired by GERD patients cannot be expected.

Meanwhile, Korean Patent Publication No. 10-2019-0091879 (Patent Document 1), Korean Patent Registration No. 10-2006777 (Patent Document 2), and Korean Patent Publication No. 10-2021-0012919 (Patent Document 3) disclose a combination product comprising esomeprazole, a proton pump inhibitor, and sodium hydrogen carbonate as active ingredients.

Esomeprazole, the active ingredient of patent documents 1 to 3, is mainly

metabolized by the hepatic metabolizing enzyme CYP2C19, which is subject to genetic polymorphisms, resulting in large individual variations in medicinal efficacy. In comparison, only a small amount of rabeprazole demethylated and rabeprazole sulfone are metabolized by CYP2C19 and CYP3A4, respectively, and rabeprazole is mainly metabolized to rabeprazole-thioether by non-enzymatic metabolism. Therefore, compared to esomeprazole, rabeprazole is less affected by CYP2C19, which results in less individual variation in terms of pharmacokinetics and pharmacodynamics, and therefore has the advantages of better medicinal efficacy compared to other proton pump inhibitors such as esomeprazole, and less burden on drug interactions with other drugs.

In other words, the formulations of the above patent documents 1 to 3 may have a faster onset of action compared to the conventional rabeprazole enteric-coated tablets, but it is difficult to consider them as improved formulations of the conventional rabeprazole enteric-coated tablets because a new problem of large individual variation may occur by using esomeprazole as a proton pump inhibitor.

[Related Art Document]

[Patent Document]

Korean Patent Publication No. 10-2019-0091879

Korean Patent Registration No. 10-2006777

Korean Patent Publication

【Disclosure】

【Technical Problem】

The present invention is to improve the disadvantages of conventional compositions containing the active ingredient rabeprazole, and to provide an oral pharmaceutical composition comprising an effective amount of rabeprazole or a pharmaceutically acceptable salt thereof, and sodium hydrogen carbonate.

5 Specifically, the present invention is to provide a combination preparation that provides immediate effect through rapid absorption, high bioavailability, and reduced side effects compared to conventional enteric-coated preparations.

【Technical Solution】

10 The present invention relates to an orally administered pharmaceutical composition for the treatment of gastrointestinal diseases comprising rabeprazole or a pharmaceutically acceptable salt thereof and sodium bicarbonate as active ingredients, wherein the pharmaceutical composition may include from 10 to 30 mg of rabeprazole or a pharmaceutically acceptable salt thereof and at least 600
15 mg of sodium bicarbonate.

According to one embodiment of the present invention, the pharmaceutical composition may include 20 mg of rabeprazole sodium and 800 mg of sodium bicarbonate, and when administered orally, the sodium bicarbonate may neutralize the pH of gastric juice, thereby delaying the rate of degradation of
20 rabeprazole while achieving rapid symptomatic improvement.

According to one embodiment of the present invention, the pharmaceutical composition may optionally further include additives such as binders, disintegrants, disintegrating agents, lubricants, and the like, and may be formulated by pelletizing or granulating, and may also be formulated by directly

compressing the raw material. In the case of formulation by granulation, the product can be prepared specifically by the wet granulation method.

According to one embodiment of the present invention, the binding agent may be one or two or more selected from the group consisting of povidone, gelatin,
 5 gum arabic, ethanol, agar powder, cellulose acetate, carboxymethylcellulose, carboxymethylcellulose calcium, methylcellulose, microcrystalline cellulose, dextrin, hydroxy cellulose, hydroxypropyl starch, hydroxy methylcellulose, glucose, sodium caseinate, glycerin, stearic acid, sodium carboxymethylcellulose, sodium methylcellulose, purified shellac, starch, hydroxy propyl cellulose,
 10 hydroxy propyl methylcellulose, polyvinyl alcohol, and polyvinylpyrrolidone.

