159159

G00002

DESCRIPTION

PREPARATION FOR MEASURING GASTRIC EMPTYING ABILITY

TECHNICAL FIELD

The present invention relates to a technique for the diagnostic measurement of the gastric emptying ability (gastric emptying rate). In concrete terms, the present invention relates to preparations which can measure the reduction or acceleration of the gastric emptying ability in a noninvasive manner using respiration, and a method for measuring the gastric emptying ability using these preparations.

The present invention allows the safe and easy examination of reduction or acceleration of the gastric emptying ability. Specifically, the preparations of the present invention are useful for the objective diagnosis of the motor function of the stomach, and are useful for evaluating the pharmacological effects or therapeutic effects of drugs relating to the motor function of the stomach in individual subjects.

BACKGROUND ART

In the field of internal medicine, the treatment of stomach ulcer and duodenal ulcer has made a great transition from treatment by means of surgical procedures to noninvasive drug treatments as a result of progress

made in drugs such as H_2-antagonists, stomach acid secretion inhibiting agents and the like.

On the other hand, there has been an increase in subjects who, while showing no signs of ulcer in endoscopic examinations, nevertheless complain of symptoms such as nausea, urge to vomit, feeling of bloating, heavy stomach, heartburn, loss of appetite, upper abdominal pain and the like (such subjects are referred to collectively as "subjects with general physical complaints"). Such general physical complaints are generally diagnosed on the basis of the symptoms reported by the subjects, and it is extremely difficult to diagnose such complaints in an objective and quantitative manner. Furthermore, the difficulty of such diagnosis delays appropriate treatment, and also causes a deterioration in the quality of life (QOL) of such subjects with general physical complaints. It has recently been found that such general physical complaints reported by subjects have a close correlation with a lowering of the gastric emptying ability (GER), and it has been reported that a lowering of the gastric emptying rate is observed in approximately half of all subjects suffering from general physical complaints.

Accordingly, it would appear that if it were possible to measure the gastric emptying rate easily and

with high precision without placing a burden on the subject, this would make a great contribution to the appropriate diagnosis and treatment of subjects suffering from general physical complaints.

However, conventional methods for measuring the gastric emptying rate are expensive, and are invasive so that such methods place a psychological and physical burden on the subject. Moreover, the time for which the subject is constrained is long in the case of such methods, and the measurement precision is insufficient. For example, among conventional methods for measuring the gastric emptying rate, the isotope method (e. g., scintigraphy or the like) uses a radioactive isotope; as a result, the administration of this method is complicated. Furthermore, since this method requires an expensive γ-ray camera, the use of this method is restricted to special facilities. Furthermore, in the case of the X-ray impermeable marker method, the marker is not discharged from the stomach simultaneously with the food contents, but is instead discharged from the stomach after all of the food contents have bee discharged; as a result, the actual gastric emptying ability cannot be accurately examined. Furthermore, in the case of the acetaminophen method, there is a danger of drug allergy and liver damage due to the side effects

of acetaminophen; furthermore, since this drug is subject to other effects in the body such as absorption in the small intestine, metabolization by the liver, excretion from the kidneys and the like, the stomach eliminative function cannot be accurately examined. Furthermore, since the concentration of acetaminophen in the blood is measured after a fixed period time has elapsed, the invasive procedure of blood collection is required.

Furthermore, methods such as a method in which the stomach volume and stomach contents are measured by means of ultrasonic waves (ultrasound method), a method in which the gastric emptying rate is measured by MRI (magnetic resonance imaging method), a method in which the motor function of the stomach is evaluated by measuring an electrogastrogram (elctrogastrography) and the like have also been proposed as other methods for measuring the gastric emptying rate; however, such methods suffer from the following problems: (i) There are problems in the precision of the diagnostic method, (ii) there are no fixed criteria, so that evaluations vary according to the evaluator, and (iii) the subject must be constrained for a long period of time while the diagnosis is being made.

DISCLOSURE OF THE INVENTION

It is an object of the present invention to provide preparations that allow the easy and noninvasive measurement of the gastric emptying ability. More concretely, it is an object of the present invention to provide preparations that allow the measurement and evaluation of the gastric emptying ability using respiration. Furthermore, it is also an object of the present invention to provide a simple method for measuring the gastric emptying rate using the abovementioned preparations. Moreover, it is also an object of the present invention to provide a method for diagnosing and evaluating the eliminative function (motor function) of the stomach in examined subjects, and a method for evaluating the pharmacological effects and therapeutic effects of drugs relating to the motor function of the stomach in individual subjects, utilizing the abovementioned method for measuring the gastric emptying rate.

Generally, when food is consumed and enters the stomach, this food is gradually physically pulverized into small particles as a result of being subjected to the effects of acids and enzymes, and as a result of being subjected to the effects of muscular contractions of the stomach wall. Then, at the point in time at which

the food has been converted into particle with a size of approximately 1 to 2 mm, this food is transferred into the intestines via the pylorus. The present inventors focused on the mechanism of digestion and evacuation in the stomach, and conducted diligent research in an effort to fine a method for the simple measurement of the gastric emptying ability. As a result, the present inventors discovered that in the case of preparations which are prepared so that these preparations are gradually disintegrated and dissolved inside the stomach, there is a fixed correspondence between the elution behavior of the components of the preparation inside the stomach and the gastric emptying ability (motor activity of the stomach). On the basis of this finding, the present inventors confirmed that the gastric emptying rate can easily be measuring the elution behavior of this slow-release preparation that is disintegrated and released [in the stomach]. Furthermore, the present inventors confirmed that if a compound that is eliminated in the exhalation as carbon dioxide gas following metabolization is labeled and used in the preparation of the abovementioned slow-release preparation that is disintegrated and released, the gastric emptying ability can be measured in a noninvasive manner from the exhalation behavior of carbon dioxide.

The first preparation of the present invention (hereafter referred to as a stomach-soluble type preparation) was perfected on the basis of such findings. Specifically, the first preparation of the present invention (stomach-soluble type preparation) is a preparation for measuring the gastric emptying rate as described in items 1 through 9 below:

Item 1. A preparation for measuring the gastric emptying rate comprising a composition containing a compound (labeled compound) that is labeled with either an isotope of C or O, or with isotopes of both, and that is converted into labeled CO_2 in the body and eliminated in the exhalation, this preparation being characterized in that the preparation is prepared as a slow-release preparation that is disintegrated and released.

Item 2. The preparation for measuring the gastric emptying rate according to item 1, wherein the behavior of the preparation following oral administration to the subject is such that (i) the preparation remains inside the stomach for a certain period of time after entering the stomach, without being immediately discharged from the stomach, (ii) the surface of the preparation is gradually eroded by the muscular contractions of the stomach wall so that the preparation is disintegrated, and as this erosion and disintegration occurs, the

labeled compound is gradually eluted into the stomach, and (iii) the eluted labeled compound is then converted into labeled carbon dioxide gas inside the stomach, and is eliminated in the exhalation, or is eliminated in the exhalation as labeled carbon dioxide gas following absorption and metabolization.

Item 3. The preparation for measuring the gastric emptying rate according to item 1 or item 2, wherein the preparation can expand to a size which is such that the preparation does not pass through the pylorus for a certain period of time following oral administration.

Item 4. The preparation for measuring the gastric emptying rate according to any of items 1 through 3, which is characterized in that the preparation contains a disintegration inhibiting agent in addition to a labeled compound.

Item 5. The preparation for measuring the gastric emptying rate according to item 4, wherein the disintegration inhibiting agent consists of at least one substance selected from a group consisting of water-soluble high polymers, fats and sugars.

Item 6. The preparation for measuring the gastric emptying rate according to item 4 or item 5, wherein the disintegration inhibiting agent consists of at least one substance selected from a group consisting of

hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose, cellulose acetate phthalate, hardened oils, carnauba wax, sugars and sugar alcohols.

Item 7. The preparation for measuring the gastric emptying rate according to any of items 1 through 6, wherein the isotope consists of at least one isotope selected from a group consisting of ^{13}C, ^{14}C and ^{18}O.

Item 8. The preparation for measuring the gastric emptying rate according to any of items 1 through 7, wherein the labeled compound consists of at least one compound selected from a group consisting of alkali metal, alkaline earth metal and ammonium carbonates and hydrogencarbonates.

Item 9. The preparation for measuring the gastric emptying rate according to any of items 1 through 8, wherein the labeled compound consists of at least one compound selected from a group consisting of acetic acid, glycine, octanoic acid and alkali metal salts thereof.

Furthermore, these preparations have a preparation configuration for oral administration such as tablets, capsules, pills, powders, granules or the like.

As a result of further research based on the abovementioned findings, the present inventors discovered that if a labeled compound that generates carbon dioxide gas as result of dissolution or a metabolic reaction is

prepared as a preparation that dissolves in the intestines, this preparation will dissolve or be subjected to further metabolization in the intestines, so that the preparation is eliminated in the exhalation as labeled carbon dioxide gas. The inventors also discovered that the gastric emptying ability can be measured noninvasively by tracking the behavior of this labeled carbon dioxide gas, and that as a result, the gastric emptying rate can easily be evaluated. Furthermore, two types of gastric and intestinal motor patterns are generally known in humans and animals, i. e., a fasting mode pattern and an ingestion mode pattern; however, the present inventors confirmed that the gastric emptying rate can be measured in accordance with these various motor modes by appropriately devising the size of the abovementioned preparation that dissolves in the intestines.

