A pharmaceutical composition for modified release, comprising (1) (R)-2-(2-aminothiazol-4-yl)-4’-[2-[2-hydroxy-2-phenylethyl]amino]ethyl]acetic acid anilide, or a pharmaceutically acceptable salt thereof, (2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less, and (3) a hydrogel-forming polymer having an average molecular weight of approximately 100,000 or more, or a viscosity of 12 mPa·s or more at a 5% aqueous solution at 25°C, is disclosed.
Figure 1

![Graph showing dissolution rate over time for different conditions:]

- Solid line: Before preservation
- Dashed line: 60°C (preserved for 3 months)
- Dotted line: 40°C, 75% RH (preserved for 3 months)

Dissolution rate (%) vs. Time (hr)
PHARMACEUTICAL COMPOSITION FOR MODIFIED USE


TECHNICAL FIELD

[0002] The present invention relates to a pharmaceutical composition for modified release capable of reducing food effects, which are observed in conventional tablets, by combining an active ingredient with specific ingredients to control a releasing rate of the active ingredient.

[0003] More particularly, the present invention relates to a pharmaceutical composition comprising (R)-2-(2-aminothiazol-4-yl)-4’-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt thereof, an additive which ensures penetration of water into the pharmaceutical composition (hereinafter sometimes referred to as a hydrophilic base), and a polymer which forms a hydrogel, in which the changes in AUC and Cmax caused by the intake of food can be decreased by controlling a releasing rate of the active ingredient.

BACKGROUND ART

[0004] (R)-2-(2-aminothiazol-4-yl)-4’-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide has been created by Astellas Pharma Inc., and it has been reported that this compound has not only both an activity of promoting insulin secretion and an activity of enhancing insulin sensitivity, but also an antiobastic activity and an antihypertensive activity based on an activity of selectively stimulating a P3 receptor, and is useful in treating diabetes (see, for example, patent literature 1).

[0005] Further, it has been reported that the compound can be used as a therapeutic agent for overactive bladder, such as overactive bladder accompanied by prostatic hyperplasia, or overactive bladder accompanied by urinary urgency, urinary incontinence, and urinary frequency (see, for example, patent literature 2).

[0006] A clinical trial of (R)-2-(2-aminothiazol-4-yl)-4’-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide in the form of conventional formulations revealed disadvantages, for example, that pharmacokinetic data unexpectedly varied according to the presence or absence of the intake of food (not published). For example, the rate of decrease of Cmax in a fed state was 67%, and the rate of decrease of AUC in the fed state was 47%, in comparison with those in a fasting state. In this case, Cmax in the fasted state was three times higher than that in the fed state. These problems are considered to be raised by, for example, the changes in pharmacokinetics caused by food, and therefore, the development of a formulation capable of avoiding the effects by food intake is desired.

[0007] As a technique of preparing a formulation for modified release, a hydrogel sustained release tablet containing an additive which ensures penetration of water into the tablet, and a hydrogel-forming polymer is disclosed (see, for example, patent literature 3).

[0008] However, patent literature 3 does not refer to (R)-2-(2-aminothiazol-4-yl)-4’-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide, and further improvements are needed to produce a pharmaceutical composition.

CITATION LIST

[0009] Patent Literature

[0010] Summary of Invention

Technical Problem

[0010] An object of the present invention is to provide a pharmaceutical composition for modified release comprising (R)-2-(2-aminothiazol-4-yl)-4’-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt thereof, in which the pharmaceutical composition has efficacy the same as or higher than those of conventional formulations and has no limitations on food intake, and a process of manufacturing the pharmaceutical composition.

Solution to Problem

[0011] The elimination half-life (T1/2) of (R)-2-(2-aminothiazol-4-yl)-4’-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide is long (approximately 18 to 24 hours), and thus, a formulation thereof for modified release is not necessarily needed to maintain its blood level. Taking into consideration the results of the clinical trial described above, the present inventors conducted intensive studies to design the formulation by paying attention to the control of a release rate of the drug from a formulation to the extent that the release is not affected by food intake or the like, rather than the addition of release control.

[0012] On the basis of blood concentration profiles (in a fasted state after the intake of food) after administration of a conventional formulation (rapid release formulation), the absorption rate of the drug in a fed state was calculated by a deconvolution method to predict continuous absorption for about 4 hours. The present inventors considered from this result that a formulation capable of continuous drug release for 4 hours or more would be able to reduce the effects by food, because the drug release from the formulation would become the rate-limiting step for absorption.

[0013] The present inventors carried out a clinical trial in human using three types of formulations in which the release rate of the drug was controlled (Time when the release percentage of the drug from the unit formulation was 80% (T80%)-4 hr, 6 hr, and 10 hr), and found that all formulations could reduce the effects by food, to complete the present invention.

[0014] It is generally known that the retention time in the stomach and the release rate of formulations for modified release vary according to the presence or absence of food intake, and as a result, there is a possibility that blood concentration profiles is changed. However, surprisingly, when using this formulation, the change of the blood concentration profiles was small in the presence or absence of food intake.