According to one embodiment of the present invention, the disintegrating agent may be one or two or more selected from the group consisting of cross povidone, hydroxy propyl methylcellulose, agar powder, bentonite, sodium carboxymethylcellulose, calcium carboxymethylcellulose, sodium lauryl sulfate,
 15 1-hydroxypropylcellulose, casein, gelatin, amylose, calcium phosphate, gum arabic, pectin, ethyl cellulose, magnesium aluminum silicate, light anhydrous silicic acid, corn starch, methylcellulose, hydroxypropyl starch, sodium alginate, calcium citrate, silicic anhydride, dextran, polyvinyl acetate, alginate, guar gum, polyvinylpyrrolidone, gelling starch, amylopectin, sodium polyphosphate, white
 20 sugar, and d-sorbitol.

According to one specific embodiment of the present invention, the excipients may be one or two or more selected from the group consisting of D-mannitol, low-substituted hydroxypropyl cellulose, corn starch, potato starch, wheat starch, lactose, white sugar, glucose, fructose, precipitated calcium

carbonate, synthetic aluminum silicate, calcium mono hydrogen phosphate, calcium sulfate, sodium chloride, purified lanolin, microcrystalline cellulose, dextrin, sodium monohydrate, methylcellulose, sodium carboxymethylcellulose, kaolin, urea, colloidal silica gel, hydroxypropyl starch, hydroxy propyl
 5 methylcellulose, propylene glycol, casein, calcium lactate, and primo gel.

According to one specific embodiment of the present invention, the lubricant may be one or two or more selected from the group consisting of sodium stearyl fumarate, calcium stearate, sodium stearate, zinc stearate, magnesium stearate, aluminum stearate, talc, kaolin, sodium salicylate, polyethylene glycol,
 10 hydrogenated soybean oil, magnesium oxide, synthetic aluminum silicate, high-quality fatty acids, and silicone oil, polyethylene glycol fatty acid ether, sodium chloride, sodium oleate, light anhydrous silicic acid, hydrogenated vegetable oil, pomegranate, petrolatum, magnesium salicylate, liquid paraffin, sodium lauryl sulfate, macrogol, anhydrous silicic acid, high gold alcohol, paraffin oil, starch,
 15 sodium acetate, dl-lysine.

The pharmaceutical composition of the present invention have a significantly faster time to maximum blood concentration than conventional enteric-coated formulations, and according to one embodiment, the time to maximum blood concentration (Tmax) of rabeprazole when administered orally
 20 can be from 0.3 to 1.5 hours.

According to one specific embodiment, the pharmaceutical composition of the present invention, wherein a 90% confidence interval of the mean difference is log 0.8 to log 1.25 when an area under the blood concentration curve(AUC) of rabeprazole is log-transformed and subjected to statistically

processing compared to control drug.

Further, the pharmaceutical compositions of the present invention are characterized in that they do not include an enteric solubilizing mechanism, resulting in immediate elution of the active ingredient after oral administration.

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【Advantageous Effects】

The pharmaceutical composition of the present invention has a higher bioavailability than rabeprazole alone by improving the stability of rabeprazole, which is unstable at low pH, with sodium hydrogen carbonate.

10 Further, it has a higher C_{max} and faster T_{max} than existing enteric-coated formulations, resulting in rapid absorption and immediate inhibition of gastric acid secretion.

In addition, by using rabeprazole as a proton pump inhibitor with less enzymatic metabolism than other proton pump inhibitors such as esomeprazole,
15 it is characterized by low individual variation and excellent bioavailability.

In addition, it contains the minimum amount of sodium bicarbonate necessary to raise the internal pH of the stomach, resulting in rapid antacid action with fewer side effects, making it suitable for rapid symptom improvement, especially for patients with gastroesophageal reflux disease
20 (GERD) showing symptoms such as heartburn.

【Brief Description of the Drawings】

FIG. 1 illustrates the change in pH as a function of sodium bicarbonate

dose in a solution of artificial gastric juice and water.