The second preparation of the present invention (hereafter referred to as an intestine-soluble type preparation) was perfected on the basis of such findings. Specifically, the second preparation of the present invention (intestine-soluble type preparation) is a preparation for measuring the gastric emptying rate as described in items 10 through 15 below:

Item 10. A preparation for measuring the gastric emptying rate in which a composition containing a compound (labeled compound) that is labeled with either an isotope of C or O, or with isotopes of both, and that is converted into labeled CO_2 in the body and eliminated in the exhalation, is covered by a material that dissolves in the intestines.

Item 11. The preparation for measuring the gastric emptying rate according to item 10, wherein the behavior of the preparation following oral administration to the subject is such that (1) the preparation remains inside the stomach for a certain period of time after entering the stomach, without being discharged from the stomach, (2) the preparation is discharged from the stomach by the housekeeper eliminating movement of the stomach, and (3) the preparation is then dissolved in the intestines, and the labeled compound eluted from the interior of the preparation is converted into labeled carbon dioxide gas inside the intestines, and is eliminated in the exhalation, or is eliminated in the exhalation as labeled carbon dioxide gas following absorption and metabolization.

Item 12. The preparation for measuring the gastric emptying rate according to item 10, wherein the behavior of the preparation following oral administration to the

subject is such that (1) the preparation enters the stomach, (2) the preparation is discharged from the stomach accompanying the eliminative movement of food, and (3) the preparation is then dissolved in the intestines, and the labeled compound eluted from the interior of the preparation is converted into labeled carbon dioxide gas inside the intestines, and is eliminated in the exhalation, or is eliminated in the exhalation as labeled carbon dioxide gas following absorption and metabolization.

Item 13. The preparation for measuring the gastric emptying rate according to any of items 10 through 12, wherein the isotope consists of at least one isotope selected from a group consisting of ^{13}C, ^{14}C and ^{18}O.

Item 14. The preparation for measuring the gastric emptying rate according to any of items 10 through 13, wherein the labeled compound consists of at least one compound selected from a group consisting of alkali metal, alkaline earth metal and ammonium carbonates and hydrogencarbonates.

Item 15. The preparation for measuring the gastric emptying rate according to any of items 10 through 14, wherein the labeled compound consists of at least one compound selected from a group consisting of acetic acid, glycine, octanoic acid and alkali metal salts thereof.

Furthermore, the abovementioned preparation can be prepared in a preparation configuration for oral administration such as tablets, capsules, pills, powders, granules or the like.

Furthermore, the present invention provides a method for measuring the gastric emptying rate using at least one preparation for measuring the gastric emptying rate, i. e., either the first preparation or second preparation described above. In concrete terms, this method can be performed (for example) by orally administering any of the stomach-soluble type preparations described in the abovementioned items 1 through 9 or intestine-soluble type preparations described in the abovementioned items 10 through 15 to the subject, and then measuring the behavior of the labeled compound in the body, or measuring the amount or behavior of the labeled compound that is eliminated from the body. Preferably, this involves measurement of the amount or behavior of labeled CO_2 that is eliminated in the exhalation.

The gastric emptying rate of the subject can be evaluated by utilizing such a method. Accordingly, the present invention [also] provides a diagnostic evaluation method for the gastric emptying rate of humans or animals. In concrete terms, this method can be performed (for example) by orally administering any of the stomach-

soluble type preparations described in the abovementioned items 1 through 9 or intestine-soluble type preparations described in the abovementioned items 10 through 15 to a subject for whom a reduction or acceleration of the gastric emptying rate is suspected, and then comparing the behavior of the labeled compound inside the body after a specified [period of time], or the amount or behavior of the labeled compound that is eliminated from the body, with the behavior of the labeled compound inside the body or amount or behavior of the labeled compound eliminated from the body that is obtained for a healthy subject using the same preparation for measuring the gastric emptying rate. Preferably, the method is performed by comparing the amount or behavior of labeled CO_2 that is eliminated in the exhalation for the abovementioned healthy subject and subject in which a reduction or acceleration of the gastric emptying rate is suspected. Furthermore, the evaluation of the abovementioned gastric emptying rate can be performed more accurately by using two separate preparations, i. e., a stomach-soluble type preparation and an intestine-soluble type preparation, in combination.

Furthermore, in the case of drugs relating to the motor function of the stomach, the pharmacological effect or therapeutic effect on individual subjects can be

evaluated by utilizing the abovementioned method. Accordingly, the present invention [also] relates to a method for evaluating the pharmacological effect or therapeutic effect of drugs relating to the motor function of the stomach. In concrete terms, this method can be performed by orally administering any of the stomach-soluble type preparations described in the abovementioned items 1 through 9 or intestine-soluble type preparations described in the abovementioned items 10 through 15 to the subject before and after the administration of a drug relating to the motor function of the stomach, measuring the behavior of the labeled compound inside the body after a specified [period of time] or the amount or behavior of the labeled compound eliminated from the body in each case, and comparing the results obtained before the administration of the abovementioned drug with the results obtained after the administration of the drug. Preferably, the method of the present invention is performed by comparing the amount or behavior of labeled CO_2 eliminated in the exhalation prior to the administration of the abovementioned drug with the amount of behavior of labeled CO_2 eliminated in the exhalation following the administration of the abovementioned drug. Furthermore, the evaluation of the pharmacological effect or

therapeutic effect of the abovementioned drug can be performed more accurately by using two separate preparations, i. e., a stomach-soluble type preparation and an intestine-soluble type preparation, in combination.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph which shows the elution behavior (solubility) obtained in a case where the slow-release tablets of Example 6 (stomach-soluble type tablets, 10 tablets) were tested alone in a test solution (pH 4.8) in Test Example 1 (Japan Pharmacopoeia (13^{th} Ed.), paddle method). The horizontal axis indicates the dissolution time (minutes), while the vertical axis indicates the solubility (%) of the tablets. The open circles indicate a case in which the paddle rpm was set at 75 rpm, and the closed circles indicate a case in which the paddled rpm as set at 200 rpm (the same is true in Figs. 2 and 3 below).

Fig. 2 is a graph which shows the elution behavior (solubility) obtained in a case where the slow-release tablets of Example 6 (stomach-soluble type tablets, 10 tablets) were tested in a test solution (pH 4.8) together with 100 g of beads in Test Example 1 (Japan Pharmacopoeia (13^{th} Ed.), paddle method).

Fig. 3 is a graph which shows the elution behavior (solubility) obtained in a case where the slow-release

tablets of Example 6 (stomach-soluble type tablets, 10 tablets) were tested in a test solution (pH 4.8) together with 200 g of beads in Test Example 1 (Japan Pharmacopoeia (13^{th} Ed.), paddle method).

Fig. 4 is a graph which shows the results obtained in Test Example 2. Specifically, this graph shows the average respiratory elimination pattern for four beagle dogs that were given the capsule-enclosed intestine-soluble granules of the present invention (closed triangles) or an aqueous solution of sodium hydrogen carbonate ($NaH^{13}CO_3$ solution) (closed squares), with the time elapsed following administration being shown in the horizontal axis and the Δ value (‰) being shown on the vertical axis. Furthermore, the closed diamond symbols indicate the respiratory elimination pattern obtained in a case where beagle dogs treated in advance with an anti-choline agent (propantheline) (stomach elimination retardation model) were given the capsule-enclosed intestine-soluble granules of the present invention.

BEST MODE FOR CARRYING OUT THE INVENTION

(1) First Preparation (Stomach-Soluble Type Preparation)

The first preparation of the present invention is a composition containing a compound which is labeled with an isotope of C or O, or with both isotopes, and which is converted into labeled CO_2 in the body and eliminated in

the exhalation; this preparation is a preparation used to measure the gastric emptying rate, which is prepared in the form of a slow-release preparation of the type that is disintegrated and released in the stomach.

There are no particular restrictions on the compound labeled with an isotope of C or O or isotopes of both that is used in the abovementioned preparation for measuring the gastric emptying rate, as long as this compound is dissolved inside the stomach following oral administration, and is subsequently disintegrated or metabolized (in some cases), and eliminated in the exhalation or body fluids (urine, blood, sputum, perspiration or the like).

A desirable example of such a compound is a compound which is converted into carbonate ions (CO_3^{-2}), hydrogencarbonate ions (HCO_3^{-1}) or carbon dioxide gas (CO_2) after being dissolved in the stomach, and after being subsequently disintegrated or metabolized in some cases, and which appears as carbon dioxide gas in the exhalation.

