Description

Title of Invention: Pharmaceutical composition including sodium alkyl sulfate

Technical Field

[0001]

The present invention relates to a pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof and sodium alkyl sulfate, in particular, the pharmaceutical composition for oral administration.

Background Art

[0002]

Bioavailability is an indicator showing the level of an administered drug to reach in blood circulating throughout the body and to act thereon, and a clinically important parameter that is closely associated with medicinal effects and toxicity. In general, a drug having low bioavailability may not provide expected medicinal effects, or due to large fluctuations in one individual or between individuals, it may be difficult to predict and/or control medicinal effects and toxicity. Accordingly, in the development of drug products, it is important to obtain appropriate drug bioavailability. In the case of a drug for oral administration, the drug is affected by absorption ratio from intestinal tract and the metabolism in the liver and/or intestinal tract. In particular, in the case of a poorly water-soluble drug, it becomes important to improve the drug dissolution from a formulation or the drug solubility in water to obtain appropriate bioavailability.

[0003]

As way for improving the dissolution or absorption of a drug, the particle size reduction or solubilization of a drug substance, and a method of mixing a solubilizer such as a surfactant with a drug substance have been generally known. However, preferable surfactants are different

depending on the structure and properties of an active ingredient and the type of the formulation, and it is not easy to find an optimal formulation for a poorly water-soluble drug.

[0004]

It has been known that sodium lauryl sulfate, one of anionic surfactants, can be included in a pharmaceutical formulation, as a stabilizer, a surfactant, a lubricant, a solubilizer, a base, a binder, a brightener, an excipient, a disintegrant, an emulsifier, a foaming agent, a dispersant, or the like. For example, it was reported that sodium lauryl sulfate was added to granules containing a specific compound as a solubilizing agent to prepare a pharmaceutical formulation (Patent Literature 1).

[0005]

On the other hand, as a compound having excellent FGFR inhibitory action and exhibiting antitumor activity, (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one (hereinafter also referred to as "Compound A") has been reported (Patent Literatures 2 to 6).

Regarding Compound A, neither the improvement of the dissolution thereof, nor the combined use of Compound A with sodium alkyl sulfate for other purposes has been reported.

Citation List

Patent Literature

[0006]

Patent Literature 1: JP Patent Publication (Kokai) No. 2016-104762 A

Patent Literature 2: International Publication No. WO2013/108809

Patent Literature 3: International Publication No. WO2015/008844

Patent Literature 4: International Publication No. WO2015/008839

Patent Literature 5: International Publication No. WO2016/159327

Patent Literature 6: International Publication No. WO2017/150725

Summary of Invention

Technical Problem

[0007]

While Compound A has excellent FGFR inhibitory action and antitumor activity, there was room for improvement in ensuring appropriate bioavailability when formulated. For example, improvement of the dissolution in a neutral pH range and the absorption of Compound A has been required. Accordingly, it is an object of the present invention to provide a pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt thereof, having more excellent dissolution, stability, and absorption, and being easily produced.

Solution to Problem

[0008]

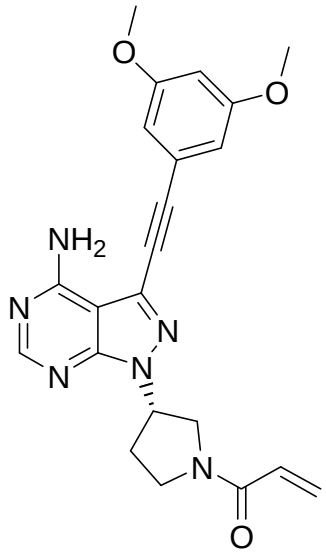
The present inventors have added various compounds into a composition comprising Compound A or a pharmaceutically acceptable salt thereof, and conducted various studies regarding the presence or absence of the effect of improving dissolution, stability and absorption of Compound A. As a result, it was found that, by adding sodium alkyl sulfate to Compound A or a pharmaceutically acceptable salt thereof, a pharmaceutical composition having excellent dissolution, stability and absorption and also excellent manufacturability can be obtained. The present inventors have further conducted studies to find more effective excipients to be used in the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt thereof and sodium alkyl sulfate, thereby achieving the present invention.

[0009]

Specifically, the present invention relates to the following [1] to [15].

[1] A pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one having the following structure, or a pharmaceutically acceptable salt thereof, and sodium lauryl sulfate:

[Formula 1]



(Compound A)

[2] The composition according to [1] above, comprising sodium lauryl sulfate in a range of 0.05 to 15 parts by mass, relative to 1 part by mass of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one.

[3] The composition according to [1] or [2] above, comprising sodium lauryl sulfate in a range of 0.2 to 5 parts by mass, relative to 1 part by mass of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one.

[4] The composition according to any one of [1] to [3] above, further comprising at least one compound selected from the group consisting of crospovidone, carmellose sodium, and carmellose calcium.

[5] The composition according to [4] above, comprising crospovidone.

[6] The composition according to any one of [1] to [5] above, comprising sodium lauryl sulfate in a range of 0.2 to 5 parts by mass, and further comprising crospovidone in a range of 0.2 to 5 parts by mass, relative to 1 part by mass of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one.

[7] The composition according to any one of [1] to [6] above, further comprising at least one compound selected from the group consisting of D-mannitol and lactose.

[8] The composition according to any one of [1] to [7] above, in the form of syrup, a powder, a granule, a tablet, or a capsule.

