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DESCRIPTION

Description

Technical Field

[0001] The present invention relates to a pharmaceutical composition containing 4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof and hydroxypropyl- β -cyclodextrin, particularly a pharmaceutical composition for oral administration.

Background Art

[0002] Cyclodextrins and derivatives thereof are widely generally known as an excipient for improving the solubility of a hydrophobic compound in water. However, most of them are liquid formulations in which the whole or a part of a hydrophobic compound is included inside a cyclodextrin. Therefore, a solid formulation in which a cyclodextrin or a derivative thereof is physically added to improve the solubility is not well known.

[0003] At present, as a compound having excellent c-Met/VEGFR2 inhibitory activity and showing antitumor activity, 4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinoline-6-carboxamide (hereinafter, also referred to as "compound 1") has been reported (PTL 1 and 2, and NPL 1 and 2). It has also been reported that the compound 1 is useful as a therapeutic agent for osteoporosis (PTL 3). Further, mesylates of the compound 1 and crystals thereof have also been reported (PTL 4).

[0004] However, these reports contain no mention of a pharmaceutical composition containing the compound 1 or a pharmaceutically acceptable salt thereof and a cyclodextrin or a derivative thereof.

Citation List

Patent Literature

[0005]

PTL 1: WO 2009/125597

PTL2: WO 2013/100014

PTL 3: WO 2015/046484

PTL4: WO 2016/175305

Non Patent Literature

[0006]

NPL 1: Molecular Cancer Therapeutics; 12(12); pp. 2685-96, 2013

NPL 2: European Journal of Cancer; 48(6); p. 94; 2012

Summary of Invention

Technical Problem

[0007] The present invention provides a pharmaceutical composition which has excellent stability, disintegratability, and absorbability, is easily prepared, and contains the compound 1 or a pharmaceutically acceptable salt thereof.

Solution to Problem

[0008] In view of this, the present inventor found that by adding hydroxypropyl- β -cyclodextrin (HP- β -CD) to the compound 1 or a pharmaceutically acceptable salt thereof, a pharmaceutical composition which has excellent stability, has excellent stability, disintegratability, and absorbability, and is easily prepared can be obtained, and thus completed the present invention. Herein is also described:

· A pharmaceutical composition for preventing and/or treating a tumor, containing 4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof and hydroxypropyl- β -cyclodextrin.

An antitumor agent, containing 4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof and

hydroxypropyl- β -cyclodextrin.

Use of 4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof and hydroxypropyl- β -cyclodextrin for producing an antitumor agent.

- A method for preventing and/or treating a tumor, including a step of administering a pharmaceutical composition containing 4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof and hydroxypropyl- β -cyclodextrin to a subject in an effective amount for the treatment and/or prevention.

- Use of a pharmaceutical composition containing 4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof and hydroxypropyl- β -cyclodextrin for preventing and/or treating a tumor.

- A pharmaceutical composition for inhibiting c-Met and/or VEGFR2, containing 4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof and hydroxypropyl- β -cyclodextrin.

- An inhibitor for c-Met and/or VEGFR2, containing 4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof and hydroxypropyl- β -cyclodextrin.

Use of 4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof and hydroxypropyl- β -cyclodextrin for producing an inhibitor for c-Met and/or VEGFR2.

- Use of a pharmaceutical composition containing 4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof and hydroxypropyl- β -cyclodextrin for inhibiting c-Met and/or VEGFR2.

Advantageous Effects of Invention

[0009] According to the present invention, a pharmaceutical composition which has excellent stability, disintegratability, and absorbability, is easily prepared, and contains the compound 1 or a pharmaceutically acceptable salt thereof and a cyclodextrin derivative as defined in claim 1 can be provided.

Brief Description of Drawings

[0010]

[Fig. 1] Fig. 1 shows the results of powder X-ray diffraction spectrum (XRD) measurement of a mesylate salt of the compound 1.

[Fig. 2] Fig. 2 shows the results of XRD measurement of HP- β -CD.

[Fig. 3] Fig. 3 shows the results of XRD measurement of a physically mixed product of a mesylate salt of the compound 1 and HP- β -CD.

[Fig. 4] Fig. 4 shows the results of XRD measurement of a spray-dried product of a mesylate salt of the compound 1 and HP- β -CD.

[Fig. 5] Fig. 5 shows the results of solid proton nuclear magnetic resonance (^1H -NMR) measurement of a mesylate salt of the compound 1.

[Fig. 6] Fig. 6 shows the results of ^{13}C -NMR measurement of HP- β -CD.

[Fig. 7] Fig. 7 shows the results of ^{13}C -NMR measurement of a physically mixed product of a mesylate salt of the compound 1 and HP- β -CD.

[Fig. 8] Fig. 8 shows the results of infrared absorption spectrum (IR) measurement of a mesylate salt of the compound 1.

[Fig. 9] Fig. 9 shows the results of IR measurement of HP- β -CD.

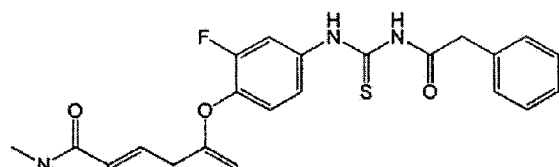
[Fig. 10] Fig. 10 shows the results of IR measurement of a physically mixed product of a mesylate salt of the compound 1 and HP- β -CD.

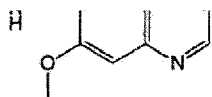
[Fig. 11] Fig. 11 shows the results of IR measurement in the fingerprint regions of a mesylate salt of the compound 1, HP- β -CD, and a physically mixed product of the mesylate salt of the compound 1 and HP- β -CD in this order from the top.

Description of Embodiments

[0011] An active ingredient of the pharmaceutical composition of the present invention is the compound 1. The compound 1 is 4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinoline-6-carboxamide and the structure thereof is shown below.

[Chem. 1]





(compound 1)

[0012] As the pharmaceutically acceptable salt of the compound 1 to be used in the present invention, salts such as acid addition salts are exemplified, and preferred is a mesylate salt, and more preferred is mono mesylate.

[0013] The compound 1 or a pharmaceutically acceptable salt thereof may be a solvate (for example, a hydrate or the like) or a non-solvate, and in the present invention, both are included in "the compound 1 or a pharmaceutically acceptable salt thereof. The compound 1 or a pharmaceutically acceptable salt thereof can be produced by a method described in, for example, PTL 1 or 4.

[0014] The compound 1 or a pharmaceutically acceptable salt thereof to be used in the present invention is contained in an amount of preferably 67 mass% or less, more preferably from 5 to 40 mass%, further more preferably from 10 to 20 mass% with respect to the total pharmaceutical composition.

[0015] The following cyclodextrin derivatives are described herein: α -cyclodextrin β -cyclodextrin (β -CD), and γ -cyclodextrin (γ -CD), but also hydroxypropyl- β -cyclodextrin (HP- β -CD), sulfobutylether- β -cyclodextrin (SBE- β -CD). However, from the viewpoint of dissolubility, stability, absorbability, etc., the cyclodextrin derivative of the present invention is hydroxypropyl- β -cyclodextrin. The amount of hydroxypropyl- β -cyclodextrin to be used in the present invention may be any as long as the absorbability of the compound 1 or a pharmaceutically acceptable salt thereof to be used in the present invention is improved, and the toxicity of hydroxypropyl- β -cyclodextrin is not appeared.