Compounds which dissolve and generate carbonate ions or hydrogencarbonate ions may be broadly cited as examples of compounds that quickly appear as carbon dioxide gas in the exhalation following dissolution; examples of such compounds include alkali metal carbonates such as sodium carbonate, potassium carbonate

and the like, alkaline earth metal carbonates such as calcium carbonate, magnesium carbonate and the like, ammonium carbonate, alkali metal hydrogencarbonates such as potassium hydrogencarbonate, sodium hydrogencarbonate and the like, and ammonium hydrogencarbonate. Furthermore, especially if these compounds are used in combination with acidic compounds such as citric acid, tartaric acid, malic acid or the like, the compounds will quickly appear in the exhalation as carbon dioxide gas. Especially desirable for use are sodium carbonate, potassium carbonate, sodium hydrogencarbonate and potassium hydrogencarbonate.

Furthermore, amino acids, proteins, organic acids or salts thereof (e. g., alkali metal salts such as Na salts or the like), sugars, fats and the like may be cited as examples of compounds that appear as carbon dioxide gas in the exhalation after being dissolved inside the stomach and subsequently disintegrated or metabolized. After being digested and absorbed, all of these substances generate carbon dioxide gas in the exhalation as a result of liver metabolism. Here, examples of amino acids that can be used include glycine, phenylalanine, tryptophan, methionine, valine, histidine and the like; examples of organic acids that can be used include acetic acid, lactic acid, pyruvic acid, butyric acid, octanoic

acid, propionic acid and alkali metal salts of these acids; examples of sugars that can be used include glucose, galactose, xylose, lactose and the like; and examples of fats that can be used include medium-chain triglycerides such as trioctanoin or the like. However, the present invention is not limited to these compounds. Examples of compounds that are especially desirable for use include amino acids such as glycine or the like, organic acids such as acetic acid, octanoic acid or the like, and alkali metal salts of such organic acids (sodium salts or potassium salts).

Concrete examples of isotopes that can be used to label such compounds include ^{13}C, ^{14}C and ^{18}O. Such isotopes may be radioactive or non-radioactive; however, from the standpoint of safety, non-radioactive isotopes are preferable. In particular, ^{13}C is especially desirable for use as such an isotope.

There are no particular restrictions on the labeling method using these isotopes; commonly used methods may be widely employed. Furthermore, compounds which are universally known as labeled compounds that are labeled with these isotopes, and compounds that are commercially available, may be widely used (see Sasaki, "5.1 Use of Stable Isotopes in Clinical Diagnoses"; Kagaku no Ryoiki 107, "Use of Stable Isotopes in Medicine, Pharmacology

and Biology", pp. 149-163 (1975) Nankodo; Kajiwara, RADIOISOTOPES, 41, 45-48 (1992) and the like).

The preparation of the present invention used to measure the gastric emptying rate (stomach-soluble type preparation) is characterized in that this preparation is a solid disintegration and release type slow-release preparation used for oral administration, which consists of the abovementioned isotope-labeled compound or a composition containing this compound.

A disintegration and release type slow-release preparation is a preparation in which the release of the labeled compound containing the abovementioned isotope (constituting the active ingredient of the preparation of the present invention) from the preparation is controlled by the disintegration characteristics of the preparation; this term is used in a sense that includes preparations in which the abovementioned labeled compound is gradually and continuously released and eluted as the preparation breaks down. In cases where such a disintegration and release type slow-release preparation is orally administered, the surface of the preparation is gradually erodes by the movement of the muscular contractions of the stomach wall so that the preparation is disintegrated, and as this erosive disintegration occurs, the active

ingredient contained in the preparation, i. e., the labeled compound, is gradually released into the stomach.

Such disintegration and release type slow-release preparations may include (for example) preparations that show zero-order release behavior in elution tests stipulated by the Japan Pharmacopoeia, as well as preparations that show zero-order release behavior in the case of in vivo elution inside the stomach following oral administration.

It is desirable that the preparation of the present invention be a preparation which remains in the stomach for a certain period of time after entering the stomach (without being immediately discharged from the stomach), and in which the surface of the preparation is gradually eroded and disintegrated by the movement of the muscular contractions of the stomach wall, so that the labeled compound containing the abovementioned isotope is gradually eluted into the stomach as the abovementioned erosive disintegration occurs. Furthermore, as was described above, the labeled compound that is eluted inside the stomach may be immediately converted into labeled carbon dioxide gas inside the stomach, or may be eliminated in the exhalation as labeled carbon dioxide after being absorbed and metabolized by the intestines or liver, depending on the type of compound that is used.

It is sufficient if the stomach-soluble type preparation of the present invention is a preparation that shows the abovementioned disintegration and elution behavior; as long as these conditions are satisfied, there are no restrictions on the configuration of the preparation, components other than the labeled compound, proportions at which the respective components are mixed, or method used to prepare the preparation. Examples of preparation configurations and components other than the labeled compound that may be used are indicated below; however, the stomach-soluble type preparation of the present invention is not limited in any way by these examples.

A preparation with a particle diameter which is such that the preparation will not pass through the pylorus of the stomach, e. g., a particle diameter greater than 1 to 2 mm, may be cited as an example of a preparation that is not immediately discharged form the stomach after entering the stomach. In concrete terms, a preparation with a particle diameter of 5 to 10 mm (and in some cases 2 to 30 mm) can ordinarily be used. However, the present invention is not limited to this particle size range. For example, even a preparation which has a particle size that is smaller than 1 to 2 mm at the time of administration may be used if this preparation absorbs

moisture such as body fluids or the like inside the stomach and thus expands or swells to a size that will not pass through the pylorus of the stomach. Such a preparation can be prepared so that the preparation contains a substance that has the effect of absorbing moisture and swelling in addition to the labeled compound. Examples of such swelling substances include gelatin, hydrogel and reaction products of gelatin and N-acetyl-homocysteinethiolactone or the like; all substances of this type that are universally known in the art may be used. Such swelling substances may be used singly, or may be used in combinations consisting of two or more substances.

In order to prepare a preparation that shows zero-order elution behavior, e. g., a preparation in which the surface of the preparation is gradually eroded and disintegrated by the movement of the muscular contractions of the stomach wall, it is desirable to add a disintegration inhibiting agent to the preparation in addition to the labeled compound.

Examples of disintegration inhibiting agents that can be used include all agents of this type that are universally known in the art. For example, water-soluble high polymers that are generally known as disintegration inhibiting agents may be widely used. Concrete examples

of such water-soluble high polymers include water-soluble high polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose, cellulose acetate phthalate and the like; methyl methacrylate - butyl methacrylate - dimethylaminoethyl methacrylate copolymers such as aminoacryl methacrylate copolymer E (commercial name: Oidragit E100, manufactured by Ream Pharma); the acid-soluble high polymer known as polyvinylacetyl diethylacetate (commercial name: AEA, manufactured by Sankyo; acrylic acid copolymers or methacrylic acid copolymers such as hydroxypropylmethylcellulose phthalate (commercial names: HP-55, HP-50, manufactured by Shin'etsu Kagaku), methacrylic acid - methyl methacrylate copolymers (commercial name: Oidragit S100, manufactured by Ream Pharma) or the like; and weak-alkali-soluble high polymers such as hydroxypropylmethylcellulose acetate succinate (commercial name: AQOAT, manufactured by Shin'etsu Kagaku), carboxymethylethylcellulose, cellulose acetate phthalate and the like. These water-soluble high polymers may be used singly, or may be used in arbitrary combinations consisting of two or more polymers. Hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose and cellulose acetate phthalate are desirable for use, and hydroxypropylcellulose and

hydroxypropylmethylcellulose are especially desirable for use.

Furthermore, fats may be cited as examples of disintegration inhibiting agents. Concrete examples of such fats include esters (glycerides) of glycerol with fatty acids such as stearic acid, palmitic acid or the like; cocoa butter, hydrogenated oils, hardened oils, carnauba wax and the like. Furthermore, sugars may also be cited as examples of disintegration inhibiting agents. Examples of such sugars include sugars such as sucrose, white sugar, corn syrup and the like, and sugar alcohols such as sorbitol, mannitol and the like. These disintegration inhibiting agents may be used singly, or may be used in arbitrary combinations consisting of two or more agents.

There are no particular restrictions on the amount of disintegration inhibiting agent that is contained in the stomach-soluble type preparation of the present invention, as long as the effect of the present invention can be manifested. For example, in cases where a water-soluble high polymer is used, it is ordinarily desirable that the amount of disintegration inhibiting agent used be in the range of 10 to 90 parts by weight per 100 parts by weight of the stomach-soluble type preparation, and this amount is preferably in the range of 20 to 80 parts

by weight. Furthermore, in cases where a fat is used, it is ordinarily desirable that that the amount of disintegration inhibiting agent used be in the range of 1 to 90 parts by weight per 100 parts by weight of the stomach-soluble type preparation, and this amount is preferably in the range of 2 to 60 parts by weight, and in cases where a sugar is used, it is ordinarily desirable that the amount of disintegration inhibiting agent used be in the range of 50 to 99 parts by weight per 100 parts by weight of the stomach-soluble type preparation, and this amount is preferably in the range of 80 to 99 parts by weight.