[9] A method for improving the dissolution of (S)-1-(3-(4-amino-3-((3,5-

dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one from a pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof, wherein the method comprises adding sodium lauryl sulfate to the pharmaceutical composition.

[10] A method for improving the absorption of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one, wherein the method comprises adding sodium lauryl sulfate to a pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof.

[11] A method for improving the manufacturability of a pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof, wherein the method comprises adding sodium lauryl sulfate to the pharmaceutical composition.

[12] Use of sodium lauryl sulfate for improving the dissolution of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof.

[13] Use of sodium lauryl sulfate for improving the absorption of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof.

[14] Use of sodium lauryl sulfate for improving the manufacturability of a pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof.

[15] Use of sodium lauryl sulfate for producing a pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof.

The present description includes the content disclosed in Japanese Patent Application No. 2018-051620, from which the present application claims priority.

## Advantageous Effects of Invention

[0010]

The present invention can provide a pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt thereof and sodium alkyl sulfate, which has excellent dissolution, stability and absorption, and is also excellent in terms of manufacturability such as lubricative property and flowability.

## Brief Description of Drawings

[0011]

[Figure 1] Figure 1 shows the results of evaluation of the ejection force required when the tablets of Formulation Example 37 and Comparative Example 20 are discharged from a tableting machine.

## Description of Embodiments

[0012]

The pharmaceutical composition of the present invention comprises, as an active ingredient, Compound A or a pharmaceutically acceptable salt thereof. The pharmaceutical composition of the present invention may also comprise other active ingredients, as long as it exhibits the effects of the present invention. The structure of Compound A ((S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one) is shown below.

[0013]

[Formula 2]

improving the manufacturability of a pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt thereof.

[0088]

In another aspect, the present invention provides use of sodium lauryl sulfate for producing a pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt thereof.

Examples

[0089]

Hereinafter, the present invention will be more specifically described by way of examples. However, these examples are not intended to limit the scope of the present invention. The present invention is sufficiently described in the examples, but it will be understood that various alternations or modifications can be carried out by a person skilled in the art. Accordingly, such alterations or modifications are included in the present invention, unless they are deviated from the scope of the present invention.

Various types of reagents used in the examples were commercially available products, unless otherwise specified.

[0090]

[Test Example 1] Solubility Test

As described in Formulation Examples 1 and 2 and Comparative Examples 1 to 15, test solutions, in which (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one (Compound A) was combined with various types of surfactants, were prepared as follows, and the obtained test solutions were used in solubility tests, as described below.

[0091]

< Formulation Example 1 >

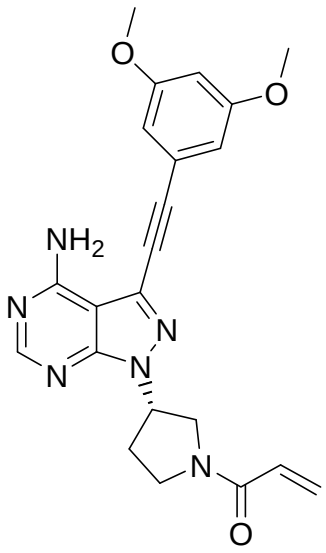
0.05 g of Sodium lauryl sulfate (manufactured by SERVA, Research grade) was dissolved in 50 mM phosphate buffer (50 mL) of pH 6.8, and 25 mg of Compound A was then suspended in the solution, followed by heating the suspension at 37°C for 60 minutes, to obtain

# CLAIMS

[Claim 1]

A pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one having the following structure, or a pharmaceutically acceptable salt thereof, and sodium lauryl sulfate:

[Formula 1]




[Claim 2]

The composition according to claim 1, comprising sodium lauryl sulfate in a range of 0.05 to 15 parts by mass, relative to 1 part by mass of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one.

[Claim 3]

The composition according to claim 1 or 2, comprising sodium lauryl sulfate in a range of 0.2 to 5 parts by mass, relative to 1 part by mass of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one.

[Claim 4]

The composition according to any one of claims 1 to 3, further comprising at least one compound selected from the group consisting of crospovidone, carmellose sodium, and carmellose calcium.

[Claim 5]

The composition according to claim 4, comprising crospovidone.

[Claim 6]

The composition according to any one of claims 1 to 5, further comprising at least one compound selected from the group consisting of D-mannitol and lactose.

[Claim 7]

The composition according to any one of claims 1 to 6, in the form of syrup, a powder, a granule, a tablet, or a capsule.

[Claim 8]

A method for improving the dissolution of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one from a pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof, wherein the method comprises adding sodium lauryl sulfate to the pharmaceutical composition.

[Claim 9]

A method for improving the absorption of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one, wherein the method comprises adding sodium lauryl sulfate to a pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof.

[Claim 10]

A method for improving the manufacturability of a pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-

d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof, wherein the method comprises adding sodium lauryl sulfate to the pharmaceutical composition.

[Claim 11]

Use of sodium lauryl sulfate for improving the dissolution of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof.

[Claim 12]

Use of sodium lauryl sulfate for improving the absorption of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof.

[Claim 13]

Use of sodium lauryl sulfate for improving the manufacturability of a pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof.

[Claim 14]

Use of sodium lauryl sulfate for producing a pharmaceutical composition comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyrrolidinyl)-2-propen-1-one or a pharmaceutically acceptable salt thereof.