[0015] The present invention is characterized by providing a pharmaceutical composition for modified release which is not affected by the effects of food intake and exhibits a decreased change in AUC or Cmax.
[0016] The present invention provides:
[1] a pharmaceutical composition for modified release, comprising (1) (R)-2-(2-aminothiazol-4-yl)-4’-[2-(2-hydroxy-2-phenylethyl)aminoethyl]acetic acid anilide, or a pharmaceutically acceptable salt thereof, (2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less, and (3) a hydrogel-forming polymer having an average molecular weight of approximately 100,000 or more, or a viscosity of 12 mPa·s or more at a 5% aqueous solution at 25°C;
[2] the pharmaceutical composition for modified release of [1], wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, D-sorbitol, xylitol, lactose, sucrose, anhydrous maltose, D-fructose, dextran, glucose, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol, polyoxyethylene sorbitan higher fatty acid ester, sodium chloride, magnesium chloride, citric acid, tartaric acid, glycine, β-alanine, lysine, hydrochloride, and meglumine;
[3] the pharmaceutical composition for modified release of [2], wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, lactose, sucrose, sodium chloride, and polyoxyethylene polyoxypropylene glycol;
[4] the pharmaceutical composition for modified release of any one of [1] to [3], wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 75% by weight with respect to the total weight of the pharmaceutical composition;
[5] the pharmaceutical composition for modified release of [4], wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition;
[6] the pharmaceutical composition for modified release of any one of [1] to [5], wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium hydroxyethyl cellulose, and a carboxyvinyl polymer;
[7] the pharmaceutical composition for modified release of [6], wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, and hydroxypropyl cellulose;
[8] the pharmaceutical composition for modified release of any one of [1] to [7], wherein an amount of the hydrogel-forming polymer is 1% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition;
[9] the pharmaceutical composition for modified release of any one of [1] to [8], further comprising an antioxidant;
[10] the pharmaceutical composition for modified release of [9], wherein the antioxidant is one compound, or two or more compounds selected from the group consisting of butyl hydroxytoluene, propyl gallate, and sodium ascorbate;
[11] the pharmaceutical composition for modified release of claim 10, wherein the antioxidant is butyl hydroxytoluene;
[12] the pharmaceutical composition for modified release of any one of [9] to [11], wherein an amount of the antioxidant is 0.025% by weight to 0.25% by weight;
[13] the pharmaceutical composition for modified release of any one of [1] to [12], further comprising a stabilizer;
[14] the pharmaceutical composition for modified release of [13], wherein the stabilizer is one compound, or two or more compounds selected from the group consisting of yellow ferric oxide, red ferric oxide, and black iron oxide;
[15] the pharmaceutical composition for modified release of [14], wherein the stabilizer is yellow ferric oxide and/or red ferric oxide;
[16] the pharmaceutical composition for modified release of any one of [13] to [15], wherein an amount of the stabilizer is 0.05% by weight to 1% by weight;
[17] a process of manufacturing a pharmaceutical composition for modified release, characterized by comprising mixing (1) (R)-2-(2-aminothiazol-4-yl)-4’-[2-(2-hydroxy-2-phenylethyl)aminoethyl]acetic acid anilide, or a pharmaceutically acceptable salt thereof with (2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less and (3) a hydrogel-forming polymer having an average molecular weight of approximately 100,000 or more, or a viscosity of 12 mPa·s or more at a 5% aqueous solution at 25°C, wherein an amount of the additive is 5% by weight to 75% by weight with respect to the total weight of the pharmaceutical composition, and an amount of the hydrogel-forming polymer is 1% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition;
[18] the process of [17], wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, D-sorbitol, xylitol, lactose, sucrose, anhydrous maltose, D-fructose, dextran, glucose, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol, polyoxyethylene sorbitan higher fatty acid ester, sodium chloride, magnesium chloride, citric acid, tartaric acid, glycine, β-alanine, lysine, hydrochloride, and meglumine; and
[19] the process of [17] or [18], wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, hydroxyethyl cellulose, and a carboxyvinyl polymer.

[0017] As formulation techniques for reducing or avoiding the changes in pharmacokinetics such as AUC or Cmax accompanied by food intake, a formulation technique concerning a sustained-release pharmaceutical composition containing tamsulosin hydrochloride is disclosed (see Japanese Unexamined Patent Publication (Kokai) No. 2005-162736 and Japanese Unexamined Patent Publication (Kokai) No. 2005-162737). This formulation technique is limited to tamsulosin, and applied to a formulation containing the drug at a low dose (0.4 mg per unit formulation). This formulation enables to control the release of tamsulosin therefrom by being mainly composed of a sustained-release base. By contrast, the pharmaceutical composition contains the drug at a high dose (i.e., high content per unit formulation), and it is considered difficult to control the release rate of the drug from a formulation containing the sustained-release base at a low
content, and therefore, the present invention is technically quite different from the formulation disclosed in these references.

Effects of Invention

According to the present invention, a pharmaceutical composition for modified release which has no limitations on food intake and is stable (for example, reduction of changes in a sequential dissolution profile) can be provided.

Further, a pharmaceutical composition for modified release in which AUC is not reduced can be provided.

With respect to a conventional formulation, the rate of decrease of Cmax in the fed state was 67% in comparison with that in a fasted state. By contrast, with respect to the pharmaceutical composition for modified release of the present invention, the rate of decrease of Cmax in the fed state was 42% in comparison with that in a fasted state, and this result showed that reduction of Cmax caused by food intake could be significantly alleviated by forming its formulation into the pharmaceutical formulation for modified release.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a graph showing dissolution profiles of the pharmaceutical composition for modified release prepared in Example 11, and the time course thereof.

DESCRIPTION OF EMBODIMENTS

The pharmaceutical composition for modified release of the present invention will be explained hereinafter.

The term “rapid release formulation (conventional formulation)” as used herein means a formulation in which the dissolution rate of the drug from the formulation is 85% or more after 30 minutes from the beginning a dissolution test, which is carried out in accordance with a dissolution test (paddle method) described in the United States Pharmacopoeia under the conditions that 900 mL of an appropriate test fluid (such as a USP buffer, pH 6.8) is used and the paddle rotation speed is 100 rpm. Alternatively, the term means a formulation in which the dissolution rate of the drug from the formulation is 85% or more after 30 minutes from the beginning a dissolution test, which is carried out in accordance with a dissolution test, method 2 described in the Japanese Pharmacopoeia under the conditions that 900 mL of an appropriate test fluid (such as a McIlvaine buffer, pH 6.8) is used and the paddle rotation speed is 50 rpm.

The term “pharmaceutical composition for modified release” as used herein means a formulation in which the dissolution rate of the drug from the formulation is less than 85% after 30 minutes from the beginning a dissolution test carried out under the above conditions, and the drug release is controlled to the extent that the effects by food are reduced. More particularly, it is a formulation in which an additive (hydrophilic base) which ensures penetration of water into the formulation is combined with a polymer which forms a hydrogel.

The wording “the effects by food are reduced”, as used herein means, for example, a 10% reduction, a 20% reduction in another embodiment, and a 30% reduction in still another embodiment, in comparison with Cmax of a conventional formulation. Alternatively, the term means, for example, a 10% reduction with respect to the rates of decrease of Cmax and AUC in administration after food intake, in comparison with Cmax and AUC in administration in the fasted state, a 20% reduction in another embodiment, and a 30% reduction in still another embodiment.

The rates of decrease of Cmax and AUC are calculated by the following equations:

\[
R_{d(Cmax)} = \left( \frac{C_{max(FS)} - C_{max(FI)}}{C_{max(FS)}} \right) \times 100
\]

\[
R_{d(AUC)} = \left( \frac{AUC(FS) - AUC(FI)}{AUC(FS)} \right) \times 100
\]

The term “formulation in which the effects by food are reduced” as used herein means a formulation in which the dissolution rate of the drug from the formulation is 75% or less after 1.5 hours and 100% or less after 4 hours from the beginning a dissolution test, which is carried out under the above conditions [in accordance with a dissolution test (paddle method) described in the United States Pharmacopoeia under the conditions that 900 mL of an appropriate test fluid (such as a USP buffer, pH 6.8) is used and the paddle rotation speed is 50 to 200 rpm]. In another embodiment, the term means a formulation in which the dissolution rate of the drug from the formulation is 75% or less after 1.5 hours and 75% or more to 100% or less after 7 hours.