There are no particular restrictions on the configuration of the stomach-soluble type preparation of the present invention, as long as this preparation is solid. For example, the preparation may take the form of tablets, pills, stomach-soluble capsules, a granular agent, a powdered agent or the like. Furthermore, in cases where granular agents and powdered agents are used, it is desirable to construct the agent so that the agent swells by absorbing moisture inside the stomach, and thus is not immediately dissolved or discharged from the stomach, but is instead gradually dissolved and disintegrated (from the swollen surfaces thus formed) by the contractile motion of the stomach wall.

Furthermore, the same is true in the case of stomach-soluble capsules filled with granules or a powder. Tablets or pills may be uncoated; alternatively, the surfaces of such agents may be covered by a stomach-soluble coating agent.

In the stomach-soluble type preparation of the present invention, all types of carriers and additives ordinarily used in the art may be added as other components in accordance with the configuration of the preparation, as long as these substances cause no loss of the action or effect of the present invention. For example, the preparation of the present invention may be a composition prepared by adding excipients such as lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid or the like; binders such as simple syrup, liquid glucose, liquid starch, gelatin solution, carboxymethylcellulose, shellac, methylcellulose, potassium phosphate, polyvinylpyrrolidone or the like; disintegration agents such as dried starch, sodium alginate, powdered agar, powdered laminaran, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearic acid monoglycerides, starch, lactose and the like; absorption-promoting agents such as quaternary ammonium bases, sodium laurylsulfate and

the like; moisturizers such as glycerol, starch and the like; lubricating agents such as refined talc, stearates, powdered boric acid, polyethylene glycol and the like; and other additives (e. g., odor improving agents, flavoring agents, sweeteners, stabilizing agents and the like).

The stomach-soluble type preparation for measuring the gastric emptying rate provided by the present invention is ordinarily administered to the subject together with water, and acts as follows in accordance with the type of labeled compound that is used.

For example, in cases where the labeled compound is $NaH^{13}CO_3$, which quickly appears as labeled carbon dioxide gas in the exhalation following dissolution inside the stomach, the administered preparation is rubbed by the stomach wall as a result of the contractile movement of the stomach, so that the surface of the preparation is scraped away and the agent is physically pulverized, thus gradually reducing the size of the preparation until the preparation is finally discharged from the pylorus. As the tablet agent is reduced in size, the isotope-labeled compound $NaH^{13}CO_3$ is successively eluted from the tablet agent, and as this compound is eluted, labeled carbon dioxide gas $^{13}CO_2$ is successively eliminated in the exhalation. The elimination behavior of the $^{13}CO_2$ in the

exhalation in cases where the stomach-soluble type preparation of the present invention is administered (in concrete terms, this behavior is indicated by the ratio of $^{13}CO_2$ to carbon dioxide gas $^{12}CO_2$ eliminated in the exhalation, i. e.,[$^{13}CO_2/^{12}CO_2$]) is characterized by the following: specifically, on the basis of the elution characteristics that are peculiar to this preparation, the rise of the $^{13}CO_2$ elimination rate (initial rate) is significantly slower than in a case where a solution of $NaH^{13}CO_3$ is administered, and this rate shows a substantially steady state (plateau state) for a certain period of time after a specified period of time has elapsed.

For example, the amount of $^{13}CO_2$ that is present for a specified time in such a plateau state, the Δ(‰) value of the carbon dioxide gas (i. e., the difference in the $^{13}CO_2/^{12}CO_2$ concentration ratio (δ ^{13}C value) in the exhalation found in respective exhalation samples collected before and after the administration of the preparation) or the initial rate [of elimination] can be used as an indicator of the gastric emptying rate. For example, if the carbon dioxide gas Δ(‰) value or initial rate for a healthy subject is used as a standard, then a diagnosis of a drop in the gastric emptying ability can

be made in cases where a subject shows a lower carbon dioxide gas Δ(‰) value or initial rate.

Furthermore, in cases where the labeled compound is an organic acid such as acetic acid or the like or an amino acid such as glycine or the like, this compound appears as labeled carbon dioxide gas after being dissolved inside the stomach, absorbed in the intestines and metabolized by the liver; accordingly, detection is slower than in the case described above. However, since the rate is governed by the dissolution stage of the tablets inside the stomach, elimination behavior similar to that of the abovementioned compounds such as $NaH^{13}CO_3$ and the like is shown.

Furthermore, in regard to the administration of the preparation of the present invention for measuring the gastric emptying rate, this preparation for measuring the gastric emptying rate may be administered alone, or may be administered together with test food, or immediately before or after the ingestion of test food. A desirable method is a method in which the preparation of the present invention for measuring the gastric emptying rate is administered immediately after the ingestion of test food.

There are no particular restrictions on the test food used here, as long as the food does not interfere

with the action and effect of the preparation of the present invention in measuring the gastric emptying rate. Furthermore, either solid food, fluid food or liquid food may be used; however, solid food is preferable.

(2) Second Preparation (Intestine-Soluble Type Preparation)

The second preparation of the present invention is a preparation for measuring the gastric emptying rate (intestine-soluble type preparation) in which a composition containing a compound that is labeled with either an isotope of C or O, or with isotopes of both, and that is converted into labeled CO_2 in the body and eliminated in the exhalation, is covered by a base agent that dissolves in the intestines.

There are no particular restrictions on the compound labeled with an isotope of C or O or isotopes of both that is used in the abovementioned preparation for measuring the gastric emptying rate, as long as this compound is dissolved inside the stomach following oral administration, and is subsequently disintegrated or metabolized (in some cases), and eliminated in the exhalation or body fluids (urine, blood, sputum, perspiration or the like).

A desirable example of such a compound is a compound which is converted into carbonate ions (CO_3^{-2}),

hydrogencarbonate ions (HCO_3^{-1}) or carbon dioxide gas (CO_2) after being dissolved in the stomach, and after being subsequently disintegrated or metabolized in some cases, and which appears as carbon dioxide gas in the exhalation.

Compounds which dissolve and generate carbonate ions or hydrogencarbonate ions may be broadly cited as examples of compounds that quickly appear as carbon dioxide gas in the exhalation following dissolution; examples of such compounds include alkali metal carbonates such as sodium carbonate, potassium carbonate and the like, alkaline earth metal carbonates such as calcium carbonate, magnesium carbonate and the like, ammonium carbonate, alkali metal hydrogencarbonates such as potassium hydrogencarbonate, sodium hydrogencarbonate and the like, and ammonium hydrogencarbonate. Among these compounds, more preferable are sodium carbonate, potassium carbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate.

Furthermore, these compounds may be used in combination with acidic compounds such as citric acid, tartaric acid, malic acid and the like. In concrete terms, it is possible to hasten the appearance of carbon dioxide gas in the exhalation following oral administration by preparing the abovementioned labeled compound with an acidic compound. Furthermore, it is

possible to measure the gastric emptying rate with good precision, without affecting the acidity of the stomach of the subject even in cases where the subject tends to hypoacidity, by using an acidic compound as a separately administered preparation in combination with an intestine-soluble agent containing the abovementioned labeled compound.

Furthermore, amino acids, proteins, organic acids or salts thereof (e. g., alkali metal salts such as Na salts or the like), sugars, fats and the like may be cited as examples of compounds that appear as carbon dioxide gas in the exhalation after being dissolved inside the stomach and subsequently disintegrated or metabolized. After being digested and absorbed, all of these substances generate carbon dioxide gas in the exhalation as a result of liver metabolism. Here, examples of amino acids that can be used include glycine, phenylalanine, tryptophan, methionine, valine, histidine and the like; examples of organic acids that can be used include acetic acid, lactic acid, pyruvic acid, butyric acid, octanoic acid, propionic acid and alkali metal salts of these acids; examples of sugars that can be used include glucose, galactose, xylose, lactose and the like; and examples of fats that can be used include medium-chain triglycerides such as trioctanoin or the like. However,

the present invention is not limited to these compounds. Examples of compounds that are especially desirable for use include amino acids such as glycine or the like, organic acids such as acetic acid, octanoic acid or the like, and alkali metal salts of such organic acids (sodium salts or potassium salts).

Concrete examples of isotopes that can be used to label such compounds include ^{13}C, ^{14}C and ^{18}O. Such isotopes may be radioactive or non-radioactive; however, from the standpoint of safety, non-radioactive isotopes are preferable. In particular, ^{13}C is especially desirable for use as such an isotope.

The abovementioned labeled compound that is contained in the interior of the preparation of the present invention may be prepared by itself; alternatively, this preparation may be prepared as a composition by adding any desired type of carriers or additives ordinarily used in this field as other components in accordance with the configuration of the preparation. Examples of such other components that can be used include excipients such as lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid or the like; binders such as simple syrup, liquid glucose, liquid starch, gelatin solution, carboxymethylcellulose, shellac,

methylcellulose, potassium phosphate, polyvinylpyrrolidone or the like; disintegration agents such as dried starch, sodium alginate, powdered agar, powdered laminaran, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearic acid monoglycerides, starch, lactose and the like; absorption-promoting agents such as quaternary ammonium bases, sodium laurylsulfate and the like; moisturizers such as glycerol, starch and the like; lubricating agents such as refined talc, stearates, powdered boric acid, polyethylene glycol and the like; and other additives (e.g., odor improving agents, flavoring agents, sweeteners, stabilizing agents and the like).

