DESCRIPTION

Title of Invention

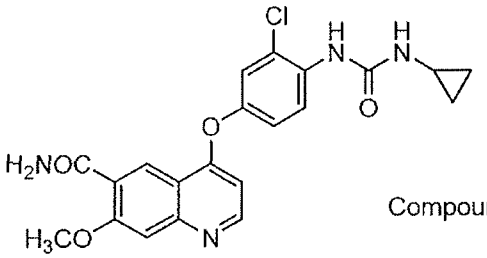
METHOD FOR SUPPRESSING BITTERNESS OF QUINOLINE DERIVATIVE

Technical Field

[0001] The present invention relates to a method for suppressing bitterness of a medicine.

Background Art

[0002] 4-(3-Chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide (hereinafter also referred to as Compound 1 or lenvatinib) or a salt thereof, which is a quinoline derivative having an antiangiogenic effect, is known (Patent Literature 1).



Compound 1:Lenvatinib

[0003] As a pharmaceutical composition comprising Compound 1 or a salt thereof, there is known a pharmaceutical composition comprising Compound 1 or a salt thereof and (i) a compound, a 5% (w/w) solution or suspension of which has a pH of 8 or more and/or (ii) a silicic acid to reduce a degradation under humidified and heated conditions or inhibit a gelation on a surface of the pharmaceutical composition (Patent Literature 2).

[0004] Besides, as a pharmaceutical composition excellent in dissolution properties of Compound 1 and stable through long-term storage, a pharmaceutical composition comprising (1) Compound 1 or a salt thereof, and (2) a basic substance is known (Patent Literature 3).

[0005] Furthermore, there is known a composition comprising a pharmacologically active ingredient of an organic sulfonate, a disintegrating agent and a water-soluble salt, a 2.5% aqueous solution of which has a pH of 3 to 9 (Patent Literature 4).

Citation List

Patent Literature

[0006] [Patent Literature 1] U.S. Patent Application Publication No. 2004/0053908

[Patent Literature 2] U.S. Patent Application Publication No. 2008/0214604

[Patent Literature 3] U.S. Patent Application Publication No. 2012/0077842

[Patent Literature 4] U.S. Patent Application Publication No. 2008/0214557

Summary of Invention

Technical Problem

[0007] Usually, when a pharmaceutical composition is administered to a patient, a pharmaceutical composition such as a capsule dissolved or suspended in water or the like is administered in some cases from the viewpoint of medication compliance. If a drug having bitterness dissolved or suspended in water or the like is administered to a patient, however, it is apprehended that the patient may have trouble taking the drug due to the bitterness, and this tendency is increased if the patient is a child. Besides, when a pharmaceutical composition is administered to a child, an administration form that can be easily swallowed, such as a suspension, is sometimes employed, but due to the size of the digestive tract of the child, there is an upper limit in the amount of a solvent used for the suspension. On the other hand, due to the physical properties of an active pharmaceutical ingredient such as consistency and solubility, not only the bitterness but also the active pharmaceutical ingredient contained in the suspension may remain in a vessel, and thus, the recovery may not be sufficient in some cases.

Solution to Problem

[0008] The present inventors have found that Compound 1 or a pharmaceutically acceptable salt thereof has bitterness. As a result of earnest studies, the present inventors have found that the bitterness of Compound 1 or the pharmaceutically acceptable salt thereof can be suppressed by mixing a basic substance such as calcium carbonate with Compound 1 or the pharmaceutically acceptable salt thereof. Besides, the present inventors have found that if an administration method comprising: 1) suspending, in an aqueous solvent in a vessel, a pharmaceutical composition comprising Compound 1 or a pharmaceutically acceptable salt thereof and a basic substance; 2) administering a suspension obtained in 1) from the vessel to a patient; 3) rinsing the vessel with an aqueous solvent; and 4) administering a rinsing solution obtained in 3) to the patient is employed, the suspension of Compound 1 can be administered to a child at high recovery without causing the child to feel bitterness and in a liquid amount administrable to the child.

[0009] Specifically, the present invention provides the following [1] to [33]:

[1] A method for suppressing bitterness of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide, comprising mixing 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-

6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof and a basic substance.

[2] The method according to [1], wherein 0.01 to 50 parts by weight of the basic substance is mixed per 1 part by weight of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof.

[3] The method according to [1], wherein 0.16 to 80 mol of the basic substance is mixed per 1 mol of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof.

[4] The method according to any one of [1] to [3], wherein the basic substance is a basic oxide, a basic carbonate or a basic hydroxide.

[5] The method according to any one of [1] to [3], wherein the basic substance is calcium carbonate or magnesium oxide.

[6] The method according to any one of [1] to [3], wherein the basic substance is calcium carbonate.

[7] The method according to any one of [1] to [6], wherein the pharmaceutically acceptable salt is a mesylate.

[8] A pharmaceutical composition, comprising 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof, and a basic substance in an amount effective for suppressing bitterness.

[9] A pharmaceutical composition, comprising 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof, the pharmaceutical composition comprising means for mixing a basic substance for suppressing bitterness.

[10] A pharmaceutical composition, comprising 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof and a basic substance, the pharmaceutical composition having bitterness suppressed.

[11] The pharmaceutical composition according to any one of [8] to [10], comprising 0.01 to 50 parts by weight of the basic substance per 1 part by weight of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof.

[12] The pharmaceutical composition according to any one of [8] to [10], wherein 0.16 to 80

mol of the basic substance is mixed per 1 mol of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof.

[13] The pharmaceutical composition according to any one of [8] to [12], wherein the basic substance is a basic oxide, a basic carbonate or a basic hydroxide.

[14] The pharmaceutical composition according to any one of [8] to [12], wherein the basic substance is calcium carbonate or magnesium oxide.

[15] The pharmaceutical composition according to any one of [8] to [12], wherein the basic substance is calcium carbonate.

[16] The pharmaceutical composition according to any one of [8] to [15], wherein the pharmaceutically acceptable salt is a mesylate.

[17] The pharmaceutical composition according to any one of [8] to [16], in a dosage form of an orally disintegrating tablet, a chewable preparation, an effervescent tablet, a dispersible tablet, a soluble tablet, a syrup, a preparation for a syrup, a troche, or an oral liquid preparation.

[18] The pharmaceutical composition according to any one of [8] to [16], being a preparation that can be suspended in an aqueous solvent upon an administration to prepare a suspension.

[19] A bitterness suppressing agent, comprising a basic substance, for 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof.

[20] The bitterness suppressing agent according to [19], wherein the basic substance added is in an amount of 0.01 to 50 parts by weight per 1 part by weight of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof.

[21] The bitterness suppressing agent according to [19], wherein the basic substance added is in an amount of 0.16 to 80 mol per 1 mol of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof.

[22] The bitterness suppressing agent according to any one of [19] to [21], wherein the basic substance is a basic oxide, a basic carbonate or a basic hydroxide.

[23] The bitterness suppressing agent according to any one of [19] to [21], wherein the basic substance is calcium carbonate or magnesium oxide.

[24] The bitterness suppressing agent according to any one of [19] to [21], wherein the basic

substance is calcium carbonate.

[25] The bitterness suppressing agent according to any one of [19] to [24], wherein the pharmaceutically acceptable salt is a mesylate.

[26] A method for administering a suspension comprising 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof, and a basic substance, the method comprising: 1) suspending, in an aqueous solvent in a vessel, a pharmaceutical composition comprising 1 to 24 mg of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof, and the basic substance; 2) administering a suspension obtained in 1) to a patient from the vessel; 3) rinsing the vessel with an aqueous solvent; and 4) administering a rinsing solution obtained in 3) to the patient.

[27] The method according to [26], wherein the 1) comprises: i) pouring the aqueous solvent in the vessel, ii) allowing the vessel to stand; and iii) shaking the vessel.

[28] The method according to [26] or [27], wherein the pharmaceutical composition is suspended in 1 to 10 mL of the aqueous solvent in 1).

[29] The method according to [28], wherein the pharmaceutical composition is suspended in about 3 mL of the aqueous solvent in 1).

[30] The method according to [26], wherein the vessel is rinsed with 1 to 10 mL of the aqueous solvent in 3).

[31] The method according to [30], wherein the vessel is rinsed with about 2 mL of the aqueous solvent in 3).

[32] A method for treating a cancer by administering a suspension containing 1 to 24 mg of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof, and a basic substance.

[33] A method for treating a cancer, comprising administering a suspension comprising 1 to 24 mg of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof, and a basic substance, the method comprising: 1) suspending, in an aqueous solvent in a vessel, a pharmaceutical composition comprising 1 to 24 mg of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof, and the basic substance; 2) administering a suspension obtained in 1) to a patient from the vessel; 3) rinsing the vessel with an aqueous

solvent; and 4) administering a rinsing solution obtained in 3) to the patient.