FIG. 2 illustrates the stability of rabeprazole over pH conditions.

FIG. 3 shows a comparison of the change in gastric pH for patients treated with a single once-daily dose of test drug (T), control drug (R), and no drug (baseline).

FIG. 4 shows a comparison of the change in gastric pH in patients treated with test drug (T), control drug (R), and no drug (baseline) after 7 days of once-daily dosing.

FIG. 5 shows a comparison of drug blood levels over time in patients receiving a single once-daily dose of test drug versus control.

FIG. 6 shows a comparison of time-of-day drug blood levels in patients receiving a once-daily dose of study drug repeated for 7 days versus patients receiving a control dose.

15 **【Best Mode of the Invention】**

The present invention provides a pharmaceutical composition for the treatment of gastrointestinal diseases comprising at least 600 mg of rabeprazole or a pharmaceutically acceptable salt thereof, and sodium bicarbonate.

【Modes of the Invention】

20 Hereinafter, the pharmaceutical composition according to the present invention will be described in detail through examples.

<Test Example 1> Test of pH raising effect depending on sodium hydrogen carbonate content

The pharmaceutical composition of the present invention elute the active ingredient rabeprazole in the stomach after oral administration. Therefore, it is necessary to raise the pH of the intragastric environment sufficiently so that the active ingredient eluted in the stomach is not activated by gastric acid. To
 5 determine the amount of sodium bicarbonate to sufficiently increase the pH of the intragastric environment, specific drug release conditions and gastric juice conditions were established in the following method.

In general, the acidity of human gastric juice is pH 1.5 to 3.5, the body secretes about 2 liters of gastric juice per day (about 83 mL/hour), and the residual
 10 amount of gastric juice in fasting is generally 20 to 30 mL. Furthermore, given the typical gastric residence time of tablets, the total amount of gastric fluid reacting with the drug was estimated to be 200 mL. In addition, the typical amount of water consumed with medication was set to 200 mL. In addition, to take into account the acidity of normal gastric juice, we prepared artificial gastric juice at
 15 pH 1.5, pH 2.5, and pH 3.5, respectively.

The pH was measured by changing the amount of sodium bicarbonate in a solution of 200 mL of gastric and 200 mL of water ($37\pm0.5^{\circ}\text{C}$), and the results are shown in the following Table 1 and FIG. 1.

【Table 1】

NaHCO ₃ (mg)		0	100	200	300	400	500
Test solution (1)	pH 1.5 200mL + water 200mL	1.77	1.85	1.95	2.08	2.26	2.6

Test solution (2)	pH 2.5 200mL + water 200mL	2.75	7.66	8.27	8.38	8.44	8.42
Test solution (3)	pH 3.5 200mL + water 200mL	3.84	8.07	8.31	8.34	8.35	8.34
NaHCO ₃ (mg)		600	700	800	900	1,000	1,100
Test solution (1)	pH 1.5 200mL + water 200mL	7.5	8.23	8.35	8.34	8.35	8.35
Test solution (2)	pH 2.5 200mL + water 200mL	8.43	8.42	8.43	8.43	8.44	8.43
Test solution (3)	pH 3.5 200mL + water 200mL	8.34	8.35	8.34	8.34	8.34	8.34

- In the case of test solution (1), the pH of the solution increased as the amount of sodium bicarbonate increased, and the pH did not show an increasing trend even with further increases from 800 mg onwards. In the case of test
- 5 solution (2) and test solution (3), it was confirmed that the amount of sodium bicarbonate over 200 mg was sufficient to neutralize stomach acid and increase

the pH. However, under the same conditions as test solution (1), the amount of sodium bicarbonate less than 800 mg was not expected to raise the pH sufficiently.

Therefore, it was confirmed that test solutions (1), (2), and (3) all
5 exhibited sufficient pH increase when containing 800 mg or more of sodium hydrogen carbonate. However, when the amount of sodium bicarbonate exceeded 800 mg, no further pH-raising effect could be expected, and side effects caused by sodium bicarbonate were expected to increase.