The intestine-soluble type preparation of the present invention for measuring the gastric emptying rate is prepared by covering the abovementioned labeled compound or a composition containing this compound with an intestine-soluble base agent.

There are no particular restrictions on the form of the abovementioned coating, as long as this coating is designed so that the coating does not dissolve inside the stomach when the preparation of the present invention is orally administered, and so that the base agent dissolves in accordance with the pH inside the intestines after the preparation is discharged from the stomach, with the

abovementioned isotope-labeled compound contained inside being dissolved at the same time as the dissolution of this coating or following the dissolution of the coating. Examples of such coating forms include film-coated agents in which the surface of the labeled compound or composition containing the labeled compound prepared in any of various forms such as powders, granules, tablets, pills or the like is coated with an intestine-soluble base agent, and capsule in which a liquid-form (including emulsions and the like), powder-form or granular labeled compound or composition containing such a compound is contained inside a capsule formed from an intestine-soluble base agent. Furthermore, these coating treatments can be accomplished using ordinary methods.

The term "intestine-soluble base agent" used in the present invention refers to a base agent that dissolves under the weakly acidic to weakly alkaline conditions seen in the pH inside the intestines (more concretely, in a pH range of 4 to 8, and preferably in a pH range of 5 to 7). In concrete terms, examples of such base agents include acrylic acid copolymers or methacrylic acid copolymers such as hydroxypropylmethylcellulose phthalate (commercial names: HP-55, HP-50, manufactured by Shin'etsu Kagaku), methacrylic acid - methyl methacrylate copolymers (commercial name: Oidragit S100, manufactured

by Ream Pharma) or the like; and intestine-soluble high polymers such as hydroxypropylmethylcellulose acetate succinate (commercial name: AQOAT, manufactured by Shin'etsu Kagaku), carboxymethylethylcellulose, cellulose acetate phthalate and the like.

The intestine-soluble type preparation of the present invention can be appropriately designed and prepared in accordance with the manner of use of the preparation, the time of administration and the like.

For example, in cases where the gastric emptying rate is measured for fasting subjects, i. e., subjects with an empty stomach, it is desirable that the preparation be designed and prepared so that the final size of the preparation is a specified size or greater.

Here, the term "specified size" used in reference to the preparation refers to a size which is such that in cases where the preparation is orally administered, the pattern of the eliminative movement of the stomach is a pattern in which the preparation remains inside the stomach for a certain period of time without being immediately discharged from the stomach, and is only discharged from the stomach by the phase III eliminative wave in the fasting mode, i. e., the housekeeper wave.

There are no particular restrictions on the size of the preparation of the present invention, as long as the

preparation has a size which is such that the preparation substantially shows the abovementioned behavior in the stomach and intestines. In concrete terms, this includes a preparation with a mean size of approximately 0.1 mm or greater (in some cases approximately 0.5 mm or greater, in some cases approximately 1 mm or greater, and in some cases approximately 2 mm or greater). However, the present invention is not limited to such sizes. Furthermore, from the standpoint of practical use, a mean size of approximately 30 mm may be cited as an example of the upper limit of the preparation size; however, the present invention is not restricted to such a limit.

Furthermore, the intestine-soluble type preparation of the present invention is not limited to a preparation that already has a fixed size at the time of administration, but may also be a preparation which swells to a fixed size as a result of absorbing moisture such as body fluids or the like following administration.

As was described above, the intestine-soluble type preparation of the present invention is covered by an intestine-soluble base agent, so that the preparation does not dissolve or disintegration in the stomach. Accordingly, when a preparation having the abovementioned size is orally administered to a subject under fasting conditions, this preparation shows the following

behavior: specifically, in a fasting mode, after remaining inside the stomach for a certain period of time, the preparation is finally discharged into the intestines from the stomach by a strong contractile movement that pushes the stomach contents toward the pylorus as a result of the manifestation of the housekeeper eliminative movement. Once the preparation has been discharged into the intestines, the intestine-soluble base agent on the surface of the preparation is dissolved by the effects of the pH inside the intestines, so that the labeled compound inside the preparation begins to be eluted. Here, for example, the labeled compound contained in the preparation quickly appears as labeled carbon dioxide gas in the exhalation after being dissolved in the intestines. For example, in a case where the labeled compound is $NaH^{13}CO_3$, this labeled compound $NaH^{13}CO_3$ is eluted inside the intestines, and as this compound dissolves, labeled carbon dioxide gas $^{13}CO_2$ is successively eliminated in the exhalation.

The elimination behavior of the $^{13}CO_2$ in the exhalation (in concrete terms, this behavior is indicated by the ratio of $^{13}CO_2$ to carbon dioxide $^{12}CO_2$ eliminated in the exhalation, i. e.,$[^{13}CO_2/^{12}CO_2]$) ordinarily shows an abrupt rise in $^{13}CO_2$ elimination based on the gastric emptying pattern that is peculiar to the subject,

especially the phase III housekeeper eliminative pattern. The housekeeper wave that occurs under fasting conditions ordinarily appears periodically every 1 to 3 hours; however, in the case of subjects in which there is a drop in the gastric emptying rate, as in diabetic patients and the like, the appearance of this housekeeper wave may be delayed, weakened or completely absent. Accordingly, in the case intestine-soluble type preparation of the present invention, the presence or absence of any drop in gastric emptying ability can be evaluated by measuring the amount of $^{13}CO_2$ over time following oral administration, or more concretely the Δ(‰) value of he carbon dioxide gas (i. e., the difference between the $^{13}CO_2/^{12}CO_2$ concentration ratio (δ ^{13}C value) in the exhalation at the respective times of sample collection following administration and the δ ^{13}C value in the exhalation prior to administration).

Furthermore, in cases where the labeled compound is (for example) an organic acid such as acetic acid or the like or an amino acid such as glycine or the like, this compound appears as labeled carbon dioxide gas after being dissolved inside the intestine, absorbed in the intestines and metabolized by the liver. Accordingly, detection thereof (exhalation elimination of the labeled $^{13}CO_2$) is slower than in the case described above.

However, since the rate is governed by elimination from the stomach by the housekeeper wave, the presence or absence of a drop in the gastric emptying rate can be evaluated in the same manner as in the case of compounds such as the abovementioned $NaH^{13}CO_3$ or the like.

As was described above, the administration of the intestine-soluble type preparation of the present invention can be performed under fasting conditions by the administration of a preparation with a specified size alone; however, this preparation can also be administration together with food such as test food or the like, or immediately prior to or following the ingestion of test food.

Specifically, in the present invention, the gastric emptying rate can also be measured for subjects who have ingested food.

In this case, it is desirable that the preparation be designed and prepared so that the final size of the preparation is smaller than the abovementioned specified size. Here, the term "specified size" refers to a size which is such that in cases where the preparation is orally administered, the pattern of the eliminative movement of the stomach is a pattern in which the preparation is discharged from the stomach along with the eliminative movement of food after entering the stomach.

There are no particular restrictions on the size of the preparation of the present invention, as long as the preparation has a size which is such that the preparation substantially shows the abovementioned behavior in the stomach and intestines. In concrete terms, this includes a preparation with a mean size of approximately 5 mm or less (in some cases approximately 2 mm or less, in some cases approximately 1 mm or less, and in some cases approximately 0.5 mm or less). However, the present invention is not limited to such sizes.

Food that has entered the stomach is physically pulverized by contraction of the stomach so that this food is gradually reduced in size, and when the food has been reduced to a specified size, the food is discharged from the pylorus. In the case of the abovementioned intestine-soluble type preparation of the present invention, when the preparation is administered in an ingestion mode, the preparation remains inside the stomach for a certain period of time together with the food, and is then discharged into the intestines together with the food when the food has been reduced to a specified size. In the preparation that has been discharged into the intestines, the intestine-soluble base agent on the surface is dissolved by the effects of the pH in the intestines, so that the labeled compound is

eluted from the inside, and labeled carbon dioxide gas is successively eliminated in the exhalation, either immediately following the dissolution of the compound, or after metabolization of the compound in the body. In other words, the respiratory eliminative behavior of the labeled carbon dioxide gas of the intestine-soluble type preparation of the present invention reflects the stomach eliminative pattern (ingestion mode) that is peculiar to each subject in the ingestion mode; accordingly, the gastric emptying ability of the subject can be evaluated from such eliminative behavior of the carbon dioxide gas.

Here, there are no particular restrictions on the food that is ingested together with the preparation, as long as the food does not interfere with the action and effect of the preparation of the present invention in measuring the gastric emptying rate. Furthermore, either solid food, fluid food or liquid food may be used. Moreover, by appropriately selecting the food (test food) that is ingested together with the preparation, it is possible to investigate and confirm more detailed eliminative functions and motor mechanisms of the stomach.