Advantageous Effects of Invention

[0010] Compound 1 or a pharmaceutically acceptable salt thereof is known as an anticancer agent for thyroid cancer and the like, and a cancer can be treated without causing a patient to feel bitterness upon drug administration by the method of the present invention.

Brief Description of Drawings

[0011] Figure 1 is a diagram illustrating relative comparison of bitterness of lenvatinib mesylate and quinine hydrochloride.

Figure 2 is a diagram illustrating concentration dependence of the bitterness suppressing effect of calcium carbonate.

Figure 3 is a diagram illustrating concentration dependence of the bitterness suppressing effect of magnesium oxide.

Figure 4 is a diagram illustrating the bitterness suppressing effect of various polymers.

Figure 5 is a diagram illustrating the bitterness suppressing effect of various low molecular weight compounds.

Figure 6 is a diagram illustrating the bitterness suppressing effect of a lenvatinib mesylate-containing composition.

Figure 7 is a diagram illustrating the bitterness suppressing effect of respective components of the lenvatinib mesylate-containing composition.

Figure 8 is a diagram illustrating results of a dissolution test of orally disintegrating tablets.

Figure 9 is a diagram illustrating the bitterness suppressing effect of a lenvatinib mesylate-containing composition.

Figure 10 is a diagram illustrating the bitterness suppressing effect of various low molecular weight compounds.

Figure 11 is a diagram illustrating the bitterness suppressing effect of various low molecular weight compounds.

Figure 12 is a diagram illustrating the bitterness suppressing effect of various silicic acid compounds.

Description of Embodiments

[0012] Herein, a basic substance may be a low molecular weight compound or a high molecular weight compound as long as it is a substance exhibiting basicity, preferable

examples include a basic oxide, a basic carbonate, a basic hydroxide or a sodium salt of a polymer having a carboxyl group, and it is more preferably calcium carbonate, magnesium carbonate, potassium carbonate, magnesium oxide, magnesium hydroxide, sodium carboxymethyl starch or croscarmellose sodium, further preferably calcium carbonate or magnesium oxide, and most preferably calcium carbonate.

[0013] Preferably 0.01 to 50 parts by weight, more preferably 0.03 to 10 parts by weight, and most preferably 0.05 to 5 parts by weight of the basic substance is mixed per 1 part by weight of a compound 1.

[0014] When the basic substance is a low molecular weight compound, preferably 0.16 to 80 mol, more preferably 0.3 to 60 mol, and most preferably 0.5 to 40 mol of the basic substance is mixed per 1 mol of Compound 1.

[0015] Herein, a pharmaceutically acceptable salt means a hydrochloride, a hydrobromide, a tosylate, a sulfate, a mesylate or an esylate, and is preferably a mesylate.

[0016] Herein, the "bitterness" of Compound 1 or the pharmaceutically acceptable salt thereof is measured by the following method. A solution of Compound 1 at a concentration of 8 mg/mL as a free form is prepared by dissolving Compound 1 or the pharmaceutically acceptable salt thereof in a 10 mM potassium chloride aqueous solution. To the thus obtained solution, an additive is added if necessary, and the resultant is stirred for 30 minutes and then centrifuged to give a liquid phase component. The bitterness of the liquid phase component is measured using a taste sensor (AC0) for measuring bitterness, and the thus obtained value is used as a bitterness index.

[0017] Herein, the term "suppress the bitterness" of Compound 1 or the pharmaceutically acceptable salt thereof means that as measured "bitterness" according to the above-described method, the relative ratio of a measured value of a sample obtained by adding an additive into a control, which comprising Compound 1 or the pharmaceutically acceptable salt thereof, to a measured value of the control is less than 100%, and preferably 70% or less. Here, the control comprising Compound 1 or the pharmaceutically acceptable salt thereof may be Compound 1 itself or the pharmaceutically acceptable salt thereof itself, or may be a mixture also comprising an additional component (such as a capsule) if necessary.

[0018] A pharmaceutical composition of the present invention is not particularly limited as long as it is a preparation in which the bitterness of Compound 1 or the pharmaceutically acceptable salt thereof may possibly be felt in a usual administration method or in an administration method comprising dissolving or suspending in water or the like without

impairing a specific function such as an enteric property. Examples of such a preparation include an orally administered preparation and a preparation applied to oral cavity described in The Japanese Pharmacopoeia, Sixteenth Edition, General Rules for Preparations, and specific examples include a tablet, an orally disintegrating tablet, a chewable preparation, an effervescent tablet, a dispersible tablet, a soluble tablet, a powder, a granule, a capsule, a syrup, a preparation for a syrup, a troche, an oral liquid preparation (such as a suspension) and an oral jelly preparation. Examples of a preferable form include an orally disintegrating tablet, a chewable preparation, an effervescent tablet, a dispersible tablet, a soluble tablet, a syrup, a preparation for a syrup, a troche and an oral liquid preparation, which stay in oral cavity for a comparatively long period of time and hence possibly cause a patient to feel the bitterness. Besides, even a dosage form of a capsule or the like can be included in the preferable form if an oral liquid preparation can be prepared from the preparation at time of use using a solvent such as water.

[0019] The pharmaceutical composition of the present invention can be produced by any of known methods such as methods described in The Japanese Pharmacopoeia, Sixteenth Edition, General Rules for Preparations. For example, a granule can be produced by adding, if necessary, a diluting agent, a binding agent, a disintegrator, a solvent or the like to Compound 1 or the pharmaceutically acceptable salt thereof, and subjecting the resultant to stirring granulation, extrusion granulation, oscillating granulation, fluidized bed granulation, spray granulation or the like. A core substance of a purified sucrose spherical granule, a lactose-crystalline cellulose spherical granule, a sucrose-starch spherical granule or a granular crystalline cellulose may be coated with an epipastic comprising an additive such as water, sucrose, hydroxypropylcellulose, methylcellulose or polyvinylpyrrolidone. The resultant may be further sized or ground. When the pharmaceutical composition of the present invention is suspended in an aqueous solvent such as water at time of use and then administered, it is possible to administer a suspension prepared by suspending a mixture (including a dosage form such as a tablet or a capsule) of 1 to 24 mg of Compound 1 or the pharmaceutically acceptable salt thereof with a basic substance in an aqueous solvent in a vessel such as a vial, a syringe or a syringe equipped with a nasogastric tube (NG tube). The amount of the aqueous solvent used for the suspension (which can be a sweet drink such as an apple juice according to patient's preference) is preferably 1 to 10 mL, more preferably 2 to 5 mL and further preferably about 3 mL. At the time of suspending, it is preferable to allow the mixture to stand still for a while, preferably about 10 minutes, after adding the

aqueous solvent, and then to shake the resultant for a while, preferably about 3 minutes. Besides, in view of definitely administering Compound 1 or the pharmaceutically acceptable salt thereof, after administering the suspension, the vessel used for the suspension may be rinsed with 1 to 10 mL, more preferably 1 to 5 mL and further preferably about 2 mL of an aqueous solvent, and the resultant rinsing solution may be further administered. Here, a numerical value with the term "about" encompasses a numerical value obtained by rounding off to the nearest whole number, and for example, "about 3" corresponds to a range of 2.5 to 3.4.

[0020] A list of reagents used in preparation and bitterness measurement of examples and comparative examples is shown in Table 1.