Based on the above test results, it was determined that the optimal
10 amount of sodium bicarbonate required to neutralize the fasting gastric internal acidity to achieve a maximum pH increase is at least 600 mg, and most preferably 800 mg or more.

<Example 2> Measuring the stability of rabeprazole according to pH
15 condition

To determine the stability of rabeprazole according to pH, the experiment was conducted as the following. In a 100 mL volume flask, 10 mL of rabeprazole solution at a concentration of 0.22 mg/mL was added, and the buffer solution was made up to exactly 100 mL to analyze the content.

20 - Buffer solution: pH7.4 Phosphate buffer, pH 9.0 Borate buffer, pH 10.0
Borate buffer

- Preparation method: According to the method published in the Korean Pharmacopoeia.

- Operation condition

Detector: UV-visible absorption spectrophotometer (measurement wavelength: 290 nm)

Column: Cosmosil C18, 4.6mm × 150 mm, 5μm or the equivalent column

Column temperature: 30°C

5 Sample temperature: 5°C

Flow rate: adjusted so that the retention time of rabeprazole is approximately 5 minutes

Eluent: Methanol and 0.05 mol/L phosphate buffer solution (pH 7.0) mixed in a volume ratio of 300 : 200.

10 - Analysis time: Approximately 3 times of the retention time of rabeprazole

* 0.05 mol/L phosphate buffer solution (pH 7.0): 0.05 M sodium phosphate monohydrate solution was added to 0.05 M potassium dihydrogen phosphate solution to adjust to pH 7.0. (Volume ratio approximately 2:1)

15 The test results are shown in the following Table 2 and FIG. 2.

【Table 2】

(measure: %)

time	pH 7.4	pH 9.0	pH 10.0
0	100	100	100
3	20	91.8	99.1
6	3.4	84.1	97.5

12	0.4	69	95
18	0	56.8	92.4
24	0	47.8	90.2
30	0	40.2	87.7
36	0	33.3	85.3
42	0	27.3	82.9

As shown in Table 2 and FIG. 2, the rate of degradation of rabeprazole decreases as the pH of the solution increases, thereby increasing the stability of the active ingredient. Specifically, in the pH 7.4 elution solution condition, 20% of rabeprazole remained undissolved after 3 hours of elution, and in the pH 9.0 or higher elution solution condition, more than 91% of rabeprazole remained after 3 hours of elution. Therefore, it is expected that the dissolution of rabeprazole is inhibited for at least 3 hours under the elution condition of pH 7.4 or higher, resulting in high stability, and the present formulation, which is a fast-release formulation comprising rabeprazole and sodium bicarbonate, can be expected to have high bioavailability of rabeprazole due to the neutralizing effect of sodium bicarbonate.

Therefore, it was decided to prepare a pharmaceutical composition comprising 800 mg of sodium bicarbonate, which is the minimum amount of sodium bicarbonate that can raise the pH to the highest level in the above Example 1.

<Example> Preparation of a tablet containing rabeprazole and sodium bicarbonate

A tablet containing 20 mg rabeprazole sodium and 800 mg sodium bicarbonate as active ingredients was prepared. First, 700 mg of sodium
5 bicarbonate was mixed with D-mannitol and low-substituted hydroxypropyl cellulose as excipients and povidone as a binder. It was then combined with ethanol and vacuum dried to form granules.

The formed granules were post-mixed with 20 mg of sodium rabeprazole, 100 mg of sodium hydrogen carbonate, cross povidone as a disintegrating agent,
10 and sodium stearyl fumarate as a lubricant, and the tablets were prepared.

The surface of the tablet was coated by selecting opadrywhite as a coating agent to prepare a film-coated tablet.