[0016] The amount of hydroxypropyl- β -cyclodextrin to be used in the present invention is preferably 30 mass% or more, more preferably from 60 to 95 mass%, further more preferably from 76 to 85 mass% with respect to the total pharmaceutical composition.

[0017] The amount of hydroxypropyl- β -cyclodextrin to be used in the present invention is preferably from 0.1 to 5.5 parts by mass, more preferably from 4.0 to 5.0 parts by mass with respect to 1 part by mass of the compound 1 or a pharmaceutically acceptable salt thereof.

[0018] As the pharmaceutical composition of the present invention, a composition in which the compound 1 or a pharmaceutically acceptable salt thereof and hydroxypropyl- β -cyclodextrin do not form a clathrate or partially form a clathrate is exemplified. That is, it can be confirmed by a powder X-ray diffraction spectrum, solid NMR, IR, etc. that in the pharmaceutical composition of the present invention, one in which the compound 1 or a pharmaceutically acceptable salt thereof and hydroxypropyl- β -cyclodextrin do not form a clathrate is present.

[0019] In addition, an error of a peak at a diffraction angle 2θ in a powder X-ray diffraction spectrum in the present invention is about $\pm 0.2^\circ$. This is an error caused by an apparatus used in measurement, preparation of a sample, a data analysis method, or the like. Therefore, when a crystal is subjected to XRD measurement in the present invention, an error of $\pm 0.2^\circ$ of the obtained diffraction angle 2θ is taken into consideration. Further, for the same reason, in the present invention, an error of a peak at a chemical shift (ppm) in a solid ^{13}C -NMR chart is about ± 1.0 ppm, and an error of a peak at an absorption band (cm^{-1}) in an infrared absorption spectrum is about ± 2 cm^{-1} .

[0020] The pharmaceutical composition of the present invention has characteristic peaks at at least 5 or more diffraction angles ($2\theta \pm 0.2^\circ$) selected from 6.5, 7.8, 9.6, 12.4, 18.8, 21.2, 23.0, 24.5, and 26.0 ($^\circ$) in powder X-ray diffraction, preferably has characteristic peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 6.5, 7.8, 9.6, 12.4, 18.8, 21.2, 23.0, 24.5, and 26.0 ($^\circ$).

[0021] The pharmaceutical composition of the present invention preferably has characteristic peaks at chemical shift values [δ (ppm)] of 162.6, 130.4, 103.1, 82.7, 73.3, 41.9, and 19.9 in a solid ^{13}C -NMR chart.

[0022] The pharmaceutical composition of the present invention preferably has characteristic peaks at at least 5 or more absorption bands selected from 1663, 1352, 1225, 1156, 1032, 720, and 553 (cm^{-1}) in an infrared absorption spectrum, more preferably has characteristic peaks at absorption bands of 1663, 1352, 1225, 1156, 1032, 720, and 553 (cm^{-1}).

[0023] The pharmaceutical composition of the present invention can be produced by physical mixing. The physical mixing refers to a production method that does not include a step in which the compound 1 or a pharmaceutically acceptable salt thereof is converted into a solution state when the pharmaceutical composition is produced. As the physical mixing, mixing to form a uniform composition by applying an appropriate operation to two or more types of solids containing the compound 1 or a pharmaceutically acceptable salt thereof, a granulation that is performed when the compound 1 or a pharmaceutically acceptable salt thereof is in a solid state, and the like are exemplified.

[0024] Examples of a granulation method that can be used when the pharmaceutical composition of the present invention is produced include a dry granulation method and a wet granulation method. Specific examples of the dry granulation method include a crushing granulation method. Further, examples of the wet granulation method include a fluidized bed granulation method, a rolling bed granulation method, an extrusion granulation method, and a high shear granulation method, and preferred is a fluidized bed granulation method.

[0025] In the physical mixing, a solvent can be added as needed. As the type of the solvent, water, ethanol, a water-ethanol mixed solution, and the like are exemplified, and preferred is water. When such a solvent is used in the physical mixing, the pharmaceutical composition of the present invention may be used as it is or after it is dried.

[0026] In the physical mixing, a fluidizer or the like can be further added. Examples of the fluidizer include silicic acid derivatives such as light anhydrous silicic acid, calcium silicate, magnesium aluminometasilicate, talc, aluminum silicate, and hydrated silicon dioxide, and preferred is light anhydrous silicic acid.

[0027] In the physical mixing, a binder can be added. As the binder, a cellulose derivative, starch, povidone, or polyvinyl alcohol can be exemplified. Examples of the cellulose derivative include hydroxypropyl cellulose, hypromellose, and methylcellulose, and preferred is hydroxypropyl cellulose.

[0028] Here, the amount of the fluidizer to be used in the present invention is generally 10 mass% or less, preferably from 0.1 to 2 mass%, more preferably from 0.2 to 1 mass% with respect to the total pharmaceutical composition.

[0029] Examples of the pharmaceutical composition of the present invention include a tablet, a granule, a powder, and a fine granule, and preferred is a tablet or a granule. In the tablet, the granule, the powder, and the fine granule, a powdery granular material that is rapidly dissolved in the oral cavity and can be taken without water is included.

[0030] Further, as the pharmaceutical composition of the present invention, a tablet can be adopted. The tablet can also be produced using commonly known excipients, and it is also possible to prepare a tablet from the above-mentioned granule using commonly known methods. As the shape of the tablet, a generally used shape such as a cylindrical shape, a disk shape, a lenticular shape, or a rod-like shape can be adopted. The size of the tablet is not particularly limited as long as a human can orally take it, however, the maximum diameter (diameter) is preferably 15 mm or less, more preferably 10 mm or less. Further, in consideration of absorbability and administration to children, etc., the maximum diameter is further more preferably 5 mm or less. Further, in consideration of the absorbability and the ease of preparation of the pharmaceutical composition of the present invention, a tablet having a cylindrical shape with a maximum diameter of 4 mm or less is preferred. The lower limit of the maximum diameter of the tablet is not particularly limited, but is generally 2 mm or more from the viewpoint of handling.

[0031] Further, when a tablet having a cylindrical shape with a diameter of 5 mm or less is adopted as the pharmaceutical composition of the present invention, the weight of the compound 1 per tablet is 10 mg or less from the viewpoint of the size and the absorbability of the tablet. After preparation of the tablet, an operation of packing a plurality of tablets in one package is sometimes generated. In that case, if there is a large difference in the diameter and the thickness of the cylindrical shape, it takes time when adjusting the packing amount by a counting plate with holes, and during the process, a few tablets may enter the hole of the counting plate or no tablet may enter the hole, and therefore, excess or shortage of the packing amount may occur. Therefore, in the case of the tablet having a cylindrical shape with a diameter of 5 mm or less, the ratio of the thickness to the diameter of the cylindrical shape is

typically from 60 to 140% as an example, preferably from 80 to 120%.

[0032] Further, in the pharmaceutical composition of the present invention, other than the compound 1 or a pharmaceutically acceptable salt thereof and hydroxypropyl- β -cyclodextrin, other excipients may be blended as needed. The excipients are not particularly limited as long as it is generally used in drug products in the pharmaceutical field, and for example, a fluidizer, a diluent, a binder, a disintegrant, a lubricant, a coating agent, a colorant, a flavor, a taste masking agent, and the like can be exemplified, however, it is not limited thereto.