[0021] [Table 1]

Component	Molecular Weight	Manufacturer	Grade/Product Name
Potassium Chloride	74.55	Wako Pure Chemical Industries, Ltd.	G.R.
L-Tartaric Acid	150.09	Wako Pure Chemical Industries, Ltd.	G.R.
Ethanol		Wako Pure Chemical Industries, Ltd.	G.R.
2M Hydrochloric Acid Aqueous Solution		Kanto Chemical Co., Inc.	2 mol/L Hydrochloric Acid (2M)
Quinine Hydrochloride Dihydrate	396.91	Wako Pure Chemical Industries, Ltd.	E.P.
Lenvatinib Mesylate	522.96	Eisai Co., Ltd.	
Calcium Carbonate	100.09	Bihoku Funka Kogyo Co., Ltd.	Precipitated Calcium Carbonate A
Magnesium Oxide	40.3	Kyowa Chemical Industry Co., Ltd.	Magnesium Oxide, Japanese Pharmacopoeia
Magnesium Carbonate	84.32	Kyowa Chemical Industry Co., Ltd.	(Heavy) Magnesium Carbonate, Japanese Pharmacopoeia
Potassium Carbonate	138.21	Wako Pure Chemical Industries, Ltd.	G.R.
Sodium Chloride	58.44	Wako Pure Chemical Industries, Ltd.	G.R.
Magnesium Chloride Hexahydrate	203.30	Wako Pure Chemical Industries, Ltd.	G.R.
Calcium Chloride	110.98	Wako Pure Chemical Industries, Ltd.	G.R.
Ferric Chloride Hexahydrate	270.30	Wako Pure Chemical Industries, Ltd.	G.R.
Magnesium Hydroxide	58.32	Kyowa Chemical Industry Co., Ltd.	Kyowa Suimag
Carmellose Calcium		Gotoku Chemical Co., Ltd.	ECG-505
Sodium Carboxymethyl		JRS Pharma	Explotab

Starch			
Carmellose		Gotoku Chemical Co., Ltd.	NS-300
Croscarmellose Sodium		FMC International Inc.	Ac-Di-Sol
Dried Methacrylic Acid Copolymer LD		Evonik Rohm GmbH	Eudragit L100-55
Hypromellose Acetate Succinate		Shin-Etsu Chemical Co., Ltd.	AQOAT AS-HF
Aminoalkyl Methacrylate Copolymer E		Evonik Rohm GmbH	Eudragit EPO
Mannitol		Rocket Japan Co., Ltd.	Pearlitol 50C
Crystalline Cellulose (PH101)		Asahi Kasei Chemicals Corporation	Ceolus PH-101, Japanese Pharmacopoeia
Hydroxypropylcellulose		Nippon Soda Co., Ltd.	HPC-L
Low-substituted Hydroxypropylcellulose		Shin-Etsu Chemical Co., Ltd.	L-HPC LH-21
Crystalline Cellulose (PH102)		Asahi Kasei Chemicals Corporation	Ceolus PH-102, Japanese Pharmacopoeia
Talc		Matsumura Sangyo Co., Ltd.	Hi-Filler #17

[0022] Test Example 1: Relative Comparison of Bitterness between Lenvatinib Mesylate and Quinine Hydrochloride

An apparatus and solutions used for the bitterness measurement are shown in Table 2, and measurement conditions for a sample using a taste perception apparatus are shown in Table 3. As a blank solution for correction, a 10 mM potassium chloride aqueous solution was subjected to the measurement. Measurement samples of Reference Examples 1 to 9 were respectively prepared by dissolving respective components shown in Table 4 in a 10 mM potassium chloride aqueous solution. The measurement with the taste perception apparatus was performed four times on each sample, and merely three results of the second to fourth measurements were used for analysis. Relative bitterness to Reference Example 7 was calculated in accordance with the following expression, and an average of the three measurement values is shown in Table 4 and Figure 1. It is noted that the relative bitterness was calculated using merely data obtained through a series of continuous measurements.

[0023] Relative bitterness to Reference Example 7 (%) = (Measured value of each sample - Measured value of 10 mM potassium chloride aqueous solution) / (Measured value of Reference Example 7 - Measured value of 10 mM potassium chloride aqueous solution) x 100%

[0024] As a result, it was found that the relative bitterness of Reference Example 1 and Reference Example 2 to Reference Example 7 was 100% or more. Accordingly, it was determined that an aqueous solution of lenvatinib mesylate at a concentration of 1.225

mg/mL or more are more bitter than a 0.1 mM quinine hydrochloride aqueous solution.

[0025] [Table 2]

Measurement Apparatus	Taste Perception Apparatus (SA402, Anritsu Corporation)
Measuring Electrode	AC0 Sensor (Intelligent Sensor Technology, Inc.)
Reference Electrode	Ag/AgCl Electrode
Sample Solution Liquid	10 mM Potassium Chloride Aqueous Solution
Reference Liquid	30 mM Potassium Chloride, 0.3 mM L-Tartaric Acid Aqueous Solution
Washing Solution	0.1 M Hydrochloric Acid Solution (Solvent: water/ethanol = 70/30 [v/v] mixture)

[0026] [Table 3]

Treatment Step	Sensor Treatment Method
1 (Washing 1)	Wash measurement sensor with washing solution for 90 seconds
2 (Washing 2)	Wash measurement sensor with reference solution for 240 seconds
3 (Washing 3)	Wash measurement sensor with reference solution for 240 seconds
4 (Stabilization and Measurement of Origin)	Set potential obtained after immersing measurement sensor in reference solution for 30 seconds as origin for measurement
5 (Pretreatment)	Immerse measurement sensor in measurement sample for 30 seconds
6 (Rinsing 1)	Rinse measurement sensor with reference solution for 3 seconds
7 (Rinsing 2)	Rinse measurement sensor with reference solution for 3 seconds
8 (Measurement)	Measure potential after immersing measurement sensor in reference solution for 30 seconds

[0027] [Table 4]

	Reference Example 1	Reference Example 2	Reference Example 3	Reference Example 4	
Quinine Hydrochloride Dihydrate (mM)					
Lenvatinib Mesylate (mg/mL)	12.25	1.225	0.123	0.012	
Relative Bitterness to Reference Example 7 (%)	446%	117%	68%	24%	
	Reference Example 5	Reference Example 6	Reference Example 7	Reference Example 8	Reference Example 9
Quinine Hydrochloride Dihydrate (mM)	1.00	0.30	0.10	0.030	0.010
Lenvatinib Mesylate (mg/mL)					
Relative Bitterness to Reference Example 7 (%)	254%	174%	100%	53%	27%

[0028] 12.25 mg/mL of lenvatinib mesylate is equivalent to 10 mg/mL of a free form of lenvatinib.

[0029] Test Example 2: Concentration Dependency of Bitterness Suppressing Effect of Calcium Carbonate

Measurement samples of Examples 1 to 6 and Comparative Example 1 were prepared in the following manner, and the bitterness was measured by employing the same apparatus and method as those of Test Example 1.

(1) Lenvatinib mesylate was dissolved in a 10 mM potassium chloride aqueous solution to a concentration of 9.8 mg/mL.

(2) To the aqueous solution prepared in (1), components other than the lenvatinib mesylate were added to attain a composition shown in Table 5, and the resultant was stirred for 30 minutes with a stirrer.

(3) The resultant was subjected to centrifugation using a centrifuge under conditions of gravitational acceleration of 20000 g or more for 20 minutes, and a supernatant solution was collected as a measurement sample. If the separation of the supernatant portion was found to be insufficient by visual check, the centrifugation was further performed under conditions of gravitational acceleration of 20000 g or more for 20 minutes, and then the supernatant solution was collected as the measurement sample. In Comparative Example 1, no solid component was added to the aqueous solution prepared in (1), and hence the aqueous solution of (1) was directly used as the measurement sample without performing the centrifugation.

[0030] The measurement with the taste perception apparatus was performed four times on each sample, and three measurement results of the second to fourth measurements were used for the analysis. The relative bitterness to Comparative Example 1 was calculated in accordance with the following equation, and an average of the three measured values is shown in Table 5 and Figure 2. It is noted that the relative bitterness was calculated using merely data obtained through a series of continuous measurements.

[0031] Relative bitterness to Comparative Example 1 (%) = (Measured value of each sample - Measured value of 10 mM potassium chloride aqueous solution) / (Measured value of Comparative Example 1 - Measured value of 10 mM potassium chloride aqueous solution) x 100%

[0032] As a result, it was found that the relative bitterness to Comparative Example 1 was decreased as the amount of potassium carbonate to be added was increased, and the relative bitterness of Examples 1 to 4 was found to be 70% or less.

[0033] [Table 5]

	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Comparative Example 1
Lenvatinib Mesylate	9.8	9.8	9.8	9.8	9.8	9.8	9.8

(mg/mL)							
Calcium Carbonate (mg/mL)	26.4	2.64	1.32	0.66	0.26	0.026	
Molar Ratio (Additive/Lenvatinib Mesylate)	14.1	1.41	0.70	0.35	0.14	0.01	
Relative Bitterness to Comparative Example 1 (%)	46%	44%	43%	66%	80%	92%	100%

[0034] 9.8 mg/mL of lenvatinib mesylate is equivalent to 8 mg/mL of a free form of lenvatinib.

[0035] Test Example 3: Concentration Dependency of Bitterness Suppressing Effect of Magnesium Oxide

In the same manner as in Test Example 2, measurement samples of Examples 7 to 12 and Comparative Example 1 respectively having compositions shown in Table 6 were prepared to measure the bitterness of the samples.