The term “stable” as used herein means that it is stable against, for example, heat, temperature, humidity, or light. More particularly, the term means that, for example, when a plastic bottle is filled with a pharmaceutical composition and sealed, and then, the bottle is preserved for three months under the conditions at 40°C and 75% RH or at 60°C, the change in the dissolution rate at the point showing a dissolution rate of 50% is within ±5% or less. Alternatively, the term means that, for example, when a pharmaceutical composition is exposed to 1.2 million Lux·hr of light, the change in the dissolution rate at the point showing a dissolution rate of 50% is within ±5% or less.

(3R,5R)-2-[2-(aminothiazol-4-yl)-4-{2-[2-hydroxy-2-phenylethyl]aminoethyl]acetic acid anilide (hereinafter sometimes referred to as compound A) is represented by the following structural formula.

![Chem. 1]

Compound A may be used in a free form which is not a salt, and may form a salt with an acid in other embodiments. Examples of such a salt include an acid addition salt with a mineral acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, or the like; and an acid addition salt with an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, citric acid, tartaric acid, carbonic acid, picric acid, medichesulfonic acid, ethanesulfonic acid, glutamic acid, or the like.
The dose of compound A may be appropriately selected in accordance with symptom, age, sex, and the like of the patient to be treated. The daily dose of compound A for oral administration to an adult is generally 0.01 to 100 mg/kg, which is administered once or divided into two to four doses per day.

The content of compound A per formulation is, for example, 1% by weight to 70% by weight, 5% by weight to 70% by weight in another embodiment, and 5% by weight to 50% by weight in still another embodiment. The content of compound A per formulation is 1 mg to 500 mg, and 10 mg to 200 mg in another embodiment.

It is necessary that the hydrogel-forming polymer used in the present invention can control the release rate of the drug, to the extent that the blood concentration profile of the drug is not affected by the presence or absence of food intake.

The molecular weight of the hydrogel-forming polymer is, for example, 100,000 or more, 100,000 to 8,000,000 in another embodiment, 100,000 to 5,000,000 in still another embodiment, and 100,000 to 2,000,000 in still another embodiment. The viscosity of the hydrogel-forming polymer is, for example, 12 mPa·s or more in a 5% aqueous solution at 25°C; 12 mPa·s or more in a 5% aqueous solution at 25°C; and 40,000 mPa·s or less in a 1% aqueous solution at 25°C. in another embodiment; 400 mPa·s or more in a 2% aqueous solution at 25°C; and, 7,500 mPa·s or less in a 1% aqueous solution at 25°C. in still another embodiment; and 400 mPa·s or more in a 2% aqueous solution at 25°C; and, 5,000 mPa·s or less in a 1% aqueous solution at 25°C. in still another embodiment.

In the pharmaceutical composition for modified release of the present invention, the release period of time of the drug from the formulation can be arbitrarily controlled by adjusting the viscosity of the polymer which is used as the hydrogel-forming polymer.

The hydrogel-forming polymer used in the present invention is not particularly limited, so long as the release of the drug can be controlled to the extent that the effects of food on compound A may be reduced. Examples of the hydrogel-forming polymer include polyethylene oxide, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, hydroxyethyl cellulose, and carboxyvinyl polymers. Examples of the hydrogel-forming polymer in another embodiment include polyethylene oxide, hydroxypropyl methylcellulose, and hydroxypropyl cellulose.

Examples of polyethylene oxide (hereinafter sometimes referred to as PEO) include product names, Polyox WSR-308 [average molecular weight: 8,000,000, viscosity: 10,000-15,000 mPa·s (1% aqueous solution at 25°C.)], Polyox WSR-303 [average molecular weight: 7,000,000, viscosity: 7,500-10,000 mPa·s (1% aqueous solution at 25°C.)], Polyox WSR Coagulant [average molecular weight: 5,000,000, viscosity: 5,500-7,500 mPa·s (1% aqueous solution at 25°C.)], Polyox WSR-301 [average molecular weight: 4,000,000, viscosity: 1,650-5,500 mPa·s (1% aqueous solution at 25°C.)], Polyox WSR-N-60K [average molecular weight: 2,000,000, viscosity: 2,000-4,000 mPa·s (2% aqueous solution at 25°C.)], Polyox WSR-N-12K [average molecular weight: 1,000,000, viscosity: 400-800 mPa·s (2% aqueous solution at 25°C.)], Polyox WSR-N-12K [average molecular weight: 900,000, viscosity: 8,800-17,600 mPa·s (5% aqueous solution at 25°C.)], Polyox WSR-205 [average molecular weight: 600,000, viscosity: 4,500-8,800 mPa·s (5% aqueous solution at 25°C.)], Polyox WSR-N-750 [average molecular weight: 300,000, viscosity: 600-1200 mPa·s (5% aqueous solution at 25°C.)], Polyox WSR-N-50 [average molecular weight: 200,000, viscosity: 55-90 mPa·s (5% aqueous solution at 25°C.)], and Polyox WSR-N-10 [average molecular weight: 100,000, viscosity: 12-50 mPa·s (5% aqueous solution at 25°C.)] (DOW).

Examples of hydroxypropyl methylcellulose (hereinafter sometimes referred to as HPMC) include product name Metrolose 90SH50000 [viscosity in a 2% aqueous solution at 20°C: 2,900-3,900 mPa·s], Metolose SB-4 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 4 mPa·s), TC-5RW (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 6 mPa·s), TC-5S (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 15 mPa·s), TC-5R (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 6 mPa·s), TC-5S (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 4.5 mPa·s), TC-5E (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 3 mPa·s), Metolose 60SH-50 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 50 mPa·s), Metolose 65SH-50 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 50 mPa·s), Metolose 90SH-100 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 100 mPa·s), Metolose 90SH-200 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 100 mPa·s), Metolose 65SH-400 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 400 mPa·s), Metolose 90SH-400 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 400 mPa·s), Metolose 90SH-1500 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 1,500 mPa·s), Metolose 60SH-400 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 4,000 mPa·s), Metolose 65SH-400 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 4,000 mPa·s), Metolose 90SH-4000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 4,000 mPa·s), Metolose 90SH-4000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 4,000 mPa·s), Metolose 90SH-15000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 15,000 mPa·s), Metolose 90SH-15000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 15,000 mPa·s), Metolose 90SH-15000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 15,000 mPa·s), and Metolose 90SH-30000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 30,000 mPa·s).