<Example 3> Evaluation of formulation suitability by binder and disintegrating agent content ratio

15 To calculate the relative content ratio of binder and disintegrating agent suitable for formulation for the pharmaceutical compositions according to the above embodiments, tablets were prepared as in Examples 1 to 8 of the following Table 3 by setting different relative weight % of disintegrating agent based on the total weight of binder.

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【Table 3】

(measure: weight%)

classification	Example 1	Example 2	Example 3	Example 4
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binder disintegrating agent weight % to total weight	12.50	20.69	23.68	50.00
구분	Example 5	Example 6	Example 7	Example 8
binder disintegrating agent weight % to total weight	63.16	76.32	102.63	128.95

The flowability, hardness, abrasiveness, and disintegration of Examples

1 to 8 were evaluated and are shown in the following Table 4.

5 【Table 4】

Classification	flowability	Crystallinity		disintegration
Classification	flowability	hardness	abrasiveness	disintegration
Example 1	○	○	○	X
Example 2	○	X	X	X
Example 3	○	○	○	X
Example 4	○	○	○	△

Example 5	○	○	○	○
Example 6	○	○	○	○
Example 7	○	○	○	○
Example 8	○	○	○	○

(○: good, △: fair, X: poor)

According to the results in the above Table 4, all Examples 1 to 8 had uniform particle size and good flowability. However, in the case of Examples 1 to 3, the relative content of disintegrating agent was excessively low, resulting in weak disintegration, and in the case of Example 2, the hardness and abrasiveness were also inadequate, resulting in poor tablet ability. In the case of weak disintegration as in Examples 1 to 3, the bioavailability of rabeprazole may be significantly reduced because the pH of the gastric environment cannot be raised rapidly by sodium bicarbonate after oral administration.

Meanwhile, Examples 4 to 6 were found to be suitable in terms of flowability, hardness, abrasiveness, and disintegration, and were evaluated to have the most excellent effect when administered orally.

However, although Examples 7 and 8 had good disintegration, the relative content of the disintegrating agent was excessive, which could significantly reduce the stability of the formulation, and it was expected that breakage and friability of the tablets would occur during storage.

Examples 4 to 6 were subjected to elution by film coating with an off-dry coating agent, and all showed adequate elution rates. Based on these results, it

was concluded that the disintegrating agent is preferably included in the range of 30 to 90 wt% with respect to the total weight of the binder, and that it is most preferable in terms of elution characteristics and formulation stability when included in the range of 45 to 80 wt%.

5 Based on the above test results, Example 5 was finally selected as the test drug among the Examples 4 to 6, which exhibited desirable elution characteristics.

 <Example 4> Comparative effectiveness test of test drug and control drug

 Healthy adults aged 19 to 55 years old were administered a single dose
10 of Parisette tablets as a control and the test drug (Example 5) once daily, and the pH was monitored with a pH meter catheter inserted into the gastrointestinal tract for 24 hours, and the results are shown in FIG. 3.

 In FIG. 3, the gastric internal pH results measured for -1 day (24 hours before administration) before administration of the test drug are labeled as
15 baseline, the pH monitoring results measured for 1 day (24 hours after administration) after administration of the test drug (Example 5) are labeled as T, and the gastric internal pH monitoring results measured for 1 day (24 hours after administration) after administration of parietal tablets as a control are labeled as R. The results are shown in FIG. 3.

20 As shown in FIG. 3, both the test group treated with the test drug (T) and the control group treated with the control drug (R) showed an increase in gastric pH after administration from baseline, but unlike the control group, the test group showed a significant effect on the increase in gastric internal pH in the early post-administration period (0-240 minutes). Specifically, the time to

maximum blood concentration (Tmax) of rabeprazole was achieved within 0.3 to 1.5 hours, preferably within 1.0 hours.

This fast-acting effect is due to, first, the antacid effect of sodium bicarbonate, which raises the internal pH of the stomach, and second, the rapid
5 absorption of rabeprazole sodium compared to the existing enteric-coated formulation, which inhibits gastric acid secretion.