As a result, it was found, as illustrated in Figure 3, that the relative bitterness to Comparative Example 1 was decreased as the amount of magnesium oxide to be added was increased, and the relative bitterness of Examples 7 to 11 was found to be 70% or less.

[0036] [Table 6]

	Example 7	Example 8	Example 9	Example 10	Example 11	Example 12	Comparative Example 1
Lenvatinib Mesylate (mg/mL)	9.8	9.8	9.8	9.8	9.8	9.8	9.8
Magnesium Oxide (mg/mL)	26.4	2.64	1.32	0.66	0.26	0.026	
Molar Ratio (Additive/Lenvatinib Mesylate)	35.0	3.50	1.75	0.87	0.35	0.03	
Relative Bitterness to Comparative Example 1 (%)	16%	12%	9%	7%	44%	89%	100%

[0037] 9.8 mg/mL of lenvatinib mesylate is equivalent to 8 mg/mL of a free form of lenvatinib.

[0038] Test Example 4: Bitterness Suppressing Effect of Various Polymers

In the same manner as in Test Example 2, measurement samples of Examples 13 to 14 and Comparative Examples 1 to 6 respectively having compositions shown in Table 7 were prepared to measure the bitterness of the samples.

As a result, it was found, as illustrated in Figure 4, that the relative bitterness to Comparative Example 1 of Examples 13 and 14 each containing a sodium salt of a polymer

having a carboxyl group was 70% or less.

[0039] [Table 7]

	Comp. Ex 1	Comp Ex 2	Ex 13	Comp Ex 3	Ex 14	Comp Ex 4	Comp Ex 5	Comp Ex 6
Lenvatinib Mesylate (mg/mL)	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8
Carmellose Calcium (mg/mL)		13.2						
Sodium Carboxymethyl Starch (mg/mL)			13.2					
Carmellose (mg/mL)				13.2				
Croscarmellose Sodium (mg/mL)					13.2			
Dried Methacrylic Acid Copolymer LD (mg/mL)						13.2		
Hypromellose Acetate Succinate (mg/mL)							13.2	
Aminoalkyl Methacrylate Copolymer E (mg/mL)								13.2
Relative Bitterness to Comparative Example 1 (%)	100%	122%	65%	109%	62%	113%	109%	160%

[0040] 9.8 mg/mL of lenvatinib mesylate is equivalent to 8 mg/mL of a free form of lenvatinib.

[0041] Test Example 5: Bitterness Suppressing Effect of Various Low Molecular Weight Compounds

In the same manner as in Test Example 2, measurement samples of Examples 15 to 17 and Comparative Examples 1 and 7 to 10 respectively having compositions shown in Table 8 were prepared to measure the bitterness of the samples.

As a result, it was found, as illustrated in Figure 5, that the relative bitterness to Comparative Example 1 of Examples 15 to 17 each containing a basic compound was 70% or less.

[0042] [Table 8]

	Comp Ex 1	Ex 15	Ex 16	Comp Ex 7	Comp Ex 8	Comp Ex 9	Comp Ex 10	Ex 17
Lenvatinib Mesylate (mg/mL)	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8
Magnesium Carbonate (mg/mL)		1.11						
Potassium Carbonate (mg/mL)			1.81					
Sodium Chloride (mg/mL)				0.77				
Magnesium Chloride Hexahydrate (mg/mL)					2.67			

Calcium Chloride (mg/mL)						1.46		
Ferric Chloride Hexahydrate (mg/mL)							3.55	
Magnesium Hydroxide (mg/mL)								0.77
Molar Ratio (Additive/Lenvatinib Mesylate)		0.70	0.70	0.70	0.70	0.70	0.70	0.70
Relative Bitterness to Comparative Example 1 (%)	100%	52%	17%	96%	83%	83%	89%	37%

[0043] 9.8 mg/mL of lenvatinib mesylate is equivalent to 8 mg/mL of a free form of lenvatinib.

[0044] Test Example 6: Bitterness Suppressing Effect of Composition comprising Lenvatinib Mesylate

In the same manner as in Test Example 2, the bitterness of Example 18 and Comparative Example 1 respectively having compositions shown in Table 9 was measured.

[0045] The measurement sample of Example 18 was prepared by the following method: The amounts of respective raw materials used in preparation of a sized granule are shown in Table 10. Lenvatinib mesylate and calcium carbonate were charged and mixed in a vertical granulator. To thus obtained mixture, mannitol, crystalline cellulose (PH101) and low-substituted hydroxypropylcellulose were added to be mixed in the vertical granulator. To the resultant mixture, an aqueous solution of hydroxypropylcellulose and an appropriate amount of purified water were gradually added in this order under stirring. After completing the addition, the resultant was further stirred in the vertical granulator to obtain a granulated granule. The granulated granule was dried using a fluidized bed with an inlet air temperature set to 70°C, and the resultant was sized using a Comil equipped with a screen having a pore size of 1 mm to obtain a sized granule. The sized granule, crystalline cellulose (PH102) and talc were mixed in a tumbler mixer to obtain a composition comprising lenvatinib mesylate, the composition of which is shown in Table 9. After adding a 10 mM potassium chloride aqueous solution to the composition comprising lenvatinib mesylate to a concentration shown in Table 9, the resultant was stirred for 30 minutes with a stirrer. After stirring, the centrifugation operation described in (3) of Test Example 2 was performed to collect a supernatant portion as a measurement sample.

As a result, it was found that the relative bitterness of Example 18 to Comparative Example 1 was 70% or less.

[0046] [Table 9]

	Comparative Example 1	Example 18
Lenvatinib Mesylate (mg/mL)	9.8	9.8[a)]
Calcium Carbonate (mg/mL)		26.4[a)]
Mannitol (mg/mL)		7.0[a)]
Crystalline Cellulose (PH101) (mg/mL)		8.0[a)]
Hydroxypropylcellulose (mg/mL)		2.4[a)]
Low-substituted Hydroxypropylcellulose (mg/mL)		20.0[a)]
Crystalline Cellulose (PH102) (mg/mL)		4.0
Talc (mg/mL)		2.4
Relative Bitterness to Comparative Example 1 (%)	100%	20%

[0047] 9.8 mg/mL of lenvatinib mesylate is equivalent to 8 mg/mL of a free form of lenvatinib.

a) is equivalent to 73.6 mg of the sized granule

[0048] [Table 10]

	Granule for Example 18 (g)
Lenvatinib Mesylate	2450
Calcium Carbonate	6600
Mannitol	1750
Crystalline Cellulose (PH101)	2000
Hydroxypropylcellulose	600
Low-substituted Hydroxypropylcellulose	5000

[0049] Test Example 7: Bitterness Suppressing Effect of Each Component of Lenvatinib Mesylate-containing Composition

Compositions of measurement samples and measurement results of the relative bitterness of Example 19 and Comparative Examples 1 and 11 to 15 to Comparative Example 1 are shown in Table 11 and Figure 7. The measurement of the relative bitterness was performed in the same manner as in Test Example 2. In this examination, the bitterness suppressing effect of each component of the lenvatinib mesylate-containing composition of Example 18 was evaluated.

As a result, it was found, as illustrated in Figure 7, that the relative bitterness to Comparative Example 1 of Example 19 containing calcium carbonate was 70% or less.

[0050] [Table 11]

	Comp Ex 1	Ex 19	Comp Ex 11	Comp Ex 12	Comp Ex 13	Comp Ex 14	Comp Ex 15
Lenvatinib Mesylate (mg/mL)	9.8	9.8	9.8	9.8	9.8	9.8	9.8
Calcium Carbonate (mg/mL)		26.4					
Mannitol (mg/mL)			70				
Crystalline Cellulose (PH101) (mg/mL)				8.0			

Hydroxypropylcellulose (mg/mL)					2.4		
Low-substituted Hydroxypropylcellulose (mg/mL)						20.0	
Crystalline Cellulose (PH102) (mg/mL)				4.0			
Talc (mg/mL)							2.4
Relative Bitterness to Comparative Example 1 (%)	100%	42%	210%	138%	284%	218%	192%

[0051] 9.8 mg/mL of lenvatinib mesylate is equivalent to 8 mg/mL of a free form of lenvatinib.

[0052] Test Example 8: Dissolution Test of Orally Disintegrating Tablet

Reagents shown in Table 12 were used to obtain orally disintegrating tablets on the basis of prescription shown in Table 13 in accordance with procedures shown in Table 14. A dissolution test was performed under conditions shown in Table 14, and results illustrated in Figure 8 were obtained.