Examples of hydroxypropyl cellulose (hereinafter sometimes referred to as HPC) include HPC-SSL (product name, Nippon Soda Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: 2.0-2.9 mPa·s), HPC-SL (product name, Nippon Soda Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: 3.0-5.9 mPa·s), HPC-I (product name, Nippon Soda Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: 6.0-
[0040] Examples of methylcellulose (hereinafter sometimes referred to as MC) include Metolose SM15 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 15 mPaS), Metolose SM225 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 25 mPaS), Metolose SM100 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 100 mPaS), Metolose SM400 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 400 mPaS), Metolose SM1500 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 1,500 mPaS), and Metolose SM4000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20°C: approximately 4,000 mPaS).

[0041] Examples of carboxymethyl cellulose sodium (hereinafter sometimes referred to as CMC-Na) include product names, Sunrose F-30MC [viscosity: 250-350 mPaS (1% aqueous solution at 25°C)], Sunrose F-150MC [average molecular weight: 200,000, viscosity: 1,200-1,800 mPaS (1% aqueous solution at 25°C)], Sunrose F-600MC [viscosity: 6,000-8,000 mPaS (1% aqueous solution at 25°C)], Sunrose F-1000MC [average molecular weight: 420,000, viscosity: 8,000-12,000 mPaS (the same)], Sunrose F-1400MC [viscosity: 12,000-15,000 mPaS (1% aqueous solution at 25°C)], and Sunrose F-300MC [average molecular weight: 300,000, viscosity: 2,500-3,000 mPaS (the same)] (Nippon Paper Chemicals Co., Ltd.).

[0042] Examples of hydroxyethyl cellulose (hereinafter sometimes referred to as HEC) include product names, HEC DAICEL SE850 [average molecular weight: 1,480,000, viscosity: 2,400-3,000 mPaS (1% aqueous solution at 25°C)], and HEC DAICEL SE900 [average molecular weight: 1,500,000, viscosity: 4,000-5,000 mPaS (1% aqueous solution at 25°C)] (Daicel Chemical Industries, Ltd.).

[0043] Examples of carboxyvinyl polymers include Carbopol 71G (viscosity: 4,000-11,000 mPaS), Carbopol 971P (viscosity: 4,000-11,000 mPaS), Carbopol 981 (viscosity: 4,000-10,000 mPaS), Carbopol 941 (viscosity: 4,000-10,000 mPaS), Carbopol 934 (viscosity: 30,500-40,000 mPaS), and Carbopol 934P (viscosity: 29,400-39,400 mPaS) (B.F. Goodrich Chemical).

[0044] These hydrogel-forming polymers may be used alone, or as an appropriate combination of two or more thereof. A combination of different lots may be used.

[0045] The content of the hydrogel-forming polymer is not particularly limited, so long as it is an amount capable of controlling the release of the drug to the extent that the release of the drug is not affected by the presence or absence of food intake. The content of the hydrogel-forming polymer, for example, 1% by weight to 70% by weight with respect to the total weight of the formulation, and 3% by weight to 70% by weight in another embodiment. The content of the hydrogel-forming polymer is 5% by weight to 70% by weight with respect to the total weight of the formulation, 10% by weight to 60% by weight in another embodiment, and 10% by weight to 40% by weight in still another embodiment. The content of the hydrogel-forming polymer is 0.1% by weight to 1,000% by weight with respect to the amount of drug, 1% by weight to 500% by weight in another embodiment, and 5% by weight to 300% by weight in still another embodiment.

[0046] A polymer of which the viscosity (before mixing) is beyond the specific range can be used as an appropriate combination with one or more other polymers, in case that the mixture obtained by mixing these plural polymers has a viscosity (as measured before the use) within the specific range.

[0047] In the additive which ensures penetration of water into the pharmaceutical composition of the present invention (hydrophilic base), the amount of water necessary to dissolve 1g of the hydrophilic base at 20±5°C is 10ml or less, 6ml or less in another embodiment, 5ml or less in still another embodiment, and 4ml or less in still another embodiment. When the hydrophilic base has a high solubility to water, the effect that allows water to penetrate into the formulation is high.

[0048] Examples of the hydrophilic base include water-soluble polymers, such as polyethylene glycol [PEG: for example, product names PEG 400, PEG 1500, PEG 4000, PEG 6000, and PEG 20000 (NOF Corporation)], polyvinyl pyrrolidone (PVP: for example, product name PVP K30 (BASF)), and the like; sugar alcohols, such as D-mannitol, D-sorbitol, xylitol, and the like; saccharides, such as lactose, sucrose, anhydrous maltose, D-fructose, dextron (for example, Dextran 40), glucose, and the like; surfactants, such as polyoxyethylene hydrogenated castor oil [HICO: for example, Cremophor RH40 (BASF), HICO-40, HICO-60 (Ni- kko Chemicals)], polyoxyethylene polyoxypropylene glycol [for example, Pluron F68 (Asahi Denka and the like)], polyoxyethylene sorbitan higher fatty acid esters [Tween: for example, Tween 80 (Kanto Chemical)], and the like; salts, such as sodium chloride, magnesium chloride, and the like; organic acids, such as citric acid, tartaric acid, and the like; amino acids, such as glycine, β-alanine, lysine hydrochloride, and the like; and aminosaccharides, such as meglumine and the like.

[0049] As another embodiment, PEG, PVP, D-mannitol, D-sorbitol, xylitol, lactose, sucrose, anhydrous maltose, D-fructose, dextron, glucose, polyoxyethylene polyoxypropylene glycol, sodium chloride, magnesium chloride, citric acid, tartaric acid, glycine, β-alanine, lysine hydrochloride, or meglumine may be used. As still another embodiment, PEG, PVP, D-mannitol, lactose, sucrose, sodium chloride, polyoxyethylene polyoxypropylene glycol, or the like may be used.

[0050] These hydrophilic bases may be used alone, or as an appropriate combination of two or more thereof.

[0051] The content of the hydrophilic base is not particularly limited, so long as it is an amount capable of controlling the release of the drug to the extent that the release of the drug is not affected by food. The content of the hydrophilic base is, for example, 5% by weight to 75% by weight, 5% by weight to 70% by weight in another embodiment, and 20% by weight to 60% by weight in still another embodiment.