(3) Method for Measuring the Gastric Emptying Rate

The present invention also provides a method for measuring the gastric emptying rate using the abovementioned preparations for measuring the gastric

emptying rate (stomach-soluble type preparation and intestine-soluble type preparation). Measurement of the gastric emptying rate can be accomplished by administering the preparation of the present invention for measuring the gastric emptying rate (stomach-soluble type preparation or intestine-soluble type preparation) containing the abovementioned labeled compound to living animals or humans, collecting the exhalation, urine, feces, blood or other body fluids, and preferably the exhalation, and investigating the behavior of the compound of the amount of the labeled substance that is eliminated in the collected samples.

For example, in cases where the exhalation is used as the collected sample and ^{13}C is used as the isotope, the gastric emptying rate can be measured by orally administering the preparation of the present invention for measuring the gastric emptying rate (stomach-soluble type preparation or intestine-soluble type preparation) to the subject, collecting samples of the exhalation over time, and measuring the behavior of the amount of $^{13}CO_2$ eliminated in the exhalation over time as the ratio of $^{13}CO_2/^{12}CO_2$ (δ ^{13}C value), according to ordinary ^{13}C exhalation examination methods.

In the case of the preparation of the present invention for measuring the gastric emptying rate, both

the stomach-soluble type preparation and intestine-soluble type preparation are unaffected by physiological factors such as absorption or metabolization in cases where a compound that dissolves and generates carbonate ions or hydrogencarbonate ions such as sodium hydrogencarbonate or the like is used as the labeled compound. Accordingly, measurements that directly reflect the movement of the stomach can be made; furthermore, physiological reactions (eliminative functions) can be investigated in greater detail by testing with the test food varied (e. g., by loading with fats or the like).

Furthermore, evaluation of the gastric emptying rate can be accurately performed with much greater precision by performing repeated administration of the stomach-soluble type preparation or intestine-soluble type preparation of the present invention instead of a single administration, or by performing such administration a multiple number of times under different conditions such as fasting conditions and ingestion conditions or the like. In addition, the gastric empty ability can be evaluated with a higher degree of precision by performing an evaluation that combines both the results obtained by measuring the gastric emptying rate using the stomach-soluble type preparation and the results obtained by

measuring the gastric emptying rate using the intestine-soluble type preparation.

The measurement and analysis of the labeled substance contained in the collected samples vary according to whether the isotope used is radioactive or non-radioactive; however, such analysis can be performed using commonly used analysis methods such as the liquid scintillation counter method, mass analysis method, infrared spectroscopic analysis method, light emission analysis method, magnetic resonance spectrum method or the like. From the standpoint of measurement precision, the infrared spectroscopic analysis method and mass analysis method are especially desirable.

The method used to administer the preparation of the present invention for measuring the gastric emptying rate (stomach-soluble type preparation or intestine-soluble type preparation) is as described above; however, there are no particular restrictions on this method.

The amount of labeled compound that is contained in an administration unit of the preparation of the present invention varies according to the sample being measured and the type of labeled compound used, and therefore cannot be set as a specific value. This amount can be appropriately adjusted and set on a case by case basis. For example, in both the first preparation and second

preparation, in cases where measurement is performed by a exhalation test using sodium hydrogencarbonate ($NaH^{13}CO_3$) as the labeled substance, it is desirable that the preparation contain 1 to 2000 mg, and preferably 10 to 200 mg, of sodium hydrogencarbonate ($NaH^{13}CO_3$) per unit administration. Furthermore, in cases where measurement is performed by a exhalation test using acetic acid ($CH_3{}^{13}COOH$) as the labeled compound, it is desirable that the preparation contain 1 to 200 mg, and preferably 10 to 200 mg, of acetic acid per unit administration.

A reduction or acceleration of the gastric emptying rate in the subject can be diagnosed and evaluated by utilizing the abovementioned method for measuring the gastric emptying rate. In concrete terms, such a diagnosis can be accomplished by comparing the behavior of the labeled compound in the body or the amount or behavior of the labeled compound eliminated from the body measured for a subject by the abovementioned method with a standard control (behavior of the labeled compound in the body or the amount or behavior of the labeled compound eliminated from the body measured for a healthy subject).

For example, the gastric emptying rate of a subject can be diagnosed and evaluated by administering the preparation of the present invention for measuring the

gastric emptying rate (stomach-soluble type preparation or intestine-soluble type preparation) to the subject, measuring the amount of labeled carbon dioxide gas ($^{13}CO_2$) that is eliminated in the exhalation following this administration, or the carbon dioxide gas Δ (‰) value (i. e., the difference between the δ ^{13}C value following administration of the preparation and the δ ^{13}C value prior to administration of the preparation), over time, and comparing this eliminative pattern with the eliminative pattern obtained for a standard control (healthy subject).

Furthermore, as was described above, the first preparation of the present invention, i. e., the stomach-soluble type preparation for measuring the gastric emptying rate, is characterized by the fact that the amount of labeled carbon dioxide gas ($^{13}CO_2$) or carbon dioxide gas Δ (‰) value maintains a plateau state after a fixed period of time has elapsed. Accordingly, in cases where the first preparation is used, the gastric emptying rate of the subject can also be diagnosed and evaluated using the method described below instead of the method described above. First, the gastric emptying rate of a healthy subject is measured beforehand as described above, and the resulting behavior over time is used as a standard control. Next, the same preparation for

measuring the gastric emptying rate is administered to a subject for whom a drop in the gastric emptying rate is suspected, such as a subject suffering from the non-specific complaint, and the amount of $^{13}CO_2$ in the exhalation or the carbon dioxide gas Δ (‰) value is measured at least one point in time positioned in the plateau state of the standard control. In this case, the presence or absence of a drop in the gastric emptying rate can be evaluated according to whether the carbon dioxide gas Δ(‰) value of the subject is higher or lower than the carbon dioxide gas Δ(‰) value of the standard control. Such a method is useful in that the gastric emptying rate can be simply evaluated by collecting a small number of exhalation samples without constraining the subject for a long period of time. Furthermore, the presence or absence of a drop in the gastric emptying rate can also be evaluated from the initial rate of $^{13}CO_2$ eliminated in the exhalation. If this method is used, the time for which the subject is constrained can be greatly shortened. In this case, it may be judged that there has been a drop in the gastric emptying rate in cases where the initial rate of $^{13}CO_2$ eliminated in the exhalation that is measured for the subject is slower than the initial rate of $^{13}CO_2$ measured for the standard control.

Furthermore, by using such a method for measuring the gastric emptying rate, it is possible to the pharmacological effects of drugs relating to the motor function of the stomach, and the therapeutic effects of such drugs on individual subjects. In concrete terms, such an evaluation can be performed by measuring the gastric emptying rate using the preparation of the present invention for measuring the gastric emptying rate before and after the administration of s drug relating to the motor function of the stomach to the subject, and comparing the respective results. In this way, the pharmacological effect of the abovementioned drug itself can be evaluated. Furthermore, the therapeutic effects of individual drugs on the subject can also be evaluated. As a result, this method can also be used as a means of selecting drugs that are suited to individual subjects. Furthermore, drugs having effects that forcibly adjust the peristaltic movement of the stomach in an accelerating or inhibitory manner, such as prokinetics, stomach motor function accelerating agents or stomach motor function inhibiting agents may be cited as examples of drugs relating to the motor function of the stomach.

Examples

The present invention will be described more thoroughly below in terms of examples and test examples.

However, the present invention is not limited in any way by these examples.

Example 1 Stomach-Soluble Type Preparation

Sodium hydrogencarbonate ($NaH^{13}CO_3$)	100 mg
Hydroxypropylcellulose (HPC-L, Shin'etsu Kagaku)	50 mg
Magnesium stearate	1 mg
Total	151 mg

A disintegration and release type slow-release tablet agent with a diameter of 10 mm was prepared using ordinary methods by mixing the abovementioned components. When this preparation was subjected to an in vitro elution test (according to the 13th revised Japan Pharmacopoeia), it was confirmed that the preparation showed zero-order release behavior.

Example 2 Stomach-Soluble Type Preparation

Sodium hydrogencarbonate ($NaH^{13}CO_3$)	100 mg
Lactose	40 mg
Hydroxypropylmethylcellulose	40 mg
Magnesium stearate	2 mg
Total	182 mg

A disintegration and release type slow-release tablet agent with a diameter of 10 mm was prepared using ordinary methods by mixing the abovementioned components.

Example 3 Stomach-Soluble Type Preparation

Sodium hydrogencarbonate ($NaH^{13}CO_3$)	100 mg
Lactose	40 mg
Hydroxypropylcellulose (HPC-L, Shin'etsu Kagaku)	40 mg
Magnesium stearate	2 mg
Total	182 mg

A disintegration and release type slow-release tablet agent with a diameter of 10 mm was prepared using ordinary methods by mixing the abovementioned components.