[0033] The pharmaceutical composition of the present invention is useful as an antitumor agent because the compound 1 has excellent c-Met inhibitory activity and VEGFR2 inhibitory activity. A target cancer is not particularly limited, however, examples thereof include head and neck cancer, gastrointestinal cancer [for example, esophageal cancer, gastric cancer, gastrointestinal stromal tumors, duodenal cancer, liver cancer, biliary tract cancer (for example, gallbladder and bile duct cancer, etc.), pancreatic cancer, small intestine cancer, large bowel cancer (for example, colorectal cancer, colon cancer, rectal cancer, etc.), etc.], lung cancer, breast cancer, ovarian cancer, uterine cancer (for example, cervical cancer, endometrial cancer, etc.), kidney cancer, bladder cancer, prostate cancer, urothelial cancer, bone and soft tissue sarcoma, blood cancer (for example, B cell lymphoma, chronic lymphocytic leukemia, peripheral T-cell lymphoma, myelodysplastic syndrome, acute myelogenous leukemia, acute lymphocytic leukemia, etc.), multiple myeloma, skin cancer, and mesothelioma.

Examples

[0034] Hereinafter, the present invention will be further specifically described with reference to Examples, however, the invention is not limited thereto. Although the invention is sufficiently described by Examples, it is to be understood that various changes and modifications can be made by a person skilled in the art. Therefore, such changes or modifications are included in the invention unless they depart from the scope of the invention.

[0035] As various types of reagents used in Examples, commercially available products were used unless otherwise indicated.

[0036] <Powder X-Ray Diffraction Spectrum (XRD) Measurement>

[0037] Powder X-ray diffraction was performed by lightly crushing an appropriate amount of a test specimen in an agate mortar according to need and then performing measurement according to the following test conditions.

[0038]

Apparatus: RINT-2100 Ultima/PC (manufactured by Rigaku Corporation)

Target: CuK α

Scanning range: 5.0 to 40.0°

Sampling width: 0.02°

Scanning speed: 2°/min

[0039] The handling of the apparatus including data processing was performed according to the method and procedure designated for each apparatus.

<Proton Nuclear Magnetic Resonance (¹³C-NMR) Measurement>

[0040] ¹³C-NMR measurement was performed by CMX-300 Infinity (75.188829 MHz, manufactured by Chemagnetic, Inc.) using tetramethylsilane as an internal reference in the case where tetramethylsilane was contained in a deuterated solvent, and using an NMR solvent as an internal reference in the other cases. In each ¹³C-NMR chart obtained, all the δ values were expressed in ppm.

<Infrared Absorption Spectrum (IR) Measurement>

[0041] IR measurement was performed using FT-730 (HORIBA, Ltd.) by the KBr method.

[Test Example 1] Solubility Test 1

<Formulation Example 1>

[0042] HP- β -CD (0.5925 g) was dissolved in a diluted McIlvaine buffer at pH 3.0 (50 mL), followed by heating to 37°C, whereby a test solution was obtained.

<Comparative Example 1>

[0043] A test solution was obtained by heating a diluted McIlvaine buffer at pH 3.0 (50 mL) to 37°C.

<Comparative Example 2>

[0044] A test solution was obtained in the same manner as in Formulation Example 1 using γ -CD (0.5925 g) in place of HP- β -CD (0.5925 g).

<Comparative Example 3>

[0045] A test solution was obtained in the same manner as in Formulation Example 1 using SBE- β -CD (0.5925 g) in place of HP- β -CD (0.5925 g).

[0046] With respect to Formulation Example 1, Comparative Example 1, and Comparative Example 2, the solubility of the compound 1 over time was measured. To each of the test solutions, a mesylate salt of the compound 1 (0.1185 g) was added, followed by stirring at 37°C using a magnetic stirrer. The compositions of Formulation Example 1, Comparative Example 1, Comparative Example 2, and Comparative Example 3 are shown in Table 1.

[Table 1]

(unit: parts by mass)	Formulation Example 1	Comparative Example 1	Comparative Example 2	Comparative Example 3
Mesylate salt of Compound 1	1.0	1.0	1.0	1.0
HP- β -CD	5.0	-	-	-
γ -CD	-	-	5.0	-
SBE- β -CD	-	-	-	5.0

[0047] The concentration of the compound 1 in the test solution was measured after 30, 60, 120, and 240 minutes from the start of the test using liquid chromatography (HPLC) under the following conditions.

[0048]

Apparatus: Alliance 2690 (manufactured by Waters, Inc.)

Mobile phase A: 10 mM Na₂HPO₄ aqueous solution (pH 6.5)

Mobile phase B: acetonitrile

Gradient: mobile phase A/mobile phase B = 6/4 (v/v)

Column: L-column 2 ODS, 100 mm × 3.0 mm, i.d.: 3 μ m

Measurement wavelength: 240 nm

[0049] The handling of the apparatus including data processing was performed according to the method and procedure designated for each apparatus. The results are shown in Table 2.

[Table 2]

	After 30 min μg/mL	After 60 min μg/mL	After 120 min μg/mL	After 240 min μg/mL
Formulation Example 1	269.18	231.32	240.58	220.64
Comparative Example 1	17.65	15.89	14.61	11.29
Comparative Example 2	107.58	129.08	114.78	98.46

[0050] As shown in Table 2, it was found that when the same amount of a cyclodextrin derivative is present, HP-β-CD shows a higher solubility than γ-CD. On the other hand, in the case of SBE-β-CD, the error of the concentration of the compound 1 at each measurement time is large, and it is difficult to predict the absorbability thereof when it is administered to a human, and therefore, it was found that SBE-β-CD is not suitable for formulation with the compound 1.

[Test Example 2] Solubility Test 2

<Formulation Example 2>

[0051] A test solution was obtained in the same manner as in Formulation Example 1 using HP-β-CD (0.0593 g) in place of HP-γ-CD (0.5925 g).

<Formulation Example 3>

[0052] A test solution was obtained in the same manner as in Formulation Example 1 using HP-β-CD (0.1185 g) in place of HP-γ-CD (0.5925 g).

<Formulation Example 4>

[0053] A test solution was obtained in the same manner as in Formulation Example 1 using HP-β-CD (0.3555 g) in place of HP-γ-CD (0.5925 g).

[0054] With respect to Formulation Examples 1 to 4, the solubility of the compound 1 over time was measured in the same manner as in the Test Example 1. To each of the test solutions, a mesylate salt of the compound 1 (0.1185 g) was added, followed by stirring at 37°C using a magnetic stirrer. The compositions of Formulation Examples 1 to 4 are shown in Table 3.

[Table 3]

(unit: parts by mass)	Formulation Example 1	Formulation Example 2	Formulation Example 3	Formulation Example 4
Mesylate salt of Compound 1	1.0	1.0	1.0	1.0
HP- β -CD	5.0	0.5	1.0	3.0

[0055] The concentration of the compound 1 in the test solution was measured after 30, 60, 120, and 240 minutes from the start of the test using liquid chromatography (HPLC) under the same conditions. The results are shown in Table 4.

[Table 4]

	After 30 min $\mu\text{g/mL}$	After 60 min $\mu\text{g/mL}$	After 120 min $\mu\text{g/mL}$	After 240 min $\mu\text{g/mL}$
Formulation Example 1	269.18	231.32	240.58	220.64
Formulation Example 2	39.04	30.94	35.96	30.24
Formulation Example 3	59.56	61.58	54.60	50.36
Formulation Example 4	137.36	139.50	157.22	140.02

[0056] As shown in Table 4, it was found that the solubility of the mesylate salt of the compound 1 is improved in the presence of HP- β -CD, and it shows a higher solubility as HP- β -CD is present in a larger amount.