Therefore, it can be seen that by taking sodium bicarbonate and rabeprazole sodium together, it shows a rapid symptom improvement effect compared to the existing enteric-coated version of rabeprazole due to rapid drug
10 absorption with rapid antacid action.

Meanwhile, the results of repeated administration for 7 days under the same conditions are shown in Fig. 4. It can be seen that the maximum blood concentration (Tmax) of rabeprazole is achieved within 0.3 to 3.5 hours.

<Example 5> Measurement of drug blood levels

15 In healthy adults aged 19 to 55 years, PK profiles were measured in a single once-daily dose of parietal tablets as a control and the test drug (Example 5), followed by repeated once-daily dosing for 7 days to measure PK profiles again. The results are shown in Table 5 and FIGS. 5 and 6 below.

20 **【Table 5】**

Duration of administration	PK parameters	Control Drug	Test Drug
Once daily	Tmax(hr)	4.00	0.67

	C _{max} (ng/mL)	528.51	714.45
	AUC _{T(h* ng/mL)}	1127.68	1060.28
Once daily 7-day repeat	T _{max} (hr)	3.00	0.67
	C _{max} (ng/mL)	616.91	939.55
	AUC _{T(h* ng/mL)}	1230.30	1342.12

In the case of T_{max}, the control group (R) taking rabeprazole enteric-coated formulation had a T_{max} of 4 hours for a single dose and 3 hours for a 7-day repeat dose, while the test group (T) taking rabeprazole plus sodium bicarbonate had a T_{max} of 0.67 hours for both a single dose and a 7-day repeat dose, indicating rapid absorption of the drug compared to the control group. In addition, the combination of rabeprazole sodium with sodium bicarbonate ensured that rabeprazole sodium was well absorbed without enteric coating. C_{max} was 528.51 (ng/ml) in control group (R) and 714.45 (ng/ml) in test group (T) for single dose, and 616.91 (ng/ml) in control group (R) and 939.55 (ng/ml) in test group (T) for 7-day repeat dose.

According to the above results, the C_{max} of the test group is higher than that of the control group, and at the same time, the T_{max} is faster, so that the immediate drug effect can be expressed than the existing enteric-coated drugs, which can be confirmed by the higher gastric internal pH of the test group (T) compared to the control group (R) in the early time period (0~240 min) among the pharmacodynamic (PD) results in FIGS. 3 and 4.

The pharmaceutical compositions were also shown to be bioequivalent,

with a 90% confidence interval (CI) of the difference in mean values ranging from log 0.8 to log 1.25, when log-transforming the area under the blood concentration curve (AUC) of rabeprazole compared to parietal tablets.

5 **【Industrial Applicability】**

The present invention has high bioavailability, rapid absorption and immediate inhibition of gastric acid secretion, low individual variability, and is suitable for rapid symptomatic improvement in patients with gastroesophageal reflux disease (GRED).

【Claims】

1. A pharmaceutical composition for the treatment of gastrointestinal diseases comprising rabeprazole or a pharmaceutically acceptable salt thereof and at least 600 mg of sodium bicarbonate.

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2. The pharmaceutical composition for the treatment of gastrointestinal diseases of claim 1, wherein the rabeprazole or the pharmaceutically acceptable salt thereof is rabeprazole sodium.

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3. The pharmaceutical composition for the treatment of gastrointestinal diseases of claim 1, wherein the rabeprazole or the pharmaceutically acceptable salt thereof comprises from 10 to 30 mg.

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4. The pharmaceutical composition for the treatment of gastrointestinal diseases of claim 1, wherein the sodium bicarbonate comprises 800 mg.