[0053] [Table 12]

Component	Molecular Weight	Manufacturer	Grade/Product Name
Mannitol		Merck KGaA	PERTECK M200
Low-substituted Hydroxypropylcellulose		Shin-Etsu Chemical Co., Ltd.	L-HPC NBD-022
Sodium Stearyl Fumarate		JRS Pharma	Pruv
L-arginine	174.2	Merck KGaA	Emprove
Calcium Carbonate	100.09	Bihoku Funka Kogyo Co., Ltd.	Precipitated Calcium Carbonate A
Magnesium Oxide	40.3	Tomita Pharmaceutical Co., Ltd.	Magnesium Oxide XE, Japanese Pharmacopoeia
Aminoalkyl Methacrylate Copolymer E		Evonik Rohm GmbH	Eudragit EPO

[0054] [Table 13]

Component	mg/Tab	g/batch
Lenvatinib Mesylate	12.25	0.245
Mannitol	197.75	3.955
Low-substituted Hydroxypropylcellulose	25.0	0.500
Sodium Stearyl Fumarate	2.5	0.050
Additive	12.5	0.250
Total	250.0	5.00

Additive	Lot
Mannitol	Example 20
L-arginine	Example 21
Calcium Carbonate	Example 22
Magnesium Oxide	Example 23
Aminoalkyl Methacrylate Copolymer E	Example 24

[0055] [Table 14]

Step	Operation
Mixing	Well mixed with mortar and pestle
Tableting	A tablet of 250 mg with a diameter of 9 mm and 9 mmR is compression molded at 10 kN using a compression moldability analyzer (Tabflex, Okada Seiko Co., Ltd.).
Dissolution Test	NTR-6100A, Toyama Sangyo Co., Ltd. 0.1N HCl (USP) 900 mL Paddle 50 rpm (~60 min), then 250rpm (~75 min) 10 mg (per tablet) of E7080 in the free form is put. Absorbance at 308 nm (reference 400 nm) of test solution having passed through a filter (Fine Filter F72, Forte Grow Medical Co., Ltd.) is measured with a cell having a length of 10 mm to calculate dissolution rate (UV-1700, Shimadzu Corporation). Average obtained when n = 2 is described.

[0056] A list of reagents used in preparation and bitterness measurement of examples and comparative examples described below but not listed in Table 1 is shown in Table 15.

[0057] [Table 15]

Component	Molecular Weight	Manufacturer	Grade/Product Name
No. 4 Hypromellose Capsule		CAPSUGEL	Japanese Pharmacopoeia
Sodium Carbonate	105.99	Takasugi Pharmaceutical Co., Ltd.	Food Additive
Ammonium Carbonate		Takasugi Pharmaceutical Co., Ltd.	Food Additive
Sodium Hydrogencarbonate	84.01	Wako Pure Chemical Industries, Ltd.	G.R.
Potassium Hydrogencarbonate	100.12	Takasugi Pharmaceutical Co., Ltd.	G.R.
Magnesium Stearate	591.26	Mallinckrodt	Magnesium Stearate
Calcium Oxide	56.08	Ube Material Industries, Ltd.	CSQ
Calcium Hydroxide	74.09	Wako Pure Chemical Industries, Ltd.	G.R.
Sodium Hydroxide	40.00	Wako Pure Chemical Industries, Ltd.	G.R.
Alumina Magnesium Hydroxide		Kyowa Chemical Industry Co., Ltd.	Sanarumin
L-histidine	155.15	Wako Pure Chemical Industries, Ltd.	G.R.
L-arginine	174.2	Merck	EMPROVE
Synthetic Hydrotalcite		Kyowa Chemical Industry Co., Ltd.	Alcamac B
Magnesium Silicate		Tomita Pharmaceutical Co., Ltd.	Heavy
Magnesium Aluminosilicate		Tomita Pharmaceutical Co., Ltd.	
Calcium Silicate	N/A	Tokuyama Corporation	Flow Light RE

[0058] Text Example 9: Bitterness Suppressing Effect of Composition Comprising

Lenvatinib Mesylate

In the same manner as in Test Example 2, the bitterness of measurement samples of Example 25 and Comparative Example 1 respectively having compositions shown in Table 16 was measured.

[0059] The measurement sample of Example 25 was prepared by the following method. A capsule comprising lenvatinib mesylate, the composition of which is shown in Table 16, was prepared by filling a No. 4 hypromellose capsule with 100 mg of the composition comprising lenvatinib mesylate prepared in Example 18. To the capsule, a 10 mM potassium chloride aqueous solution was added to a concentration shown in Table 16, and the resultant was stirred for 30 minutes with a stirrer. After stirring, the centrifugation operation described in (3) of Test Example 2 was performed to collect a supernatant portion as a measurement sample.

The measurement result of the relative bitterness of Example 25 to Comparative Example 1 is illustrated in Figure 9. As a result, it was found that the relative bitterness of Example 25 to Comparative Example 1 was 70% or less.

[0060] [Table 16]

	Example 25	Comparative Example 1
Lenvatinib Mesylate (mg/mL)	9.8[a)]	9.8
Calcium Carbonate (mg/mL)	26.4[a)]	
Mannitol(mg/mL)	7.0[a)]	
Crystalline Cellulose (PH101) (mg/mL)	8.0[a)]	
Hydroxypropylcellulose (mg/mL)	2.4[a)]	
Low-substituted Hydroxypropylcellulose (mg/mL)	20.0[a)]	
Crystalline Cellulose (PH102) (mg/mL)	4.0	
Talc(mg/mL)	2.4	
No. 4 Hypromellose Capsule (Capsule/mL)	0.8	
Relative Bitterness to Comparative Example 1 (%)	22%	100%

[0061] 9.8 mg/mL of lenvatinib mesylate is equivalent to 8 mg/mL of a free form of lenvatinib.

a) is equivalent to 73.6 mg of the sized granule

[0062] Test Example 10: Bitterness Suppressing Effect of Various Low Molecular Weight Compounds

In the same manner as in Test Example 2, measurement samples of Examples 26 to 39 and Comparative Example 1 respectively having compositions shown in Table 17 and Table 18 were prepared to measure the bitterness of the samples.

The measurement results of the relative bitterness of Examples 26 to 32 to

Comparative Example 1 are illustrated in Figure 10. The measurement results of the relative bitterness of Examples 33 to 39 to Comparative Example 1 are illustrated in Figure 11. As a result, it was found that the relative bitterness of Examples 26 to 39 to Comparative Example 1 was 70% or less.

[0063] [Table 17]

	Ex 26	Ex 27	Ex 28	Ex 29	Ex 30	Ex 31	Ex 32	Comp Ex 1
Lenvatinib Mesylate (mg/mL)	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8
Sodium Carbonate (mg/mL)	1.39							
Ammonium Carbonate (mg/mL)		1.32						
Sodium Hydrogencarbonate (mg/mL)			1.10		3.31			
Potassium Hydrogencarbonate (mg/mL)				1.31		3.94		
Magnesium Stearate (mg/mL)							7.76	
Molar Ratio (Additive/Lenvatinib Mesylate)	0.70	1.4[a)]	0.70	0.70	2.1	2.1	0.70	
Relative Bitterness to Comparative Example 1 (%)	7%	11%	10%	12%	11%	12%	64%	100%

[0064] 9.8 mg/mL of lenvatinib mesylate is equivalent to 8 mg/mL of a free form of lenvatinib.

a) On the basis of a mass composition described in a certificate of analysis issued by the manufacturer, a molar ratio between an ammonium ion and lenvatinib mesylate was calculated.

[0065] [Table 18]

	Ex 33	Ex 34	Ex 35	Ex 36	Ex 37	Ex 38	Ex 39	Comp Ex 1
Lenvatinib Mesylate (mg/mL)	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8
Calcium Oxide (mg/mL)	0.74							
Calcium Hydroxide (mg/mL)		0.97						
Sodium Hydroxide (mg/mL)			0.52					
Alumina Magnesium Hydroxide (mg/mL)				1.06				
L-histidine (mg/mL)					2.04			
L-arginine(mg/mL)						2.29		
Synthetic Hydrotalcite (mg/mL)							1.03	
Molar Ratio (Additive/Lenvatinib Mesylate)	0.70	0.70	0.70	0.70[a)]	0.70	0.70	0.70[a)]	0.70
Relative Bitterness to Comparative Example 1 (%)	33%	34%	17%	50%	14%	17%	70%	100%

[0066] 9.8 mg/mL of lenvatinib mesylate is equivalent to 8 mg/mL of a free form of

lenvatinib.

a) On the basis of a mass composition described in a certificate of analysis issued by the manufacturer, a molar ratio between a sum of metal ions (a sum of an aluminum ion and a magnesium ion) and lenvatinib mesylate was calculated.