[0052] The pharmaceutical composition for modified release of the present invention may be prepared as various dosage forms, which include, for example, formulations for oral administration such as tablets, capsules (including microcapsules), granules, and powder, and formulations for parenteral administration such as suppositories (for example, rectal suppositories or vaginal suppositories). These formulations may be safely administered orally or parenterally.
Formulations for oral administration such as tablets, capsules, and granules may be selected in another embodiment. [0053] The pharmaceutical composition for modified release of the present invention may be prepared by mixing the drug, the hydrogel-forming polymers, and the hydrophilic base, and forming the mixture into a predetermined shape. The mixing and forming may be carried out in accordance with conventional methods widely used in the technical field for formulation. A pharmaceutically acceptable carrier may be used in the mixing and/or forming, if desired.

[0054] In the preparation of the pharmaceutical composition for modified release of the present invention, various pharmaceutical additives may be used, if desired. Such pharmaceutical additives are not particularly limited, so long as they are pharmaceutically acceptable. Examples of the pharmaceutical additives include various organic or inorganic carrier substances which are widely used as formulation materials, such as fillers, lubricants, binders, and disintegrating agents. Other formulation additives such as preservatives, antioxidants, stabilizers, film coating agents, coloring agents, and sweeteners may be used, if desired.

[0055] Examples of the fillers include lactose, sucrose, D-mannitol, D-sorbitol, starch, gelatinized starch, dextrin, crystalline cellulose, low substituted hydroxypropyl cellulose, carboxymethyl cellulose sodium, gum arabic, dextrin, pullulan, light anhydrous siliceic acid, synthetic aluminum silicate, magnesium aluminate metasilicate, and the like.

[0056] Examples of the lubricants include magnesium stearate, calcium stearate, talc, colloidal silica, and the like.

[0057] Examples of the binders include gelatinized starch, sucrose, gelatin, gum arabic, methylcellulose, carboxymethyl cellulose, carboxymethyl cellulose sodium, crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, and the like.

[0058] Examples of the disintegrating agents include lactose, sucrose, starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, croscarmellose sodium, carboxymethyl starch sodium, light anhydrous siliceic acid, low substituted hydroxypropylcellulose, and the like.

[0059] Examples of the preservatives include p-hydroxybenzoate esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, and the like.

[0060] The antioxidants are not particularly limited, so long as it can avoid the effects of dissolution behavior. Examples of the antioxidants include butylated hydroxytoluene (BHT), propyl gallate (PG), butylhydroxyanisol (BHA), ascorbic acid, sodium ascorbate, erthorbic acid, sodium nitrite, sodium bisulfite, sodium pyrosulfite, citric acid, and edetate sodium; BHT, PG, and sodium ascorbate in another embodiment; and BHT in still another embodiment.

[0061] Examples of the stabilizers include yellow ferric oxide, red ferric oxide, black iron oxide, and the like.

[0062] Examples of the film coating agents include pharmaceutically commonly-used bases, such as water-soluble polymers, plasticizers, and inorganic substances, or a combination thereof.

[0063] Examples of the coloring agents include water-soluble edible tar pigments (examples: edible pigments such as food red No. 2, food red No. 3, food yellow No. 4, food yellow No. 5, food blue No. 1, and food blue No. 2), water-insoluble lake pigments (examples: aluminum salts of the above water-soluble edible tar pigments), natural pigments (examples: β-carotene, chlorophyll, and colcothar), and the like.

[0064] Examples of the sweeteners include saccharin sodium, dipotassium glycyrhizinate, aspartame, stevia, and the like.

[0065] These carriers or formulation additives may be used alone, or as an appropriate combination of two or more thereof.

[0066] With respect to the contents thereof, they may be used in appropriate amounts. For example, the content of the antioxidant is 0.025% by weight to 0.25% by weight with respect to the total weight of the formulation, and that of the stabilizer is 0.05% by weight to 1% by weight with respect to the total weight of the formulation.

[0067] Hereinafter, the process of manufacturing the pharmaceutical composition for modified release of the present invention will be explained, the present invention is not limited to the following particular embodiments.

[0068] The pharmaceutical composition for modified release of the present invention may be prepared by known methods per se, such as dry granulation, wet granulation, fluidized bed granulation, intermittent granulation, agitator granulation, or the like.

[0069] As a method of de-lumping or pulverizing the drug, conventional crushing or pulverizing methods may be applied, for example, using an impact mill (Hosokawa Micron Corporation; Fine Impact Mill), a dry & wet mill (Powrex Corporation: Comil), or a cutting mill granulator (Dalton Corporation: Power Mill).

[0070] As a method of pulverizing the hydrophilic base, the hydrogel-forming polymer, or the formulation additives, conventional pulverizing methods may be applied, for example, using an impact mill (Hosokawa Micron Corporation; Fine Impact Mill or Sample Mill) or a jet mill (Horkos Corp; Jet Mill).

[0071] As a method of granulating the drug, conventional granulation methods may be used. Examples of such methods include a fluidized bed granulation method, an intermittent granulation method, an agitation granulation method, a high-speed agitation granulation method, a tumbling fluidized bed granulation method, an extrusion granulation method, a pulverization granulation method, a dry granulation method, and the like. In another embodiment, examples thereof include a fluidized bed granulation method, an intermittent granulation method, an agitation granulation method, a high-speed agitation granulation method, a tumbling fluidized bed granulation method, and a dry granulation method, and any method capable of granulating the drug may be used. Examples of a granulator include a fluidized bed granulator (for example, Flow Coater; Freund Corporation, or GPCG; Glatt GmbH), a granulation and coating apparatus equipped with a horizontal rotating disc having a flat powder contact portion [for example, a centrifugal fluidizing granulator (for example, CF granulator; Freund Corporation)], a granulation and coating apparatus having a rotating disk with a flat surface placed at the bottom of a fluidized bed and having an aeration portion (for example, Spiratflow, or Flowcoater with a rotor container; Freund Corporation), and a dry granulator in which material powder is directly compressed, molded, crushed, and sieved (for example, Roller Compactor; Freund Corporation).