[Test Example 3] XRD Measurement

<Formulation Example 5>

[0057] A physically mixed product (26.6 g, PM product) of a mesylate salt of the compound 1 was obtained by mixing the mesylate salt of the compound 1 (5.0 g) and HP- β -CD (22.8 g) in a mortar.

[0058] The results of powder X-ray diffraction spectrum (XRD) measurement of the mesylate salt of the compound 1 are shown in Fig. 1, the results of XRD measurement of HP- β -CD are shown in Fig. 2, the results of XRD measurement of the physically mixed product of the mesylate salt of the compound 1 and HP- β -CD obtained in Formulation Example 5 are shown in Fig. 3, and the XRD measurement of a spray-dried product of the mesylate salt of the compound 1 and HP- β -CD obtained in Comparative Example 4 described below are shown in Fig. 4.

[0059] Based on these, it was found that in the XRD measurement of the physically mixed product of the mesylate salt of the compound 1 and HP- β -CD, the product has characteristic peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 6.5, 7.8, 9.6, 12.4, 18.8, 21.2, 23.0, 24.5, and 26.0 ($^\circ$) derived from the mesylate salt of the compound 1.

[Test Example 4] ^{13}C -NMR Measurement

[0060] The results of solid proton nuclear magnetic resonance (^{13}C -NMR) measurement of the mesylate salt of the compound 1 are shown in Fig. 5, the results of ^{13}C -NMR measurement of HP- β -CD are shown in Fig. 6, and the results of ^{13}C -NMR measurement of the physically mixed product of the mesylate salt of the compound 1 and HP- β -CD obtained in Formulation Example 5 are shown in Fig. 7.

[0061] Based on these, it was found that in the solid proton nuclear magnetic resonance (^{13}C -NMR) measurement of the physically mixed product of the mesylate salt of the compound 1 and HP- β -CD, the product has characteristic peaks at chemical shift values [δ (ppm)] of 162.6, 130.4, 103.1, 82.7, 73.3, 41.9, and 19.9 derived from the mesylate salt of the compound 1.

[Test Example 5] IR Measurement

[0062] The results of infrared absorption spectrum (IR) measurement of the mesylate salt of the compound 1 are shown in Fig. 8, the results of IR measurement of HP- β -CD are shown in Fig. 9, and the results of IR measurement of the physically mixed product of the mesylate salt of the compound 1 and HP- β -CD obtained in Formulation Example 5 are shown in Fig. 10. Further, IR measurement in the fingerprint regions thereof is shown in Fig. 11.

[0063] Based on these, it was found that in the infrared absorption spectrum measurement of the physically mixed product of the mesylate salt of the compound 1 and HP- β -CD, the product has characteristic peaks at absorption bands (cm^{-1}) of 1663, 1352, 1225, 1156, 1032, 720, and 553 derived from the mesylate salt of the compound 1.

[Test Example 6] Stability Test

<Comparative Example 4>

[0064] A mesylate salt of the compound 1 (5.0 g) and HP- β -CD (22.8 g) were dissolved in a mixed solution of water (100.0 g), ethanol (250.0 g) and dichloromethane (150.0 g), followed by spray drying by a spray dryer (GB22, manufactured by Yamato Scientific Co., Ltd.), whereby a spray-dried product (19.2 g, SD product) of the mesylate salt of the compound 1 was obtained.

[0065] The compositions and the preparation methods of Formulation Example 5 and Comparative Example 4 are shown in Table 5.

[Table 5]

(unit: parts by mass)	Formulation Example 5	Comparative Example 4
Mesylate salt of Compound 1	1.0	1.0
HP- β -CD	4.6	4.6
Preparation method	PM product	SD product

[0066] With respect to Formulation Example 5 and Comparative Example 4, a change in the total amount of the related substances of the compound 1 in each formulation over time was evaluated. Each formulation was wrapped with a polyethylene/cellophane laminated film and then enclosed in an aluminum bag with a desiccant and an deoxygenating agent, and the concentration of the compound 1 in the formulations stored at 5, 25, and 40°C for 1 month and the formulations stored at 60°C for 1 week was measured using liquid chromatography (HPLC) under the following conditions.

[0067]

Apparatus: Alliance 2690 (manufactured by Waters, Inc.)

Mobile phase A: 10 mM Na₂HPO₄ aqueous solution (pH 6.5)

Mobile phase B: acetonitrile

Gradient: shown in Table 6

Column: L-column 2 ODS, 150 mm × 4.6 mm, i.d.: 5 μ m

Measurement wavelength: 220 nm

[Table 6]

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	64	36
1	64	36
11	55	45
16	52	48
20	37	63
30	37	63
31	64	36
40	64	36

[0068] The handling of the apparatus including data processing was performed according to the method and procedure designated for each apparatus. The results are shown in Table 7.

[Table 7]

	0 value	5°C 1 month	25°C 1 month	40°C 1 month	60°C 1 week
Formulation Example 5	0.25	0.37	0.39	0.38	0.30
Comparative Example 4	1.27	1.45	2.10	3.15	3.18

[0069] As shown in Table 7, it was found that the physically mixed product of the mesylate salt of the compound 1 and HP- β -CD has excellent stability as compared with the spray-dried product.

[Test Example 7] Absorbability Test 1

<Comparative Example 5>

[0070] Granulation was performed using a high shear granulator (FM-VG-25, manufactured by Powrex Corporation) while adding a 14% povidone solution (466 g) to a mesylate salt of the compound 1 (1564.2 g), D-mannitol (1188 g), and sodium starch glycolate (33 g), whereby a wet powder was obtained. The wet powder was dried using a fluidized bed granulator (NFLO-5, manufactured by Freund Corporation), and then mixed using a mixer (CV-20, manufactured by Tokujin Corporation) with sodium starch glycolate (158.4 g) and magnesium stearate (26.4 g), whereby granules for tableting were obtained. The granules for tableting were compressed into tablets using a tableting machine (VELG 0512SW2MZ, manufactured by Kikusui Seisakusho Ltd.), and thereafter, a coating solution obtained by adding hypromellose (64.8 g),

macrogol 6000 (8.1 g), titanium oxide (8.1 g), and yellow ferric oxide (0.081 g) was sprayed thereon using a coating machine (DRC-300, manufactured by Powrex Corporation), whereby coated tablets were obtained.

[0071] The compositions and the preparation methods of Formulation Example 5, Comparative Example 4, and Comparative Example 5 are shown in Table 8.

[Table 8]

(unit: parts by mass)	Formulation Example 5	Comparative Example 4	Comparative Example 5
Mesylate salt of Compound 1	1.0	1.0	1.0
HP- β -CD	4.6	4.6	-
D-mannitol	-	-	0.76
Sodium starch glycolate	-	-	0.12
Povidone	-	-	0.04
Magnesium stearate	-	-	0.02
Hypromellose	-	-	0.04
Preparation method	PM product	SD product	PM product

[0072] With respect to Formulation Example 5, Comparative Example 4, and Comparative Example 5, each formulation was administered to animals under the following conditions, and the absorbability was evaluated.

[0073]

Animals used: beagle dogs (3 male animals, Kitayama Labes Co., Ltd.)

Feeding Conditions: fasting for 20 hours from the previous day

Dose: 100 mg/body (in terms of the compound 1)

Administration method: administered with 50 mL water

Pretreatment: Pentagastrin was intramuscularly administered (10 μ g/0.1 mL/kg) 30 minutes before administering the formulation and thereafter administered twice at an interval of 45 minutes. An atropine sulfate intravenous injection was intravenously administered (20 μ g/0.04 mL/kg) 30 minutes before administering the formulation.