[0067] Test Example 11: Bitterness Suppressing Effect of Various Silicic Acid Compounds

In the same manner as in Test Example 2, measurement samples of Examples 40 to 42 and Comparative Example 1 respectively having compositions shown in Table 19 were prepared to measure the bitterness of the samples.

The measurement results of the relative bitterness of Examples 40 to 42 to Comparative Example 1 are illustrated in Figure 12. As a result, it was found that the relative bitterness of Examples 40 to 42 to Comparative Example 1 was 70% or less.

[0068] [Table 19]

	Example 40	Example 41	Example 42	Comparative Example 1
Lenvatinib Mesylate (mg/mL)	9.8	9.8	9.8	9.8
Magnesium Silicate (mg/mL)	13.2			
Magnesium Aluminosilicate (mg/mL)		13.2		
Calcium Silicate (mg/mL)			13.2	
Relative Bitterness to Comparative Example 1 (%)	11%	13%	44%	100%

[0069] 9.8 mg/mL of lenvatinib mesylate is equivalent to 8 mg/mL of a free form of lenvatinib.

[0070] Suspension Comprising Lenvatinib or Salt thereof and Administration Method

a. Preparation of Suspension using Vial and Administration Method

Water or an apple juice (100% juice manufactured by Dole Food Company, Inc.), a screw cap, a 20 mL vial (manufactured by Nichidenrika-Glass Co., Ltd.), and a syringe (20 mL, manufactured by Baxa Corporation) were prepared.

Capsules described in Examples 1 to 3 of U.S. Patent Application Publication No. 2012/0077842 were put in the 20 mL vial (specifically, one to five capsules were put in the vial).

3 mL of water or the apple juice was poured into the vial with the 20 mL syringe.

The vial was closed with the screw cap, and was allowed to stand still for about 10 minutes.

After standing for 10 minutes, the vial was shaken for about 3 minutes to dissolve capsule shell and suspend a granule, and the cap of the vial was removed to administer 3 mL

of the thus obtained suspension contained in the vial to a patient.

Rinsing Step

After administering 3 mL of the suspension from the vial, another fresh 20 mL syringe was used to pour 2 mL of water or the apple juice into the vial.

After closing the vial with the screw cap, the vial was shaken ten times, and the cap of the vial was removed to administer 2 mL of the resultant rinsing solution contained in the vial to the patient.

The total amount of the suspension and the rinsing solution to be administered per one to five capsules was 5 mL.

[0071] b. Preparation of Suspension using Syringe and Administration Method

Water or an apple juice (100% juice manufactured by Dole Food Company, Inc.), a cap, and a syringe (20 mL, manufactured by Baxa Corporation) were prepared.

The capsules described in Examples 1 to 3 of U.S. Patent Application Publication No. 2012/0077842 were put in the 20 mL syringe (specifically, one to five capsules put in the syringe). The tip of the syringe was closed with the cap. 3 mL of water or the apple juice collected using another fresh syringe was poured into the former syringe.

A piston was pushed into the end of the syringe by about 2 cm, and the syringe was allowed to stand still for about 10 minutes. After standing for 10 minutes, the syringe was shaken for about 3 minutes to dissolve capsule shell and suspend a granule. The cap was removed from the syringe, the piston was slid to remove the air from the syringe, and 3 mL of the thus obtained suspension was administered from the syringe to a patient.

Rinsing Step

After administering 3 mL of the suspension from the syringe, the cap was attached to the syringe again.

2 mL of water or the apple juice was collected using another fresh syringe, and was poured into the capped syringe.

The piston was pushed into the end of the syringe by about 2 cm, followed by shaking ten times.

The cap was removed from the syringe, the piston was slid to remove the air from the syringe, and 2 mL of the resultant rinsing solution was administered to the patient.

The total amount of the suspension and the rinsing solution to be administered per one to five capsules was 5 mL.

[0072] c. Preparation of Suspension using Syringe equipped with NG tube and

Administration Method

Water, an NG tube (40 cm, 6 Fr, manufactured by Vygon), a cap and a syringe (20 mL, manufactured by Baxa Corporation) were prepared.

The capsules described in Examples 1 to 3 of U.S. Patent Application Publication No. 2012/0077842 were put in the syringe (specifically, one to five capsules were put in the syringe). The tip of the syringe was closed with the cap. 3 mL of water collected using another fresh syringe was poured into the former syringe.

A piston was pushed into the end of the syringe by about 2 cm, and the syringe was allowed to stand still for about 10 minutes. After standing for 10 minutes, the syringe was shaken for about 3 minutes to dissolve capsule shell and suspend a granule. The cap was removed from the syringe, and the piston was slid to remove the air from the syringe. The NG tube was attached to the syringe, and 3 mL of the thus obtained suspension was administered through the NG tube to a patient.

Rinsing Step

After administering the suspension, the NG tube was removed from the syringe, and the cap was attached to the syringe again.

2 mL of water was collected using another fresh syringe, and was poured into the capped syringe.

The piston was pushed into the end of the syringe by about 2 cm, and then, the syringe was shaken ten times. The cap was removed from the syringe, and the piston was slid to remove the air from the syringe. The NG tube was attached to the syringe, and 2 mL of the resultant rinsing solution was administered through the NG tube to the patient.

The total amount of the suspension and the rinsing solution to be administered per one to five capsules was 5 mL.

[0073] Preparation of Suspension of Capsule Comprising Lenvatinib and Stability thereof

Materials:

Screw cap and vial (20 mL, manufactured by Nichidenrika-Glass Co., Ltd.)

Cap and syringe (20 mL, manufactured by BAXA Corporation)

NG tube (40 cm, 6 Fr, manufactured by Vygon)

Apple juice (100%, manufactured by Dole Food Company, Inc.)

[0074] Sample Preparation

1-1 Preparation of Suspension (using Vial)

A vial was charged with one 1, 4 or 10 mg lenvatinib capsule or five capsules of a

total lenvatinib amount of 17 mg (namely, three 1 mg capsules, one 4 mg capsule and one 10 mg capsule). 3 mL of water or the apple juice was added thereto using a syringe, and the vial was closed with the cap. The resultant vial was allowed to stand still for about 10 minutes, and then was shaken for about 3 minutes to dissolve capsule shell. The thus obtained suspension was taken out of the vial, and was subjected to dilution and centrifugation to prepare a sample liquid.

[0075] 1-2 Rinsing of Vial (First Rinsing Step)

In order to check the effect of a rinsing step, after taking out 3 mL of the suspension, 2 mL of water or the apple juice was added using a syringe, the vial was closed with the cap and then shaken at least ten times, and the resultant rinsing solution was taken out of the vial and subjected to dilution and centrifugation to prepare a sample liquid.

[0076] 1-3 Second Rinsing Step

After taking out 2 mL of the rinsing solution from the vial, 2 mL of water or the apple juice was added using a syringe, and the vial was closed with the cap. The resultant was shaken at least ten times, and the resultant rinsing solution was taken out of the vial and then subjected to dilution and centrifugation to prepare a sample liquid.

[0077] 1-4 Preparation of Suspension (using Syringe)

In the same manner as in the preparation method using the vial, a 20 mL syringe was charged with one 1, 4 or 10 mg lenvatinib capsule or five capsules of a total lenvatinib amount of 17 mg (namely, three 1 mg capsules, one 4 mg capsule and one 10 mg capsule). The syringe was closed with the cap, and after adding 3 mL of water or the apple juice thereto using another fresh syringe, a piston was pushed into the end of the syringe by about 2 cm, and the syringe was allowed to stand still for about 10 minutes. After standing for 10 minutes, the syringe was shaken for about 3 minutes to dissolve capsule shell. The piston was then pushed into the syringe to remove the air from the syringe, and the thus obtained suspension was taken out of the syringe and then subjected to dilution and centrifugation to prepare a sample liquid.

[0078] 1-5 Rinsing of Syringe (First Rinsing Step)

In order to check the effect of a rinsing step, after taken out 3 mL of the suspension, 2 mL of water or the apple juice was added thereto using another fresh syringe, the syringe was closed with the cap and then shaken at least ten times, and the resultant rinsing solution was taken out of the syringe and then subjected to dilution and centrifugation to prepare a sample liquid.

[0079] 1-6 Second Rinsing Step

After taking out 2 mL of the rinsing solution from the syringe, 2 mL of water or the apple juice was added thereto with a syringe, and the syringe was closed with the cap. The resultant was shaken at least ten times, and the resultant rinsing solution was taken out of the vial and then subjected to dilution and centrifugation to prepare a sample liquid.