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5. The pharmaceutical composition for the treatment of gastrointestinal diseases of claim 1, wherein a binding agent is one or two or more selected from the group consisting of povidone, gelatin, gum arabic, ethanol, agar powder, cellulose acetate, carboxymethylcellulose, carboxymethylcellulose calcium, methylcellulose, microcrystalline cellulose, dextrin, hydroxy cellulose, hydroxypropyl starch, hydroxy methylcellulose, glucose, sodium caseinate, glycerin, stearic acid, sodium carboxymethylcellulose, sodium methylcellulose, purified shellac, starch, hydroxy propyl cellulose, hydroxy propyl

methylcellulose, polyvinyl alcohol, and polyvinylpyrrolidone.

6. The pharmaceutical composition for the treatment of gastrointestinal diseases of claim 1, wherein a disintegrating agent is one or two or more selected
 5 from the group consisting of cross povidone, hydroxy propyl methylcellulose, agar powder, bentonite, sodium carboxymethylcellulose, calcium carboxymethylcellulose, sodium lauryl sulfate, 1-hydroxypropylcellulose, casein, gelatin, amylose, calcium phosphate, gum arabic, pectin, ethyl cellulose, magnesium aluminum silicate, light anhydrous silicic acid, corn starch,
 10 methylcellulose, hydroxypropyl starch, sodium alginate, calcium citrate, silicic anhydride, dextran, polyvinyl acetate, alginate, guar gum, polyvinylpyrrolidone, gelling starch, amylopectin, sodium polyphosphate, white sugar, and d-sorbitol.

7. The pharmaceutical composition for the treatment of gastrointestinal
 15 diseases of claim 1, wherein a excipients is one or two or more selected from the group consisting of D-mannitol, low-substituted hydroxypropyl cellulose, corn starch, potato starch, wheat starch, lactose, white sugar, glucose, fructose, precipitated calcium carbonate, synthetic aluminum silicate, calcium mono hydrogen phosphate, calcium sulfate, sodium chloride, purified lanolin,
 20 microcrystalline cellulose, dextrin, sodium monohydrate, methylcellulose, sodium carboxymethylcellulose, kaolin, urea, colloidal silica gel, hydroxypropyl starch, hydroxy propyl methylcellulose, propylene glycol, casein, calcium lactate, and primo gel.

8. The pharmaceutical composition for the treatment of gastrointestinal diseases of claim 1, wherein a lubricant is one or two or more selected from the group consisting of sodium stearyl fumarate, calcium stearate, sodium stearate, zinc stearate, magnesium stearate, aluminum stearate, talc, kaolin, sodium salicylate, polyethylene glycol, hydrogenated soybean oil, magnesium oxide, synthetic aluminum silicate, high-quality fatty acids, and silicone oil, polyethylene glycol fatty acid ether, sodium chloride, sodium oleate, light anhydrous silicic acid, hydrogenated vegetable oil, pomegranate, petrolatum, magnesium salicylate, liquid paraffin, sodium lauryl sulfate, macrogol, anhydrous silicic acid, high gold alcohol, paraffin oil, starch, sodium acetate, dl-lysine.

9. The pharmaceutical composition for the treatment of gastrointestinal diseases of claim 1, wherein a time to maximum blood concentration (T_{max}) of rabeprazole when administered orally is from 0.3 to 1.5 hours.

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10. The pharmaceutical composition for the treatment of gastrointestinal diseases of claim 1, wherein a 90% confidence interval of the mean difference is log 0.8 to log 1.25 when an area under the blood concentration curve(AUC) of rabeprazole is log-transformed and subjected to statistically processing compared to control drug.

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11. The pharmaceutical composition for the treatment of gastrointestinal diseases of claim 1, wherein the pharmaceutical composition does not comprise an enteric-soluble base.

12. The pharmaceutical composition for the treatment of gastrointestinal diseases of claim 1, wherein the pharmaceutical composition is prepared by pelleting, granulation, or direct compression.

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13. The pharmaceutical composition for the treatment of gastrointestinal diseases of claim 1, wherein the pharmaceutical composition is in the form of granules.

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14. The pharmaceutical composition for the treatment of gastrointestinal diseases of claim 13, wherein the pharmaceutical composition is prepared by a wet granulation method.