[0074] The results are shown in Table 9.

[Table 9]

	AUC ng·hr/mL
Formulation Example 5	6842
Comparative Example 4	5789
Comparative Example 5	1666

[0075] As shown in Table 9, it was found that the absorption of the mesylate salt of the compound 1 is improved by the addition of HP- β -CD, and the physically mixed product of the mesylate salt of the compound 1 and HP- β -CD shows absorbability comparable to the spray-dried product.

[Test Example 8] Absorbability Test 2

<Formulation Example 6>

[0076] Granulation was performed using a fluidized bed granulator (FL-LABO (special), manufactured by Freund Corporation) while spraying a 5% hydroxypropyl cellulose solution (1000 g) onto a mesylate salt of the compound 1 (296.3 g), HP- β -CD (1350 g), and light anhydrous silicic acid (8.8 g), whereby a granulated material was obtained. Magnesium stearate (10 g) was added to the granulated material and mixed in a polyethylene bag, whereby granules were obtained.

[0077] The compositions of Formulation Example 5 and Formulation Example 6 are shown in Table 10.

[Table 10]

(unit: parts by mass)	Formulation Example 5	Formulation Example 6
Mesylate salt of Compound 1	1.0	1.0
HP- β -CD	4.6	4.6
Light anhydrous silicic acid	-	0.03
Hydroxypropyl cellulose	-	0.17
Magnesium stearate	-	0.03

[0078] With respect to Formulation Example 5 and Formulation Example 6, each formulation was administered to animals under the following conditions, and the absorbability was evaluated.

[0079]

Animals used: beagle dogs (3 male animals, Kitayama Labes Co., Ltd.)

Feeding Conditions: fasting for 20 hours from the previous day

Dose: 400 mg/body (in terms of the compound 1)

Administration method: administered with 50 mL water

Pretreatment: Pentagastrin was intramuscularly administered (10 µg/0.1 mL/kg) 30 minutes before administering the formulation and thereafter administered twice at an interval of 45 minutes. An atropine sulfate intravenous injection was intravenously administered (20 µg/0.04 mL/kg) 30 minutes before administering the formulation.

[0080] The results are shown in Table 11.

[Table 11]

	AUC ng·hr/mL
Formulation Example 5	11258
Formulation Example 6	12810

[0081] As shown in Table 11, it was found that the granules obtained by granulating the mesylate salt of the compound 1 and HP-β-CD show absorbability comparable to the physically mixed product thereof.

[Test Example 9] Absorbability Test 3

<Formulation Example 7>

[0082] Granulation was performed using a fluidized bed granulator (NFLO-5, manufactured by Freund Corporation) while spraying a 5% hydroxypropyl cellulose solution (3000 g) onto a mesylate salt of the compound 1 (888.8 g), HP-β-CD (4050 g), and light anhydrous silicic acid (26.3 g), whereby a granulated material was obtained. Two batches of the granulated material were mixed using a mixer (CV-20, manufactured by Tokuju Corporation) with magnesium stearate (60 g), whereby granules were obtained.

<Formulation Example 8>

[0083] Granulation was performed using a fluidized bed granulator (NFLO-5, manufactured by Freund Corporation) while spraying a 5% hydroxypropyl cellulose solution (3000 g) onto a

mesylate salt of the compound 1 (888.8 g), HP- β -CD (4050 g), and light anhydrous silicic acid (26.3 g), whereby a granulated material was obtained. Magnesium stearate (2.16 g) was added to a portion (396.4 g) of the granulated material and mixed in a polyethylene bag, whereby granules were obtained. The granules were compressed into tablets with a diameter of 4 mm using a tableting machine (VELG 0512SW2MZ, manufactured by Kikusui Seisakusho Ltd.), and thereafter, a coating solution obtained by adding water (480.0 g), hypromellose (32.0 g), macrogol 6000 (4.0 g), titanium oxide (4.0 g), and yellow ferric oxide (0.2 g) was sprayed thereon using a coating machine (HC-FZ-LABO, manufactured by Freund Corporation), whereby coated tablets of the tablets with a diameter of 4 mm were obtained.

<Formulation Example 9>

[0084] A portion (292.1 g) of the granules obtained in Formulation Example 7 were compressed into tablets with a diameter of 3.5 mm using a tableting machine (VELG 0512SW2MZ, manufactured by Kikusui Seisakusho Ltd.), and thereafter, a coating solution obtained by adding water (540.0 g), hypromellose (48.0 g), macrogol 6000 (6.0 g), titanium oxide (6.0 g), and yellow ferric oxide (0.3 g) was sprayed thereon using a coating machine (HC-FZ-LABO, manufactured by Freund Corporation), whereby coated tablets of the tablets with a diameter of 3.5 mm were obtained.

[0085] The compositions and dosage forms of Formulation Examples 7 to 9 are shown in Table 12.

[Table 12]

(unit: parts by mass)	Formulation Example 7	Formulation Example 8	Formulation Example 9
Mesylate salt of Compound 1	1.0	1.0	1.0
HP- β -CD	4.6	4.6	4.6
Light anhydrous silicic acid	0.030	0.030	0.030
Hydroxypropyl cellulose	0.17	0.17	0.17
Magnesium stearate	0.034	0.031	0.031
Hypromellose	-	0.14	0.14
Macrogol 6000	-	0.017	0.017
Titanium oxide	-	0.017	0.017
Yellow ferric oxide	-	0.00084	0.00084
Dosage form	Granule	Tablet with diameter of 4 mm	Tablet with diameter of 3.5 mm

[0086] With respect to these, each formulation was administered to animals under the following conditions, and the absorbability was evaluated.

[0087]

Animals used: beagle dogs (6 male animals, Kitayama Labes Co., Ltd.)

Feeding Conditions: fasting for 20 hours from the previous day

Dose: 200 mg/body (in terms of the compound 1)

Administration method: administered with 50 mL water

Pretreatment: An atropine sulfate intravenous injection was intravenously administered (20 µg/0.04 mL/kg) 30 minutes before administering the formulation. When the test was performed at a low intragastric pH, pentagastrin was intramuscularly administered (10 µg/0.1 mL/kg) 30 minutes before administering the formulation and thereafter administered twice at an interval of 45 minutes, and when the test was performed at a high intragastric pH, omeprazole was intravenously administered (1 mg/0.25 mL/kg) 30 minutes before administering the formulation and 60 minutes thereafter once.

[0088] As a result, it was found that the tablets containing the mesylate salt of the compound 1 and HP-β-CD show absorbability comparable to the granules thereof without being affected by the intragastric pH.

[0089] This application is based on Japanese Patent Application filed on February 15, 2017 (Patent Application No. 2017-026203).

REFERENCES CITED IN THE DESCRIPTION

Cited references

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- [WO2009125597A](#) [0005]
- [WO2013100014A](#) [0005]
- [WO2015046484A](#) [0005]
- [WO2016175305A](#) [0005]
- [JP2017026203A](#) [0089]

Non-patent literature cited in the description

- Molecular Cancer Therapeutics, 2013, vol. 12, 122685-96 [0006]
- European Journal of Cancer, 2012, vol. 48, 694- [0006]

Patentkrav**1.** Farmaceutisk sammensætning omfattende:

- 4-(2-fluor-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-
5 methylquinolin-6-carboxamid eller et farmaceutisk acceptabelt salt deraf;
og
hydroxypropyl- β -cyclodextrin.