[0080] 1-7 Preparation of Suspension (using Syringe equipped with NG Tube)

In the same manner as in the preparation method using the syringe, a 20 mL syringe was charged with one 1, 4 or 10 mg lenvatinib capsule or five capsules of a total lenvatinib amount of 17 mg (namely, three 1 mg capsules, one 4 mg capsule and one 10 mg capsule). The syringe was closed with the cap, and after adding 3 mL of water thereto using another fresh syringe, a piston was pushed into the end of the syringe by about 2 cm, and the syringe was allowed to stand still for about 10 minutes. After standing for 10 minutes, the syringe was shaken for about 3 minutes to dissolve capsule shell. The piston was then pushed into the syringe to remove the air from the syringe, the NG tube was attached thereto, and the thus obtained suspension was taken out of the syringe through the NG tube and then subjected to dilution and centrifugation to prepare a sample liquid.

[0081] 1-8 Rinsing of Syringe equipped with NG Tube (First Rinsing Step)

In order to check the effect of a rinsing step, after taken out 3 mL of the suspension from the syringe through the NG tube, 2 mL of water was added thereto using another fresh syringe, the syringe was closed with the cap and then shaken at least ten times, and the resultant rinsing solution was taken out of the syringe through the NG tube and then subjected to dilution and centrifugation to prepare a sample liquid.

[0082] 1-9 Second Rinsing Step

After taking out 2 mL of the rinsing solution from the syringe through the NG tube, 2 mL of water was added thereto using another syringe, and the syringe was closed with the cap. The resultant was shaken at least ten times, and the resultant rinsing solution was taken out of the syringe through the NG tube and then subjected to dilution and centrifugation to prepare a sample liquid.

[0083] 1-10 Dilution and Centrifugation Step

The whole amount of each suspension of the 1 mg, 4 mg or 10 mg capsules was transferred to a 50 mL volumetric flask, and the whole amount of the suspension of the 17 mg capsules (including three 1 mg capsules, one 4 mg capsule and one 10 mg capsule) was transferred to a 200 mL volumetric flask, and the resultant was diluted with a diluent

(methanol, water and sodium dihydrogen phosphate dihydrate in 800:200:1 (v/v/w)) to the volume of the flask. The centrifugation was performed after extraction by stirring and an ultrasonic treatment in a water bath.

The final lenvatinib concentration of the suspensions of the 1 mg and 4 mg capsules were respectively 0.02 mg/mL and 0.08 mg/mL.

As for the suspension of the 10 mg capsule, after performing the centrifugation in the same manner as the suspensions of the 1 mg and 4 mg capsules, 5 mL of a supernatant was transferred to a 10 mL flask and then diluted with the diluent. The final lenvatinib concentration of the suspension of the 10 mg capsule was 0.10 mg/mL.

As for the suspension of 17 mg capsules, after performing the centrifugation in the same manner as the suspension of the 10 mg capsule, 5 mL of a supernatant was transferred to a 20 mL flask and then diluted with the diluent. The final lenvatinib concentration of the suspension of the 17 mg capsules was 0.085 mg/mL.

Recovery of the lenvatinib was measured under HPLC conditions shown in Table 20.

[Table 20]

HPLC	Waters Alliance
Detection	UV (Wavelength: 252 nm)
Column	YMC Pack-Pro C18 (4.6 mm × 7.5 cm, 3μm)
Column Temperature	about 35 °C
Sample Cooler Temperature	about 5 °C
Mobile Phase	Water, Acetonitrile, Perchloric Acid (70%) (800: 200: 1, v/v/v)
Flow Rate	1 mL/min (Retention Time of Lenvatinib Peak: about 4 to 5 minutes)
Injection Volume	5 μL (4, 10, 17 mg Capsule), 10 μL (1 mg Capsule)
Measurement Time	6 minutes after injection

[0084] Results of Recovery of Lenvatinib

The recoveries of the suspensions of the 1, 4, 10 and 17 mg capsules using the vial, the syringe and the syringe equipped with the NG tube are shown in Tables 21 to 24.

The selection of water or the apple juice caused no difference in the recovery. If the rinsing step was not performed, the recovery was lowered. There was no difference whether the rinsing step was performed once or twice, and the recovery of 90% or more was attained if the rinsing step was performed at least once.

[0085] [Table 21]

	Water (room temperature)	Apple Juice

				(room temperature)	
	Vial (20 mL)	Syringe (20 mL)	Syringe (20 mL+NG tube)	Vial (20 mL)	Syringe (20 mL)
3 mL (no rinsing) (average, n=3)	92.4	99.2	88.0	88.5	93.6
Rinsing Once with 2 mL (average, n=3)	96.6	100.3	94.3	97.2	95.7
Rinsing Twice with 2 mL (average, n=3)	97.2	100.4	94.7	98.3	96.0

[0086] [Table 22]

	Water (room temperature)			Apple Juice (room temperature)	
	Vial (20 mL)	Syringe (20 mL)	Syringe (20 mL+NG tube)	Vial (20 mL)	Syringe (20 mL)
3 mL (no rinsing) (average, n=3)	85.0	97.1	86.6	85.5	92.8
Rinsing Once with 2 mL (average, n=3)	96.3	98.8	99.6	95.5	95.9
Rinsing Twice with 2 mL (average, n=3)	97.5	98.9	100.3	96.9	96.5

[0087] [Table 23]

	Water (room temperature)			Apple Juice (room temperature)	
	Vial (20 mL)	Syringe (20 mL)	Syringe (20 mL+NG tube)	Vial (20 mL)	Syringe (20 mL)
3 mL (no rinsing) (average, n=3)	85.5	96.9	89.0	84.5	93.8
Rinsing Once with 2 mL (average, n=3)	97.5	99.4	96.6	94.1	98.2
Rinsing Twice with 2 mL (average, n=3)	98.9	99.6	97.3	95.4	98.7

[0088] [Table 24]

	Water (room temperature)			Apple Juice (room temperature)	
	Vial (20 mL)	Syringe (20 mL)	Syringe (20 mL+NG tube)	Vial (20 mL)	Syringe (20 mL)
3mL (no rinsing) (average, n=3)	81.6	93.6	78.1	81.5	90.9
Rinsing Once with 2 mL (average, n=3)	95.0	95.9	93.8	93.0	94.3
Rinsing Twice with 2 mL (average, n=3)	96.6	96.3	94.4	94.5	94.9

[0089] Chemical Stability of Lenvatinib in Suspension

In accordance with the description of 1-1, each of 1 mg, 4 mg and 10 mg capsules was suspended in 3 mL of water or the apple juice in a vial. The whole amount of the resultant suspension at the initial stage or 24 hours after was transferred to a 50 mL volumetric flask, and a diluent (methanol, water and sodium dihydrogen phosphate dihydrate

in 800:200:1 (v/v/w)) was added thereto for dilution to the volume of the flask. Centrifugation was performed after extraction by stirring and an ultrasonic treatment in a water bath. Each supernatant obtained after the centrifugation was measured under HPLC conditions shown in Table 25, and chemical stabilities at the initial stage and after 24 hours of the lenvatinib suspension in water or the apple juice are shown in Tables 26 to 28 in the form of the amount of a detected impurity X.

As a result of the experiments, the amount of the impurity X was not increased from the initial value even after 24 hours, and hence it was found that the lenvatinib suspension in water or the apple juice was stable for 24 hours.

[0090] [Table 25]

HPLC	Waters Alliance		
Detection	UV (Wavelength: 252 nm)		
Column	YMC Pack-Pro C18 (4.6 mm × 7.5 cm, 3μm)		
Column Temperature	about 35 °C		
Sample Cooler Temperature	about 5 °C		
Mobile Phase A	Water, Acetonitrile, Perchloric Acid (70%) (990: 10: 1,v/v/v)		
Mobile Phase B	Acetonitrile, Water, Perchloric Acid (70%) (900: 100: 1,v/v/v)		
Flow Rate	1 mL/min (Retention Time of Lenvatinib Peak: about 13 to 14 minutes)		
Gradient Program	Time (min)	Mobile Phase A (%)	Mobile Phase B (%)
	0.00	100	0
	22.00	55	45
	25.00	55	45
	25.01	100	0
	30.00	100	0
Injection Volume	20 μL (1 mg Capsule), 5 μL (4 mg Capsule), 2 μL (10 mg Capsule)		
Measurement Time	30 minutes after injection		

[0091] [Table 26]

Suspension (1 mg/3 mL)	Water		Apple Juice	
	Initial	After 24 Hours	Initial	After 24 Hours
n=1	0.05% or less	0.05% or less	0.05% or less	0.05% or less
n=2	0.05% or less	0.05% or less	0.05% or less	0.05% or less
n=3	0.05% or less	0.05% or less	0.05% or less	0.05% or less