[0072] In the dry granulation, for example, the drug, the hydrogel-forming polymer, the hydrophilic base, and addi-
The granulated products may be sieved. After the completion of the sieving, an anti-oxidant may be added. Examples of tabletting include a direct tabletting method in which the drug, the hydrophilic base, and the hydrogel-forming polymer are mixed with an appropriate additive(s), and the mixture is compression-molded to obtain tablets; a method in which a composition obtained by a wet granulation (the granulation is carried out by spraying a mixture of the drug, the hydrophilic base, the hydrogel-forming polymer, and additives with a binder liquid) or a melting granulation (the granulation is carried out by heating a mixture of the drug, the hydrophilic base, the hydrogel-forming polymer, and an appropriate low-melting substance) is formed into tablets; and the like. After the completion of the sieving, an anti-oxidant may be added. Examples of tabletting include a direct tabletting method in which the drug, the hydrophilic base, and the hydrogel-forming polymer are mixed with an appropriate additive(s), and the mixture is compression-molded to obtain tablets; a method in which a composition obtained by a wet granulation (the granulation is carried out by spraying a mixture of the drug, the hydrophilic base, the hydrogel-forming polymer, and additives with a binder liquid) or a melting granulation (the granulation is carried out by heating a mixture of the drug, the hydrophilic base, the hydrogel-forming polymer, and an appropriate low-melting substance) is formed into tablets; and the like.
EXAMPLES

[0092] The present invention will now be further illustrated by, but is by no means limited to, the following Examples.

Example 1

[0093] In a mortar, 10 g of compound A, 2.5 g of polyethylene oxide (Dow chemical product name: WSR N-60K; The same compound was used in the following Examples, unless otherwise specified,), and 7.5 g of polyethylene glycol (Sanyo Chemical Industries, Ltd.; PEG 6000; The same compound was used in the following Examples.) were mixed well. The mixture was formed into tablets using Autograph (Shimadzu; The same apparatus was used in the following Examples.) to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 400 mg.

Example 2

[0094] In a mortar, 10 g of compound A, 3.5 g of polyethylene oxide, and 6.5 g of polyethylene glycol were mixed well, and the mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 400 mg.

Example 3

[0095] In a mortar, 10 g of compound A, 6.25 g of polyethylene oxide, and 5 g of polyethylene glycol were mixed well, and the mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 425 mg.

Example 4

[0096] In a mortar, 10 g of compound A, 5 g of hydroxypropyl methylcellulose (Shin-Etsu Chemical Co., Ltd.; HPMC90SH-4000SR), and 5 g of polyethylene glycol were mixed well, and the mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 400 mg.

Example 5

[0097] In a mortar, 10 g of compound A, 5 g of hydroxypropyl methylcellulose (Shin-Etsu Chemical Co., Ltd.; HPMC90SH-100000SR), and 5 g of polyethylene glycol were mixed well, and the mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 400 mg.

Example 6

[0098] In a mortar, 10 g of compound A, 7.5 g of hydroxypropyl methylcellulose (Shin-Etsu Chemical Co., Ltd.; HPMC90SH-100000SR), and 2.5 g of polyethylene glycol were mixed well, and the mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 400 mg.

Example 7

[0099] After 400 g of compound A, 140 g of polyethylene oxide, 251.2 g of polyethylene glycol, 0.8 g of finely ground BHT (Merck; The same compound was used in the following Examples.) and 8 g of magnesium stearate were weighed out, these compounds were mixed using a mixer. The mixture was compression-molded using Roller Compactor Mini (Freund Corporation) and sieved to obtain a pharmaceutical composition for modified release (granules) of the present invention. The obtained granules were formed into tablets using a rotary tableting machine (Hata Iron Works Co., Ltd.; The same apparatus was used in the following Examples.) to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 400 mg.

Example 8

[0100] The tablets obtained in Example 7 were coated with a film coating agent [Colorcon; Opadry (containing yellow ferric oxide as a stabilizer); The same agent was used in the following Examples, unless otherwise specified.] dispersed into water to obtain a pharmaceutical composition for modified release (tablets) of the present invention.

Example 9

[0101] Into a fluidized bed granulating apparatus GPCG-5 (Freund Corporation; The same apparatus was used in the following Examples.), 1500 g of de-lumped compound A, 1050 g of polyethylene oxide, and 1764 g of polyethylene glycol were loaded, and granulated with 1550 g of a 10% by weight aqueous solution of hydroxypropyl cellulose (Nippon Soda Co., Ltd.; HPC-SI; The same compound was used in the following Examples.) to obtain a pharmaceutical composition for modified release (granules) of the present invention. The resulting pharmaceutical composition for modified release (granules) of the present invention was sieved and mixed with 4 g of finely ground BHT and 30 g of magnesium stearate, and the mixture was formed into tablets using a rotary tableting machine to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 300 mg. The obtained tablets were spray-coated with an aqueous dispersion of the film coating agent using HiCoater to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 309 mg.

Example 10

[0102] Into a fluidized bed granulating apparatus GPCG-5, 1500 g of de-lumped compound A, 1050 g of polyethylene oxide, 1764 g of polyethylene glycol, and 135 g of hydroxypropyl cellulose (HPC-SI) were loaded, and granulated with purified water to obtain a pharmaceutical composition for modified release (granules) of the present invention. The resulting pharmaceutical composition for modified release (granules) of the present invention was sieved and mixed with 4 g of finely ground BHT and 30 g of magnesium stearate, and the mixture was formed into tablets using a rotary tableting machine to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 300 mg. The obtained tablets were spray-coated with an aqueous dispersion of the film coating agent using HiCoater to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 309 mg.

Example 11

[0103] After 400 g of compound A, 100 g of polyethylene oxide, 290 g of polyethylene glycol, 2 g of finely ground BHT,
and 8 g of magnesium stearate were weighed out, these compounds were mixed using a mixer. The mixture was compression-molded using Roller Compactor Mini and sieved to obtain a pharmaceutical composition for modified release (granules) of the present invention. The obtained granules were formed into tablets using a rotary tabletting machine to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 400 mg.

Example 12

[0104] In a mortar, 10 g of compound A, 2.5 g of polyethyleneoxide (Dow chemical; product name: WSR Cougelant), and 12.5 g of polyethylene glycol were mixed well. The mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 400 mg.

Example 13

[0105] In a mortar, 10 g of compound A, 0.5 g of polyethylene oxide (Dow chemical; product name: WSR 301), and 5 g of polyethylene glycol were mixed well. The mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 310 mg.

Example 14

[0106] In a mortar, 5 g of compound A, 15 g of polyethylene oxide, and 5 g of polyethylene glycol were mixed well. The mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 250 mg.

Example 15

[0107] In a mortar, 10 g of compound A, 10 g of polyethylene oxide (Dow chemical; product name: WSR N-12K), and 5 g of D-mannitol (Towa Chemical Industry Co., Ltd; product name: Mannit P) were mixed well. The mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 500 mg.