2. Den farmaceutiske sammensætning ifølge krav 1,

- 10 hvor sammensætningen inkluderer toppe ved mindst 5 eller flere
diffraktionsvinkler $20 (\pm 0,2^\circ)$ valgt fra 6,5, 7,8, 9,6, 12,4, 18,8, 21,2, 23,0, 24,5
og 26,0 ($^\circ$) i pulverrøntgenstrukturdiffraction.

3. Den farmaceutiske sammensætning ifølge krav 1 eller 2,

- 15 hvor sammensætningen inkluderer toppe ved kemiske forskydningsværdier [δ
(ppm)] på 162,6, 130,4, 103,1, 82,7, 73,3, 41,9 og 19,9 i fast stof ^{13}C -NMR.

4. Den farmaceutiske sammensætning ifølge et hvilket som helst af kravene 1 til
3,

- 20 hvor sammensætningen inkluderer toppe ved mindst 5 eller flere absorptionsbånd
valgt fra 1663, 1352, 1225, 1156, 1032, 720 og 553 (cm^{-1}) i et infrarødt
absorptionsspektrum.

5. Den farmaceutiske sammensætning ifølge et hvilket som helst af kravene 1 til

- 25 4,
hvor hydroxypropyl- β -cyclodextrin er indeholdt i 0,1 til 5,5 massedele i forhold til
1 massedel af 4-(2-fluor-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-
-methylquinolin-6-carboxamid eller et farmaceutisk acceptabelt salt deraf.

- 30 **6.** Den farmaceutiske sammensætning ifølge et hvilket som helst af kravene 1 til
5,

hvor mængden af hydroxypropyl- β -cyclodextrin er fra 60 til 95 masse-%,
fortrinsvis fra 76 til 85 masse-% i forhold til den samlede farmaceutiske
sammensætning.

7. Den farmaceutiske sammensætning ifølge et hvilket som helst af kravene 1 til 6, yderligere omfattende:
et cellulosederivat.

5 **8.** Den farmaceutiske sammensætning ifølge et hvilket som helst af kravene 1 til 7,
hvor den farmaceutiske sammensætning er til oral indgivelse og fortrinsvis er en tablet eller et granulat, mere fortrinsvis en tablet med en maksimal diameter på 5 mm eller mindre.

10

9. Den farmaceutiske sammensætning ifølge et hvilket som helst af kravene 1 til 8,

den farmaceutiske sammensætning fremstillet ved fysisk blanding
hvor den fysiske blanding fortrinsvis er en fremstillingsfremgangsmåde, der
15 ikke inkluderer et trin, hvori 4-(2-fluor-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinolin-6-carboxamid eller et farmaceutisk acceptabelt salt deraf omdannes til en opløsningstilstand, når det farmaceutiske præparat fremstilles.

20 **10.** Den farmaceutiske sammensætning ifølge krav 9,
hvor den fysiske blanding er blanding eller granulering, hvor granuleringen fortrinsvis er en tørgranuleringsfremgangsmåde, eller en vådgranuleringsfremgangsmåde, mere fortrinsvis en knusningsgranuleringsfremgangsmåde, en granuleringsfremgangsmåde med fluidiseret leje, en granuleringsfremgangsmåde
25 med rullende leje, en ekstruderingsgranuleringsfremgangsmåde eller en højforskydningsgranuleringsfremgangsmåde.

11. Den farmaceutiske sammensætning ifølge krav 9 eller 10, yderligere omfattende:

30 et fluidiseringsmiddel.

12. Den farmaceutiske sammensætning ifølge krav 11,
hvor mængden af fluidiseringsmidlet er fra 0,1 til 2 masse-%, fortrinsvis fra 0,2 til 1 masse-% i forhold til den samlede farmaceutiske sammensætning.

35

13. Den farmaceutiske sammensætning ifølge krav 11 eller 12, hvor fluidiseringsmidlet er et kiselsyrederivat.

14. Fremgangsmåde til fremstilling af en farmaceutisk sammensætning ved at udføre fysisk blanding af 4-(2-fluor-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinolin-6-carboxamid eller et farmaceutisk acceptabelt salt deraf og hydroxypropyl- β -cyclodextrin.

15. Fremstillingsfremgangsmåden ifølge krav 14,
10 hvor den fysiske blanding er en fremstillingsfremgangsmåde, der ikke inkluderer et trin, hvori 4-(2-fluor-4-(3-(2-phenylacetyl)thioureido)phenoxy)-7-methoxy-N-methylquinolin-6-carboxamid eller et farmaceutisk acceptabelt salt deraf omdannes til en opløsningstilstand, når den farmaceutiske sammensætning fremstilles.

15

16. Fremstillingsfremgangsmåden ifølge krav 14 eller 15, hvor den fysiske blanding er blanding eller granulering.

17. Fremstillingsfremgangsmåden ifølge et hvilket som helst af kravene 14 til 16,
20 hvor den fysiske blanding er blanding, en tørgranuleringsfremgangsmåde eller en vådgranuleringsfremgangsmåde.

18. Fremstillingsfremgangsmåden ifølge et hvilket som helst af kravene 14 til 17, hvor den fysiske blanding er blanding, en knusningsgranuleringsfremgangsmåde,
25 granuleringsfremgangsmåde med fluidiseret leje, granuleringsfremgangsmåde med rullende leje, en ekstruderingsgranuleringsfremgangsmåde eller en højforskydningsgranuleringsfremgangsmåde.

DRAWINGS

Drawing

FIG. 1

Intensity (cps)

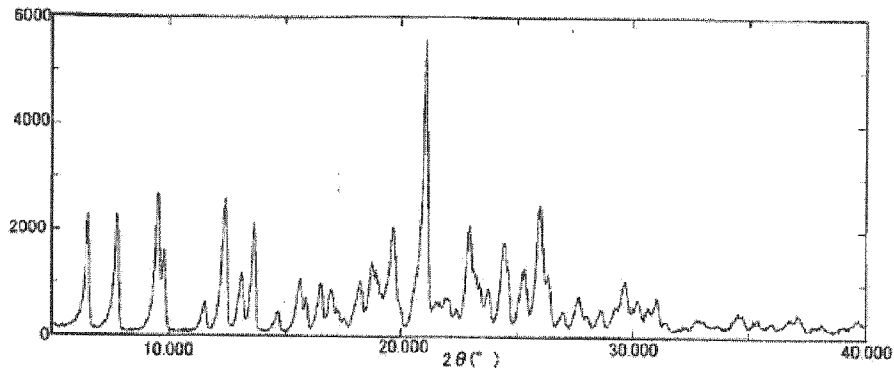


FIG. 2

Intensity (cps)

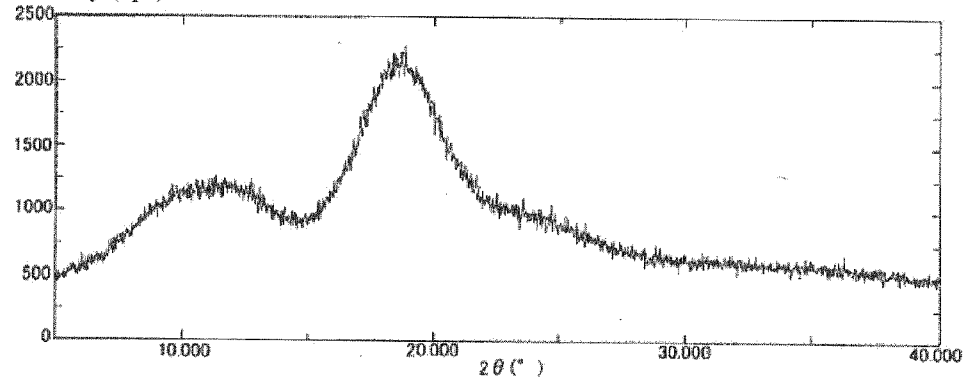


FIG. 3

Intensity (cps)