[0092] [Table 27]

Suspension (4 mg/3 mL)	Water		Apple Juice	
	Initial	After 24	Initial	After 24

		Hours		Hours
n=1	0.05% or less	0.05% or less	0.05% or less	0.05% or less
n=2	0.05% or less	0.05% or less	0.05% or less	0.05% or less
n=3	0.05% or less	0.05% or less	0.05% or less	0.05% or less

[0093] [Table 28]

Suspension (10 mg/3 mL)	Water		Apple Juice	
	Initial	After 24 Hours	Initial	After 24 Hours
n=1	0.05% or less	0.05% or less	0.05% or less	0.05% or less
n=2	0.05% or less	0.05% or less	0.05% or less	0.05% or less
n=3	0.05% or less	0.05% or less	0.05% or less	0.05% or less

[0094] Viscosity

In accordance with the description of 1-4, each of 1, 4 and 10 mg lenvatinib capsules or each combination of capsules shown in Table 30 was suspended in a syringe by using 3 mL of water. Results of viscosities (unit: η/mPas) of the respective suspensions obtained by measurement performed under conditions shown in Table 29 are shown in Table 30. There was no difference in the viscosity whether moisture-proof packed capsules were stored for 6 months at 5°C or at 40°C/75% RH (relative humidity). It is noted that the capsules were stored under the aforementioned conditions after moisture-proof packaging.

[0095] [Table 29]

Viscometer	Viscotester 550 rotational Viscometer (Thermo scientific)
Rotational Speed	90 rpm
Measurement Time	180 seconds
Number of Times of Sampling	100 Times
Sample Temperature	about 25 °C

[0096] [Table 30]

Suspension	Conditions for Storing 1, 4 or 10 mg Capsule	
	5 °C	40 °C/ 75% RH 6 months
1 mg/3 mL water	3.4	2.8
4 mg/3 mL water	2.9	3.1
10 mg/3 mL water	3.3	3.2
17 mg (*1)/ 3 mL water	95.2	89.9
23 mg (*2)/ 3 mL water	109.0	109.2
24 mg (*3)/ 3 mL water	21.5	21.4

*1: 1 mg 3 capsule, 4 mg 1 capsule, 10 mg 1 capsule
*2: 1 mg 3 capsules, 10 mg 2 capsules
*3: 4 mg 1 capsule, 10 mg 2 capsules

[0097] NG Tube Passability Test

In accordance with the description of 1-7, each of 1, 4 and 10 mg lenvatinib

capsules or each combination of capsules shown in Table 30 was suspended in a syringe by using 3 mL of water, and then an NG tube was connected to the syringe. Results of an NG tube passability test thus performed are shown in Table 31. Moisture-proof packaged capsules stored for 6 months at 5°C and at 40°C/75% RH (relative humidity) both passed through the tubes, and there was no difference in the tube passability. It is noted that the capsules were stored under the aforementioned conditions after moisture-proof packaging.

[0098] [Table 31]

Suspension	Conditions for Storing 1, 4 or 10 mg Capsule	
	5 °C	40 °C/ 75% RH 6 months
1 mg/ 3 mL water	passed	passed
4 mg/ 3 mL water	passed	passed
10 mg/ 3 mL water	passed	passed
17 mg (*1)/ 3 mL water	passed	passed
23 mg (*2)/ 3 mL water	passed	passed
24 mg (*3) / 3 mL water	passed	passed

*1: 1 mg 3 capsules, 4 mg 1 capsule, 10 mg 1 capsule
*2: 1 mg 3 capsules, 10 mg 2 capsules
*3: 4 mg 1 capsule, 10 mg 2 capsules

CLAIMS

1. A method for suppressing bitterness of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide, comprising mixing 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof and a basic substance.

2. The method according to claim 1, wherein 0.01 to 50 parts by weight of the basic substance is mixed per 1 part by weight of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof.

3. The method according to claim 1, wherein 0.16 to 80 mol of the basic substance is mixed per 1 mol of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof.

4. The method according to any one of claims 1 to 3, wherein the basic substance is a basic oxide, a basic carbonate or a basic hydroxide.

5. The method according to any one of claims 1 to 3, wherein the basic substance is calcium carbonate or magnesium oxide.

6. The method according to any one of claims 1 to 3, wherein the basic substance is calcium carbonate.

7. The method according to any one of claims 1 to 6, wherein the pharmaceutically acceptable salt is a mesylate.

8. A pharmaceutical composition, comprising 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof, and a basic substance in an amount effective for suppressing bitterness.

9. A pharmaceutical composition, comprising 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof, the pharmaceutical composition comprising means for mixing a basic substance for suppressing bitterness.

10. A pharmaceutical composition, comprising 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof and a basic substance, the pharmaceutical composition having bitterness suppressed.

11. The pharmaceutical composition according to any one of claims 8 to 10, comprising 0.01 to 50 parts by weight of the basic substance per 1 part by weight of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof.

12. The pharmaceutical composition according to any one of claims 8 to 10, wherein 0.16 to 80 mol of the basic substance is mixed per 1 mol of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof.

13. The pharmaceutical composition according to any one of claims 8 to 12, wherein the basic substance is a basic oxide, a basic carbonate or a basic hydroxide.

14. The pharmaceutical composition according to any one of claims 8 to 12, wherein the basic substance is calcium carbonate or magnesium oxide.

15. The pharmaceutical composition according to any one of claims 8 to 12, wherein the basic substance is calcium carbonate.

16. The pharmaceutical composition according to any one of claims 8 to 15, wherein the pharmaceutically acceptable salt is a mesylate.

17. The pharmaceutical composition according to any one of claims 8 to 16, in a dosage form of an orally disintegrating tablet, a chewable preparation, an effervescent tablet, a dispersible tablet, a soluble tablet, a syrup, a preparation for a syrup, a troche, or an oral liquid preparation.

18. The pharmaceutical composition according to any one of claims 8 to 16, being a preparation that can be suspended in an aqueous solvent upon an administration to prepare a suspension.

19. A bitterness suppressing agent, comprising a basic substance, for 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof.

20. The bitterness suppressing agent according to claim 19, wherein the basic substance added is in an amount of 0.01 to 50 parts by weight per 1 part by weight of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof.

21. The bitterness suppressing agent according to claim 19, wherein the basic substance added is in an amount of 0.16 to 80 mol per 1 mol of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the

pharmaceutically acceptable salt thereof.

22. The bitterness suppressing agent according to any one of claims 19 to 21, wherein the basic substance is a basic oxide, a basic carbonate or a basic hydroxide.

23. The bitterness suppressing agent according to any one of claims 19 to 21, wherein the basic substance is calcium carbonate or magnesium oxide.

24. The bitterness suppressing agent according to any one of claims 19 to 21, wherein the basic substance is calcium carbonate.

25. The bitterness suppressing agent according to any one of claims 19 to 24, wherein the pharmaceutically acceptable salt is a mesylate.

26. A method for administering a suspension comprising 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof, and a basic substance, the method comprising:

1) suspending a pharmaceutical composition comprising 1 to 24 mg of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof, and the basic substance in an aqueous solvent in a vessel;

2) administering a suspension obtained in 1) to a patient from the vessel;

3) rinsing the vessel with an aqueous solvent; and

4) administering a rinsing solution obtained in 3) to the patient.

27. The method according to claim 26, wherein 1) comprises: i) pouring the aqueous solvent in the vessel, ii) allowing the vessel to stand; and iii) shaking the vessel..

28. The method according to claim 26 or 27, wherein the pharmaceutical composition is suspended in 1 to 10 mL of the aqueous solvent in 1).

29. The method according to claim 28, wherein the pharmaceutical composition is suspended in about 3 mL of the aqueous solvent in 1).

30. The method according to claim 26, wherein the vessel is rinsed with 1 to 10 mL of the aqueous solvent in 3).

31. The method according to claim 30, wherein the vessel is rinsed with about 2 mL of the aqueous solvent in 3).

32. A method for treating a cancer, comprising administering a suspension comprising 1 to 24 mg of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof, and a basic substance.

33. A method for treating a cancer, comprising administering a suspension comprising

4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or a pharmaceutically acceptable salt thereof, and a basic substance, the method comprising:

1) suspending, in an aqueous solvent in a vessel, a pharmaceutical composition comprising 1 to 24 mg of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxyamide or the pharmaceutically acceptable salt thereof, and the basic substance;

2) administering a suspension obtained in 1) to a patient from the vessel;

3) rinsing the vessel with an aqueous solvent; and

4) administering a rinsing solution obtained in 3) to the patient.