Example 16

[0108] In a mortar, 2 g of polyethylene oxide, and 10 g of polyethylene glycol were mixed well. The mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 350 mg.

Example 17

[0109] Into a fluidized bed granulating apparatus GPCG-5, 400 g of de-lumped compound A, 1120 g of polyethylene oxide, and 2313.6 g of polyethylene glycol were loaded, and granulated with 1200 g of a 10% by weight aqueous solution of hydroxypropyl cellulose to obtain a pharmaceutical composition for modified release (granules) of the present invention. The resulting pharmaceutical composition for modified release (granules) of the present invention was sieved and mixed with 6.4 g of finely ground BHT and 40 g of magnesium stearate, and the mixture was formed into tablets using a rotary tabletting machine to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 250 mg. The obtained tablets were spray-coated with an aqueous dispersion of the film coating agent (containing yellow ferric oxide and red ferric oxide as stabilizers) using HiCoater to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 257.5 mg.

The formulations in Examples 1 to 17 are shown in Tables 1 to 3.
carried out in accordance with a USP dissolution test (paddle method). As a test fluid, 900 mL of a phosphate buffer (pH 6.8) was used. The pharmaceutical composition prepared in Comparative Example 1 was tested in accordance with a dissolution test, method 2 described in the Japanese Pharmacopoeia. As a test fluid, 900 mL of a McIlvain buffer (pH 6.8) was used, and the paddle rotation speed was 50 rpm.

[0113] The results are shown in Table 4. The dissolution rate after 1.5 hours of the pharmaceutical composition for modified release prepared in Example 5 was less than 40%. By contrast, the composition prepared in Comparative Example showed a high dissolution rate of 85% or more after 0.5 hour.

| TABLE 4 |
|-----------------|-----------------|-----------------|-----------------|
| Example 2 | Example 8 | Example 9 | Comparative Example 1 |
| 0.5 hr. | 93% | 95% | 95% |
| 1.5 hr. | 35% | 39% | 32% |
| 2.5 hr. | 57% | 61% | 54% |
| 4.5 hr. | 93% | 95% | 92% |

2. Stability Test

[0114] Plastic bottles were filled with the pharmaceutical composition for modified release prepared in Example 11, and sealed. These bottles were preserved under the conditions at 40°C and 75% RH or at 60°C for 3 months. After the preservation, each pharmaceutical composition was subjected to a dissolution test carried out in accordance with a USP dissolution test (paddle method). As a test fluid, 900 mL of a phosphate buffer (pH 6.8) was used. The results are shown in FIG. 1. The acceleration of a dissolution rate was not observed after the preservation for 3 months under the conditions at 40°C and 75% RH or at 60°C, and the results were indicative that the pharmaceutical composition was stable.

[0115] The pharmaceutical compositions for modified release prepared in Examples 8 and 9 were packed with aluminum/aluminum blister, and preserved under the conditions at 40°C and 75% RH for 6 months. After the preservation, each pharmaceutical composition was subjected to a dissolution test carried out in accordance with a USP dissolution test (paddle method). As a test fluid, 900 mL of a phosphate buffer (pH 6.8) was used. As a result, changes in the dissolution rate at the point showing a dissolution rate of approximately 50% were 2% and 3%, with respect to the pharmaceutical compositions prepared in Examples 8 and 9, respectively, and the results were indicative that the pharmaceutical compositions were stable.

[0116] The pharmaceutical composition for modified release prepared in Example 17 was exposed to 1.2 million Lux hr of light. After the exposure, the pharmaceutical composition was subjected to a dissolution test carried out in accordance with a USP dissolution test (paddle method). As a test fluid, 900 mL of a phosphate buffer (pH 6.8) was used. As a result, the change in the dissolution rate at the point showing a dissolution rate of approximately 50% was less than 1%, and the result was indicative that the pharmaceutical composition was stable.

3. Pharmacokinetics (PK) Test in Human

[0117] The pharmaceutical composition for modified release prepared in Example 8, which contained the equivalent corresponding to 200 mg of compound A, was administered to healthy persons in a fasted state or after 30 minutes from the intake of food, and the plasma levels of the drug were measured.

[0118] For comparison, 2 capsules of the pharmaceutical composition (conventional formulation) prepared in Comparative Example 1, which contained the equivalent corresponding to 160 mg of compound A, was administered to healthy persons in a fasted state or after 30 minutes from the intake of food, and the plasma levels of the drug were measured.

[0119] With respect to the conventional formulation, the rate of decrease of Cmax in the fed state was 67%, in comparison with that in a fasted state, and the rate of decrease of AUC was 47% (Cmax in the fasted state was approximately three times higher than that in the fed state). With respect to the pharmaceutical composition for modified release of the present invention, the rate of decrease of Cmax in free-feeding was 42%, in comparison with that in a fasted state, and the rate of decrease of AUC was 25%. These results indicated that the reductions of Cmax and AUC caused by food intake could be significantly alleviated by the pharmaceutical composition for modified release of the present invention.

INDUSTRIAL APPLICABILITY

[0120] According to the present invention, a pharmaceutical composition for modified release in which the changes in AUC and Cmax caused by food intake can be decreased by controlling a releasing rate of the active ingredient can be provided.

[0121] As above, the present invention was explained with reference to particular embodiments, but modifications and improvements obvious to those skilled in the art are included in the scope of the present invention.

1. A pharmaceutical composition for modified release, comprising:

(1) 10 mg to 200 mg of (R)-2-{2-aminothiazol-4-y1}-4’-{2-[2-hydroxy-2-phenylethyl]aminoethyl]acetic acid anilide, or a pharmaceutically acceptable salt thereof,

(2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less, and

(3) a hydrogel-forming polymer having an average molecular weight of approximately 100,000 to 5,000, 000, or a viscosity of 12 mPa·s at a 5% aqueous solution at 25°C to 7500 mPa·s at a 1% aqueous solution at 25°C,

wherein the hydrogel-forming polymer is present in an amount of 1% by weight to 40% by weight with respect to the total weight of the pharmaceutical composition; and

wherein a drug dissolution rate from the pharmaceutical composition is 75% or less after 1.5 hours, and 75% or more to 100% or less after 7 hours from the beginning of a dissolution test.

2. The pharmaceutical composition for modified release according to claim 1, wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, D-sorbitol, xylitol, lactose, sucrose, anhydrous maltose, D-fructose, dextran, glucose, polyoxyethylene hydrogenated castor oil, polyoxyethyl
polyoxypropylene glycol, polyoxyethylene sorbitan higher fatty acid ester, sodium chloride, magnesium chloride, citric acid, tartaric acid, glycine, β-alanine, lysine hydrochloride, and meglumine.