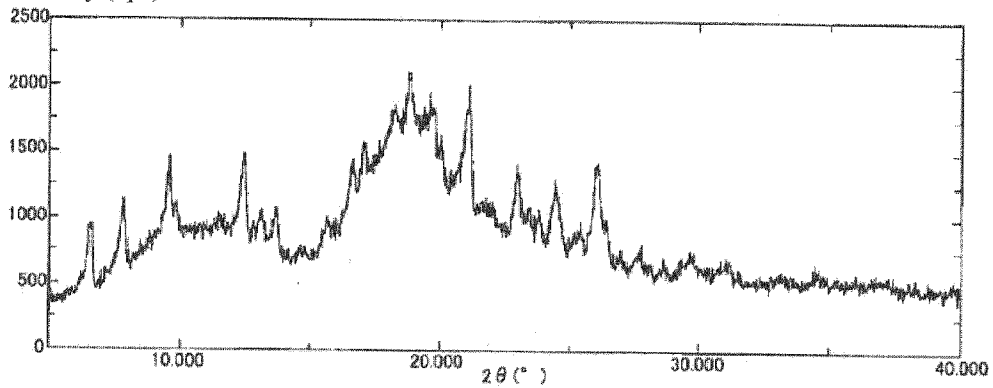


FIG. 4

Intensity (cps)