Example 4 Stomach-Soluble Type Preparation

Sodium hydrogencarbonate ($NaH^{13}CO_3$)	100 mg
Hydroxypropylcellulose (HPC-L, Shin'etsu Kagaku)	80 mg
Magnesium stearate	2 mg
Total	182 mg

A disintegration and release type slow-release tablet agent with a diameter of 10 mm was prepared using ordinary methods by mixing the abovementioned components.

Example 5 Stomach-Soluble Type Preparation

Sodium hydrogencarbonate ($NaH^{13}CO_3$)	100 mg
Lactose	20 mg
Hydroxypropylcellulose (HPC-L, Shin'etsu Kagaku)	60 mg
Magnesium stearate	2 mg
Total	182 mg

A disintegration and release type slow-release tablet agent with a diameter of 10 mm was prepared using ordinary methods by mixing the abovementioned components.

Example 6 Stomach-Soluble Type Preparation

Sodium hydrogencarbonate ($NaH^{13}CO_3$)	100 mg
Lactose	82 mg
Hardened oil (Lubri Wax-101, FREUND Sangyo)	16 mg
Magnesium stearate	2 mg
Total	200 mg

A disintegration and release type slow-release preparation with a diameter of 8 mm (thickness 2.5 mm, hardness 5 kp) was prepared by mixing the abovementioned components using an ordinary dry granulation method.

Example 7 Stomach-Soluble Type Preparation

Sodium hydrogencarbonate ($NaH^{13}CO_3$)	100 mg
Lactose	78 mg
Hardened oil (Lubri Wax-101, FREUND Sangyo)	20 mg
Purified water	40 mg
Magnesium stearate	2 mg
Final weight of tablet	200 mg

A disintegration and release type slow-release preparation with a diameter of 8 mm was prepared by mixing the abovementioned components using an kneading granulation method.

Example 8 Intestine-Soluble Type Preparation

<Core Components>

Sodium hydrogencarbonate ($NaH^{13}CO_3$)	100 mg
Refined white sugar (powdered)	150 mg

Corn starch	100 mg
Crystalline cellulose (Aviseru PH-301, Asahi Kasei)	100 mg
Caramelose calcium (ECG-5-5, Nichirin Kagaku)	50 mg
Hydroxypropylcellulose (HPC-L, Shin'etsu Kagaku)	7.5 mg
Purified water	75 mg
Anhydrous ethanol	67.5 mg
Total solid content	507.5 mg

<Intestine-Soluble Coating Liquid Components>

Hydroxypropylmethylcellulose phthalate (HP-55, Shin'etsu Kagaku)	6.0 mg
Talc	1.8 mg
Anhydrous ethanol	73.8 mg
Purified water	18.4 mg
Total	100.0 mg

Using labeled sodium hydrogen carbonate ($NaH^{13}CO_3$) as the main raw material, the respective ingredients were mixed and kneaded in accordance with the composition of

the abovementioned <core components>, and granules were manufactured by an ordinary method. Next, these core granules were spray-coated with a coating liquid having the composition described above, thus producing granules that were covered with the intestine-soluble base agent hydroxypropylmethylcellulose phthalate at the rate of 40 parts by weight per 100 parts by weight of the granules. Furthermore, the mean particle size of these granules was 1000 to 1400 μm.

Example 9 Intestine-Soluble Type Preparation

Granules for tablet making were manufactured according an ordinary method by using 50 mg of labeled sodium acetate ($CH_3{}^{13}COONa$) as the main raw material, and mixing an excipient (lactose, corn starch 50 mg), a binder (hydroxypropylmethylcellulose 50 mg), a disintegration agent (crystalline cellulose 25 mg) and a lubricating agent (magnesium stearate 3 mg). These granules were made into tablets by an ordinary method, thus producing a tablet agent (with each tablet containing 100 mg of $CH_3{}^{13}COONa$). Next, this tablet was film-coated with an intestine-soluble base agent (hydroxypropylmethylcellulose phthalate (commercial name: HP-55, Shin'etsu Kagaku)) (proportion of coating layer: 2% in 100 wt % of the tablet agent), thus producing an

intestine-soluble type preparation containing $CH_3{}^{13}COONa$ (diameter: approximately 7 mm).

Test Examples

Test Example 1

An elution test was performed in accordance with the elution test method (paddle method) of the Japan Pharmacopoeia (13th Ed.) for the slow-release tablet agent of Example 6 in order to evaluate the elution behavior of this agent in the body. In concrete terms, 10 tablets of the slow-release tablet agent (Example 6) were placed in a test vessel containing a test solution (acetic acid - ammonium acetate buffer solution (pH 4.8) 500 mL, 37 ± 0.5°C), the paddle rpm was set at 200 rpm or 75 rpm, and the elution behavior of the table agent at the respective rpm values was observed by measuring the solubility (%) over time. The results obtained are shown in Fig. 1. Furthermore, in order to evaluate the elution behavior in case where the slow-release tablet agent of the present invention is administered at the time of food ingestion, an elution test was similarly performed in which 100 g and 200 g of beads (Diapet ABS X-0119, 1400 μm ON, specific gravity 10.5, manufactured by Mitsubishi Rayon) were placed in the test vessel in addition to 10 tablets of the slow-release tablet agent (Example 6). These results are shown respectively in Figs. 2 and 3.

It was confirmed from these results that the slow-release tablet agent of the present invention shows significantly different elution behavior (solubility) according to the paddle rpm selected for the gastric emptying ability, with the elution behavior (solubility) showing a higher value at an increased rpm, and a lower value at a reduced rpm (Fig. 1). Furthermore, it was confirmed that the difference in the elution behavior is more conspicuous in the presence of beads that mimic an ingestion state (Figs. 2 and 3). This means specifically that in the case of the slow-release tablet agent of the present invention, a drop (or acceleration) in the motor function of the stomach can be evaluated by a delay (or acceleration) of the rate of elution of the labeled compound into the exhalation that is connected with a drop (or rise) in the elution behavior of the tablet in the stomach.

This indicates a possibility that exhalation tests using stomach-soluble type preparation (disintegration and release type slow-release preparation) of the present invention can monitor the gastric emptying rate (motor function of the stomach), and therefore may be very useful in performing accurate diagnoses and selecting appropriate treatment methods for subjects suffering from

general physical complaints caused by a drop in the gastric emptying rate.

Test Example 2

The gastric emptying rate was evaluated using the intestine-soluble granules prepared in Example 8. In concrete terms, 1/8 ounce capsules (long diameter: approximately 13 mm, short diameter: approximately 5 mm) were filled with the intestine-soluble granules of Example 8 so that each capsule contained 100 mg of sodium hydrogencarbonate ($NaH^{13}CO_3$), and these capsules were forcibly orally administered to fasting male beagle dogs (n = 4, referred to below as untreated group or gastric emptying normal model) as a preparation for measuring the gastric emptying rate. Following this oral administration, the pH inside the stomach was immediately adjusted by the forcible administration of 20 mL of 0.1 N aqueous solution of hydrochloric acid. Next, exhalation samples were collected over time at 15-minute intervals, and the carbon dioxide gas concentration ratio ($^{13}CO_2/^{12}CO_2$ concentration ratio: $\delta\ ^{13}C$ value) in the exhalation at each exhalation sample collection time was measured using gas chromatography (GC-MS) (ABCA-G, manufactured by Europa Scientific). The carbon dioxide gas Δ(‰) value ($\delta\ ^{13}C$ value following capsule administration - $\delta\ ^{13}C$ value prior to capsule administration) was calculated from the

difference between the δ ^{13}C value at the time of the collection of each sample and the δ ^{13}C value measured prior to the administration of the capsules.

Furthermore, as a control experiment, a sodium hydrogencarbonate solution (containing 100 mg of $NaH^{13}CO_3$) was administered to male beagle dogs (n = 4) instead of the abovementioned capsule agent; the carbon dioxide concentration ratio (δ ^{13}C value) in the exhalation was similarly measured over time, and the carbon dioxide Δ(‰) value was calculated. Furthermore, a gastric emptying delay model was artificially created by separately administering an anticholinergic agent (propantheline) to male beagle dogs (n = 4). Then, the abovementioned capsule agent was administered to the animals of the stomach elimination delay model (group receiving propantheline), after which the carbon dioxide gas concentration ratio (δ ^{13}C value) in the exhalation was similarly measured over time, and the carbon dioxide Δ(‰) value was calculated.

The results obtained are shown in Fig. 4. Fig. 4 shows the mean expiratory elimination pattern for four beagle dogs, with the time (h) elapsed following administration being shown on the horizontal axis, and the carbon dioxide Δ(‰) value being shown on the vertical axis. As is seen from this figure, the sodium

hydrogencarbonate solution ($NaH^{13}CO_3$ solution) administered as a control showed a maximum value immediately after administration, and was then rapidly eliminated from the body. On the other hand, the encapsulated intestine-soluble granules of the present invention showed a peak arrival time (Tmax) at approximately 1.3 hours following administration, and were eliminated relatively slowly. Meanwhile, in the case of the group receiving propantheline (gastric emptying delay model), the elimination of labeled carbon dioxide gas in the exhalation was slow compared to that seen in the beagle dogs of the untreated group (gastric emptying normal model), with the peak arrival time (Tmax) being approximately 2.8 hours.