3. The pharmaceutical composition for modified release according to claim 2, wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, lactose, sucrose, sodium chloride, and polyoxyethylene polyoxypolypropylene glycol.

4. The pharmaceutical composition for modified release according to claim 1, wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 75% by weight with respect to the total weight of the pharmaceutical composition.

5. The pharmaceutical composition for modified release according to claim 4, wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition.

6. The pharmaceutical composition for modified release according to claim 1, wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, hydroxyethyl cellulose, and a carboxyvinyl polymer.

7. The pharmaceutical composition for modified release according to claim 6, wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, and hydroxypropyl cellulose.

8. (canceled)

9. The pharmaceutical composition for modified release according to claim 1, further comprising an antioxidant.

10. The pharmaceutical composition for modified release according to claim 9, wherein the antioxidant is one compound, or two or more compounds selected from the group consisting of butyl hydroxytoluene, propyl gallate, and sodium ascorbate.

11. The pharmaceutical composition for modified release according to claim 10, wherein the antioxidant is butyl hydroxytoluene.

12. The pharmaceutical composition for modified release according to claim 9, wherein an amount of the antioxidant is 0.025% by weight to 0.25% by weight.

13. The pharmaceutical composition for modified release according to claim 11, further comprising a stabilizer.

14. The pharmaceutical composition for modified release according to claim 10, wherein the stabilizer is one compound, or two or more compounds selected from the group consisting of yellow ferric oxide, red ferric oxide, and black iron oxide.

15. The pharmaceutical composition for modified release according to claim 14, wherein the stabilizer is yellow ferric oxide and/or red ferric oxide.

16. The pharmaceutical composition for modified release according to claim 13, wherein an amount of the stabilizer is 0.08% by weight to 1% by weight.

17. A process of manufacturing a pharmaceutical composition for modified release, characterized by comprising mixing (1) (R)-2-(2-aminothiazol-4-yl)-4-2-(2-hydroxy-2-phenylethyl)aminoethylacetic acid anilide, or a pharmaceutically acceptable salt thereof with (2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less and (3) a hydrogel-forming polymer having an average molecular weight of approximately 100,000 or more, or a viscosity of 12 mPa·s or more at a 5% aqueous solution at 25°C, wherein an amount of the additive is 5% by weight to 75% by weight with respect to the total weight of the pharmaceutical composition, and an amount of the hydrogel-forming polymer is 1% by weight to 40% by weight with respect to the total weight of the pharmaceutical composition.

18. The process according to claim 17, wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, D-sorbitol, xylitol, lactose, sucrose, anhydrous maltose, D-fructose, dextran, glucose, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypolypropylene glycol, polyoxyethylene sorbitan higher fatty acid ester, sodium chloride, magnesium chloride, citric acid, tartaric acid, glycine, β-alanine, lysine hydrochloride, and meglumine.

19. The process according to claim 18, wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, hydroxyethyl cellulose, and a carboxyvinyl polymer.

20. The pharmaceutical composition for modified release according to claim 1, wherein a drug dissolution rate from the pharmaceutical composition is 92%, 93% or 95% after 4.5 hours from the beginning of a dissolution test.

21. The pharmaceutical composition for modified release according to claim 1, wherein the average molecular weight of the hydrogel-forming polymer is 100,000 to 2,000,000.

22. A method of reducing an effect of food intake, comprising the step of administering a pharmaceutical composition comprising a drug, which is a pharmaceutical composition for modified release comprising:

(1) 10 mg to 200 mg of (R)-2-[2-(2-aminothiazol-4-yl)-4-2-(2-hydroxy-2-phenylethyl)aminoethyl]acetic acid anilide, or a pharmaceutically acceptable salt thereof,

(2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less, and

(3) a hydrogel-forming polymer having an average molecular weight of approximately 100,000 to 5,000,000, or a viscosity of 12 mPa·s at a 5% aqueous solution at 25°C, to 7500 mPa·s at a 1% aqueous solution at 25°C,

wherein the hydrogel-forming polymer is present in an amount of 1% by weight to 40% by weight with respect to the total weight of the pharmaceutical composition; and

wherein a drug dissolution rate from the pharmaceutical composition is 75% or less after 1.5 hours, and 75% or more to 100% or less after 7 hours from the beginning of a dissolution test.

23. The method according to claim 22, wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds
selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, D-sorbitol, xylitol, lactose, sucrrose, anhydrous maltose, D-fructose, dextran, glucose, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol, polyoxyethylene sorbitan higher fatty acid ester, sodium chloride, magnesium chloride, citric acid, tartaric acid, glycine, β-alanine, lysine hydrochloride, and meglumine.

24. The method according to claim 23, wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, lactose, sucrrose, sodium chloride, and polyoxyethylene polyoxypropylene glycol.

25. The method according to claim 22, wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 75% by weight with respect to the total weight of the pharmaceutical composition.

26. The pharmaceutical composition for modified release according to claim 25, wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition.

27. The method according to claim 22, wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, hydroxyethyl cellulose, and a carboxy vinyl polymer.

28. The method according to claim 27, wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, and hydroxypropyl cellulose.

29. The pharmaceutical composition for modified release according to claim 22, further comprising an antioxidant.

30. The method according to claim 29, wherein the antioxidant is one compound, or two or more compounds selected from the group consisting of butyl hydroxytoluene, propyl gallate, and sodium ascorbate.

31. The method according to claim 30, wherein the antioxidant is butyl hydroxytoluene.

32. The method according to claim 29, wherein an amount of the antioxidant is 0.025% by weight to 0.25% by weight.

33. The method according to claim 22, further comprising a stabilizer.

34. The method according to claim 33, wherein the stabilizer is one compound, or two or more compounds selected from the group consisting of yellow ferric oxide, red ferric oxide, and black iron oxide.

35. The method according to claim 34, wherein the stabilizer is yellow ferric oxide and/or red ferric oxide.

36. The method according to claim 33, wherein an amount of the stabilizer is 0.05% by weight to 1% by weight.

37. The method according to claim 22, wherein a drug dissolution rate from the pharmaceutical composition is 92%, 93% or 95% after 4.5 hours from the beginning of a dissolution test.

38. The method according to claim 22, wherein the average molecular weight of the hydrogel-forming polymer is 100, 000 to 2,000,000.

* * * * *