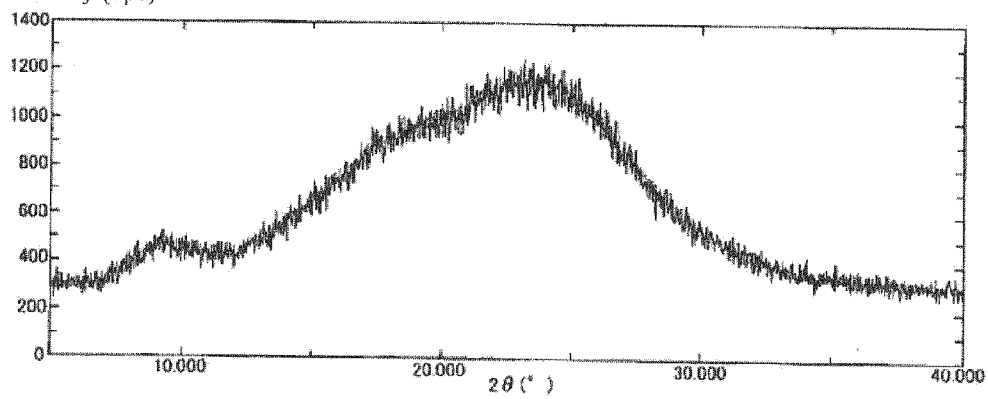


FIG. 5

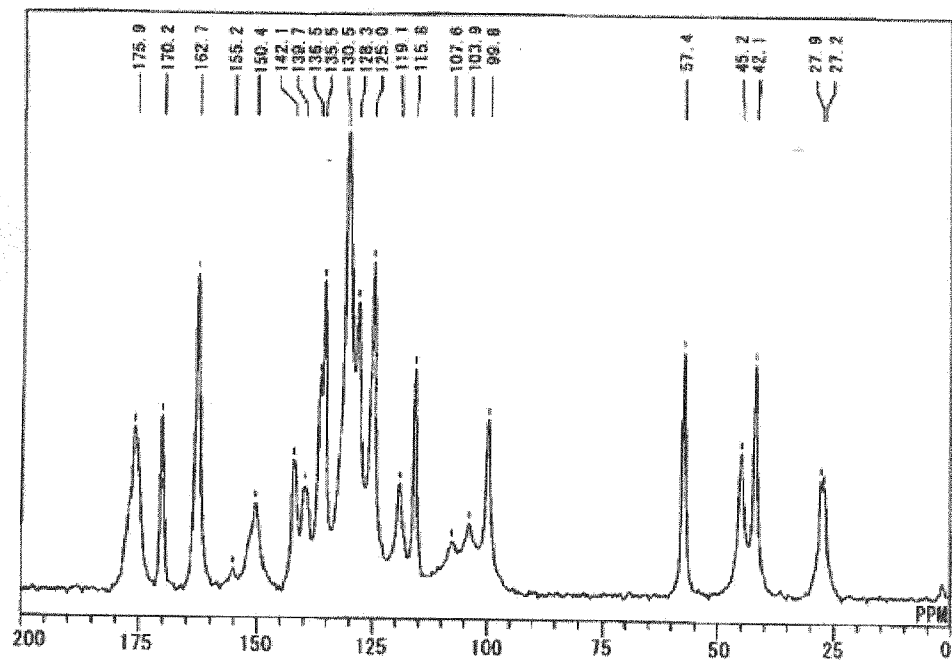


FIG. 6

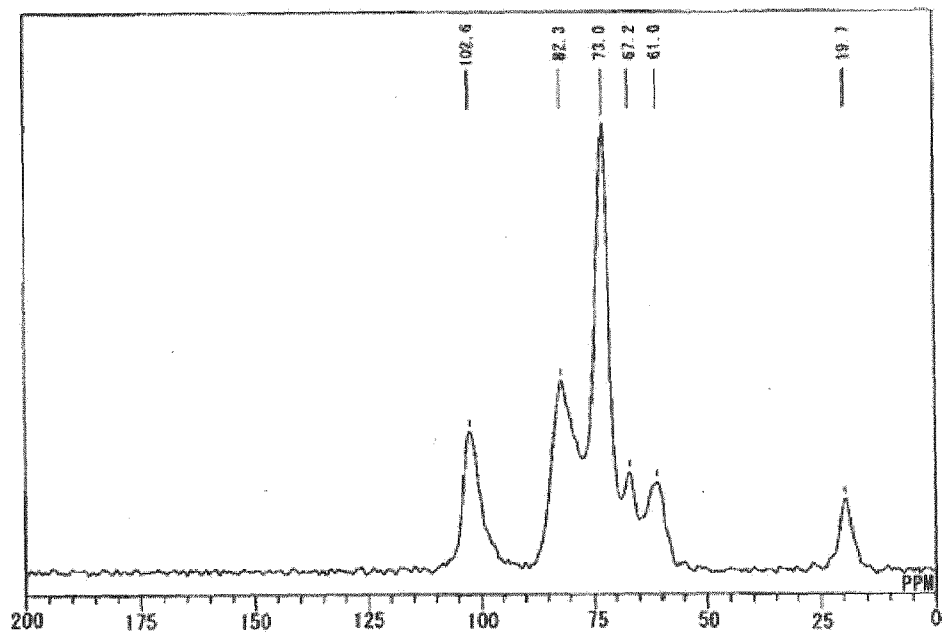


FIG. 7

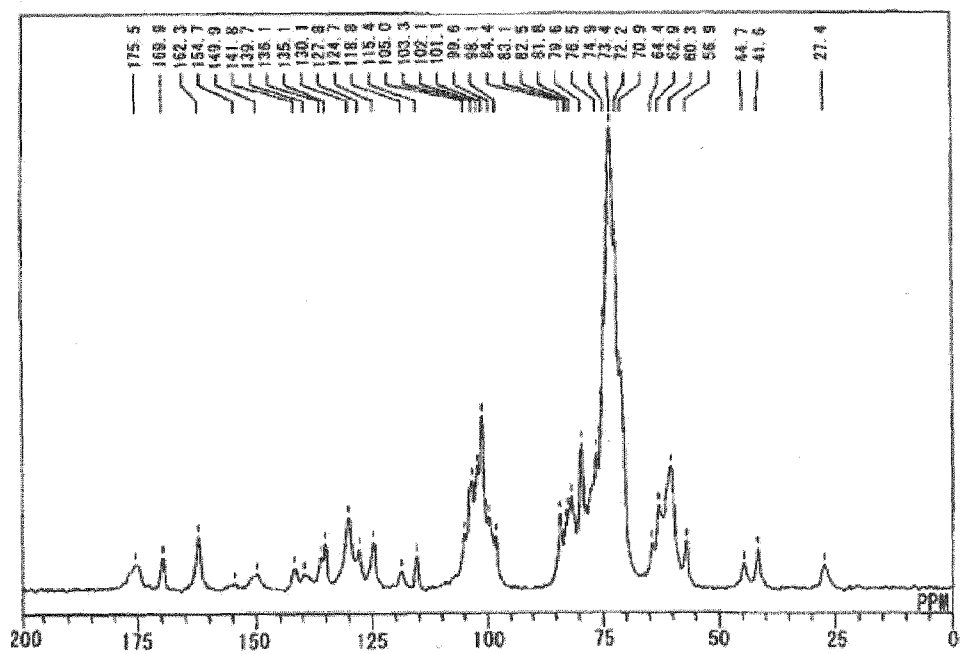


FIG. 8

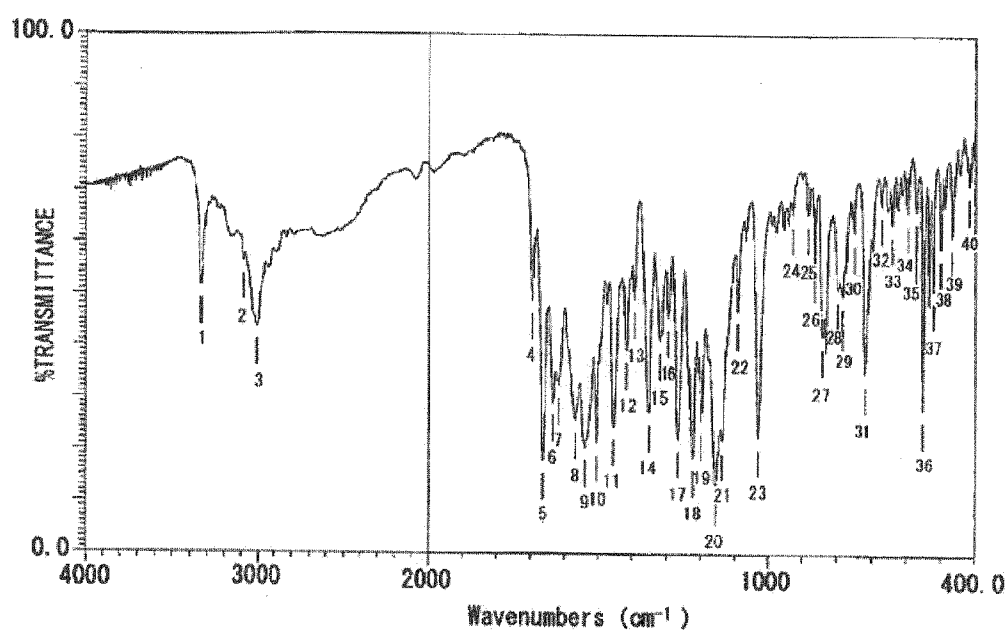


FIG. 9

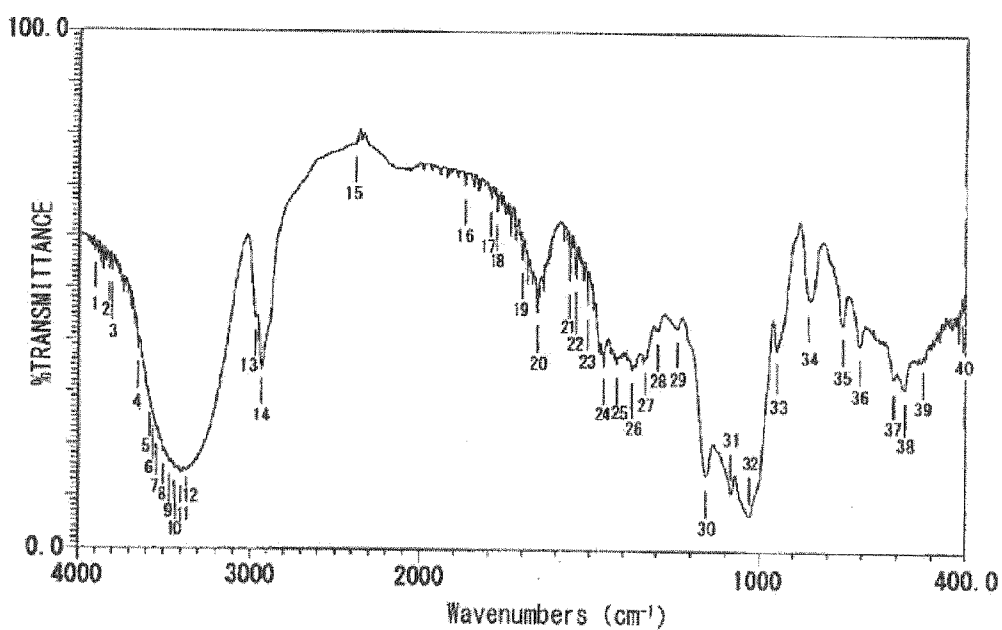


FIG. 10

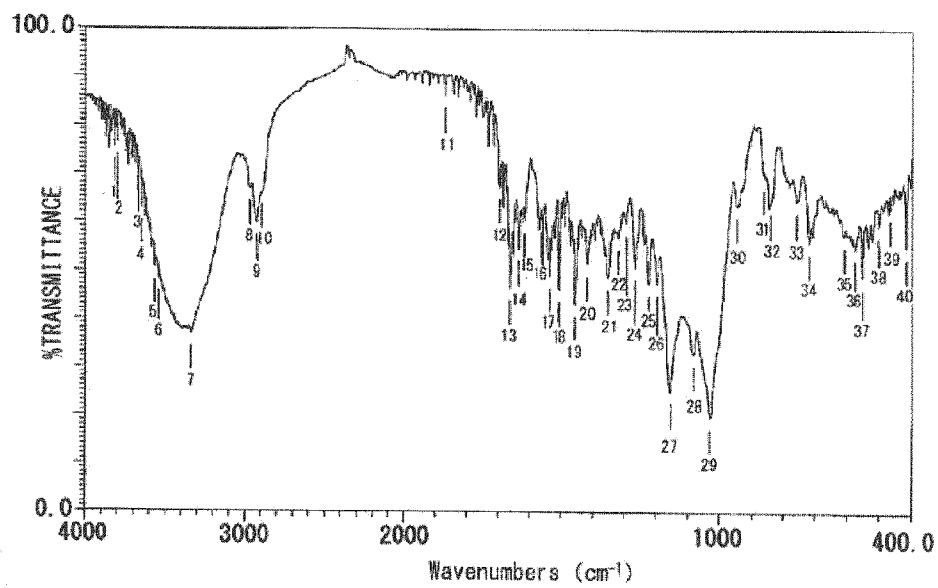


FIG. 11