It is clear from these findings that the intestine-soluble type preparation of the present invention allows the definite measurement of a drop in the gastric emptying rate in the gastric emptying delay model according to the delay of the elimination of the labeled carbon dioxide in the exhalation. This indicates that the gastric emptying ability can be evaluated by measuring the respiratory elimination pattern of the labeled carbon dioxide in a exhalation test using the preparation of the present invention.

INDUSTRIAL APPLICABILITY

The preparation of the present invention for measuring the gastric emptying rate makes it possible to measure the gastric emptying ability (gastric emptying function) in humans or animals simply and with good precision. Especially if a preparation for measuring the gastric emptying rate prepared using a labeled compound that is eliminated in the exhalation as carbon dioxide is used, the gastric emptying ability can be simply measured by means of a exhalation test without placing a psychological or physical burden on the subject.

Furthermore, by using the preparation of the present invention for measuring the gastric emptying rate, and a method for measuring the gastric emptying rate that employs this preparation, it is possible to diagnose and evaluate a drop or acceleration in the gastric emptying rate of the subject simply and with good precision. Furthermore, by using the preparation of the present invention for measuring the gastric emptying rate, and a method for measuring the gastric emptying rate that employs this preparation, it is possible to evaluate the pharmacological effects of drugs relating to the motor function of the stomach in a direct and simple manner, and to evaluate the therapeutic effects of such drugs on

individual subjects immediately after administration, and in an objective manner.

CLAIMS

1. A preparation for measuring the gastric emptying ability comprising a composition containing a compound that is labeled with at least one of isotopes of C and O, and that is converted into labeled CO_2 in the body and eliminated in the exhalation, this preparation being preparated as a slow-release preparation that is disintegrated and released.

2. The preparation for measuring the gastric emptying ability according to claim 1, wherein the preparation is a stomach-soluble preparation.

3. The preparation for measuring the gastric emptying ability according to claim 1, wherein the behavior of the preparation following oral administration to a subject is such that

(1) the preparation remains inside the stomach for a certain period of time after entering the stomach, without being immediately discharged from the stomach,

(2) the surface of the preparation is gradually eroded by the muscular contractions of the stomach wall so that the preparation is disintegrated, and as this erosion and disintegration occurs, the labeled compound is gradually eluted into the stomach, and

(3) the eluted labeled compound is then converted into labeled carbon dioxide inside the stomach, and is eliminated in the exhalation, or is eliminated in the exhalation as labeled carbon dioxide following absorption and metabolization.

4. The preparation for measuring the gastric emptying ability according to claim 1, wherein the preparation expands to such a size that the preparation does not pass through the pylorus for a certain period of time following oral administration.

5. The preparation for measuring the gastric emptying ability according to claim 1, which is characterized in that the preparation contains a disintegration inhibiting agent in addition to a labeled compound.

6. The preparation for measuring the gastric emptying ability according to claim 5, wherein the disintegration inhibiting agent consists of at least one substance selected from water-soluble high-molecular polymers, fats and sugars.

7. The preparation for measuring the gastric emptying ability according to claim 6, wherein the disintegration inhibiting agent consists of at least one substance selected from a group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose,

ethylcellulose, cellulose acetate phthalate, hardened oils, carnauba wax, sugars and sugar alcohols.

8. The preparation for measuring the gastric emptying ability according to claim 1, wherein the isotope consists of at least one isotope selected from a group consisting of ^{13}C, ^{14}C and ^{18}O.

9. The preparation for measuring the gastric emptying ability according to claim 1, wherein the labeled compound consists of an alkali metal salt, alkaline earth metal salt, or ammonium salt of carbonate or hydrogen carbonate.

10. The preparation for measuring the gastric emptying ability according to claim 1, wherein the labeled compound consists of at least one compound selected from a group consisting of acetic acid, glycine, octanoic acid and alkali metal salts thereof.

11. A preparation for measuring the gastric emptying ability which is characterized in that a composition containing a compound that is labeled with at least one of isotopes of C and O, and that is converted into labeled CO_2 in the body and eliminated in the exhalation, is covered by a base agent that dissolves in the intestines.

12. The preparation for measuring the gastric emptying ability according to claim 11, wherein the

behavior of the preparation following oral administration to a subject is such that

(1) the preparation remains inside the stomach for a certain period of time after entering the stomach, without being discharged from the stomach,

(2) the preparation is discharged from the stomach by the housekeeper eliminating movement of the stomach, and

(3) the preparation is then dissolved in the intestines, and the labeled compound eluted from the interior of the preparation is converted into labeled carbon dioxide inside the intestines, and is eliminated in the exhalation, or is eliminated in the exhalation as labeled carbon dioxide following absorption and metabolization.

13. The preparation for measuring the gastric emptying ability according to claim 11, wherein the behavior of the preparation following oral administration to a subject is such that

(1) the preparation enters the stomach,

(2) the preparation is discharged from the stomach accompanying the eliminative movement of food, and

(3) the preparation is then dissolved in the intestines, and the labeled compound eluted from the interior of the preparation is converted into labeled carbon dioxide inside the intestines, and is eliminated in the

exhalation, or is eliminated in the exhalation as labeled carbon dioxide following absorption and metabolization.

14. The preparation for measuring the gastric emptying ability according to claim 11, wherein the isotope consists of at least one isotope selected from a group consisting of ^{13}C, ^{14}C and ^{18}O.

15. The preparation for measuring the gastric emptying rate according to claim 11, wherein the labeled compound is an alkali metal salt, alkaline earth metal salt, or ammonium salt of carbonate or hydrogen carbonate.

16. The preparation for measuring the gastric emptying rate according to claim 11, wherein the labeled compound consists of at least one compound selected from a group consisting of acetic acid, glycine, octanoic acid and alkali metal salts thereof.

17. A method for measuring the gastric emptying ability, which is characterized in that the preparation for measuring the gastric emptying ability according to claim 1 or claim 11 is orally administered to a subject, and the behavior of the labeled compound inside the body or the amount or behavior of the labeled compound eliminated from the body is measured.

18. A method for measuring the gastric emptying ability which is characterized in that the preparation for measuring the gastric emptying ability according to

claim 1 or claim 11 is orally administered to a subject, and the amount or behavior of labeled CO_2 that is eliminated in the exhalation is measured.

19. A method for evaluating the gastric emptying ability of a subject for whom a reduction or acceleration of the gastric emptying ability is suspected, comprising the steps of:

orally administering the preparation for measuring the gastric emptying ability according to claim 1 or claim 11 to said subject; and

comparing the behavior of the labeled compound inside the body obtained after a specified period of time or the amount or behavior of the labeled compound that is eliminated from the body with the behavior of the labeled compound inside the body or the amount or behavior of the labeled compound eliminated from the body obtained for a healthy subject using the same preparation for measuring the gastric emptying ability.

20. A method for evaluating the gastric emptying ability of a subject for whom a reduction or acceleration of the gastric emptying ability is suspected, comprising the steps of:

orally administering the preparation for measuring the gastric emptying ability according to claim 1 or claim 11 to said subject; and

comparing the amount or behavior of labeled CO_2 that is eliminated in the exhalation after a specified period of time with the amount of behavior of labeled CO_2 eliminated in the exhalation obtained for a healthy subject using the same preparation for measuring the gastric emptying rate.

21. The method for evaluating the gastric emptying ability according to claim 19, which is characterized in that an evaluation performed using the preparation for measuring the gastric emptying ability according to claim 1 and an evaluation performed using the preparation for measuring the gastric emptying ability according to claim 11 are performed in combination.

22. A method for evaluating the pharmacological effect of a drug relating to the motor function of the stomach, or the therapeutic effect of such drug on a subject, comprising the steps of:

orally administering the preparation for measuring the gastric emptying ability according to claim 1 or claim 11 to the subject before and after the administration of a drug relating to the motor function of the stomach to the subject; and

comparing the behavior of the labeled compound inside the body or the amount or behavior of the labeled compound eliminated from the body following the

administration of said drug with the behavior of the labeled compound inside the body or the amount or behavior of the labeled compound eliminated from the body prior to the administration of said drug.

23. A method for evaluating the pharmacological effect of drugs relating to the motor function of the stomach, or the therapeutic effect of such drugs on a subject, comprising the steps of:

orally administering the preparation for measuring the gastric emptying rate according to claim 1 or claim 11 to the subject before and after the administration of a drug relating to the motor function of the stomach to the subject; and

comparing the amount or behavior of labeled CO_2 eliminated in the exhalation following the administration of said drug with the amount or behavior of labeled CO_2 eliminated in the exhalation prior to the administration of said drug.

24. The method for evaluating the pharmacological effects of a drug relating to the motor function of the stomach or the therapeutic effects of said drug on a subject according to claim 22, which is characterized in that an evaluation performed using the preparation for measuring the gastric emptying ability according to claim 1 and an evaluation performed using the preparation for

measuring the gastric emptying ability according to claim 11 are performed in combination.