

DESCRIPTION

AMORPHIZING AGENT, AMORPHOUS COMPOSITION COMPRISING
AMORPHIZING AGENT AND UTILIZATION THEREOF

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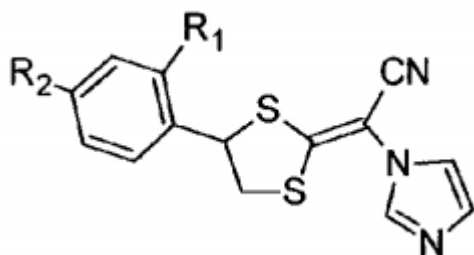
Technical Field

[0001]

The present invention relates to an amorphizing agent for a compound represented by the following General Formula (1) and/or a salt thereof, an amorphous composition comprising the amorphizing agent, and use thereof.

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[0002]



General Formula (1)

(In the formula, R₁ and R₂ each independently represent a hydrogen atom or a halogen atom.)

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Background Art

[0003]

Compounds represented by General Formula (1) such as luliconazole and lanoconazole are known to have high crystallinity and excellent antifungal activity. However, because of their high crystallization and precipitation properties, they cannot be easily handled during the production process. Those compounds also have a drawback in stability since they have poor photostability. Therefore, when

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the process of production or formulation takes a long time, the amount of analogs produced may increase (see, for example, Patent Documents 1 and 2). Moreover, these Patent Documents revealed that instantaneous crystallization occurs during their formulation to inhibit transfer of the compounds into the body, and therefore development of means for suppressing the crystallization has been an issue to be achieved for formulation of compounds represented by General Formula (1). These Patent Documents also disclose that α -hydroxy acid such as lactic acid suppresses the instantaneous crystallization of compounds represented by General Formula (1), but they do not disclose at all by what mechanism the suppression of the instantaneous crystallization can be achieved.

[0004]

As such a crystallization-suppressing technique, a technique in which an excess amount of plasticizer such as polyoxyethylene polyoxypropylene is used to prepare a liquid viscous coating has been known (see, for example, Patent Document 3). However, this technique has a drawback that the mass of the compound represented by General Formula (1) that can be contained in the coating is limited.

[0005]

It is generally known that solubility, especially the rate of dissolution, increases by amorphization. Therefore, amorphization has been an important technique for injections and the like (see, for example, Patent Document 4).

[0006]

On the other hand, regarding compounds represented by General Formula (1), although their monoclinic crystal system is known, their amorphous solids have not been known at all.

[0007]

That is, development of an amorphization technique for a compound represented by General Formula (1) and/or a salt thereof has been demanded for

improving usability of the compound represented by General Formula (1) and/or the salt thereof.

Prior Art Documents

5 [Patent Documents]

[0008]

[Patent Document 1] WO 2007/102241

[Patent Document 2] WO 2007/102243

[Patent Document 3] WO 2003/105841

10 [Patent Document 4] JP 2006-312598 A

Summary of Invention

Technical Problem

[0009]

15 The present invention was carried out under such circumstances, and an object of the present invention is to provide an amorphization technique for a compound represented by General Formula (1) and/or a salt thereof for improving usability of the compound represented by General Formula (1) and/or the salt thereof.

20 Solution to Problem

[0010]

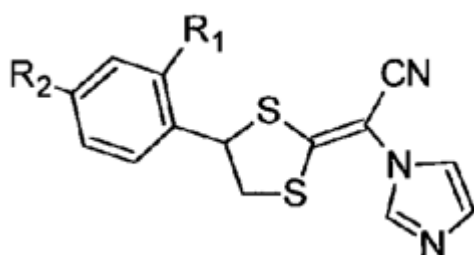
 In view of this, the present inventors intensively studied seeking an amorphization technique for a compound represented by General Formula (1) and/or a salt thereof in order to improve usability of the compound represented by General
25 Formula (1) and/or the salt thereof. As a result, the present inventors discovered that, by using one or more selected from the group consisting of water-soluble polymers and acids as an amorphizing agent, such amorphization can be achieved,

thereby completing the present invention. That is, the present invention is as described below.

[0011]

[1] An amorphizing agent for a compound represented by the following General Formula (1) and/or a salt thereof, the amorphizing agent comprising one or more selected from the group consisting of water-soluble polymers and acids:

[0012]



General Formula (1)

10 [0013]

(wherein R₁ and R₂ each independently represent a hydrogen atom or a halogen atom).

[0014]

[2] The amorphizing agent according to [1], wherein the water-soluble polymer is a water-soluble vinyl polymer or a water-soluble cellulose polymer.

[3] The amorphizing agent according to [2], wherein the water-soluble vinyl polymer is polyvinyl pyrrolidone or a carboxyvinyl polymer.

[4] The amorphizing agent according to [2], wherein the water-soluble cellulose polymer is hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, methyl cellulose, or ethyl cellulose.

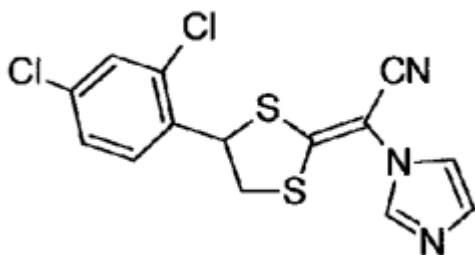
[5] The amorphizing agent according to any one of [1] to [4], wherein the acid is an organic acid.

[6] The amorphizing agent according to any one of [1] to [5], comprising a water-

soluble polymer and an acid.

[7] The amorphizing agent according to any one of [1] to [6], wherein the compound represented by General Formula (1) is luliconazole or lanoconazole:

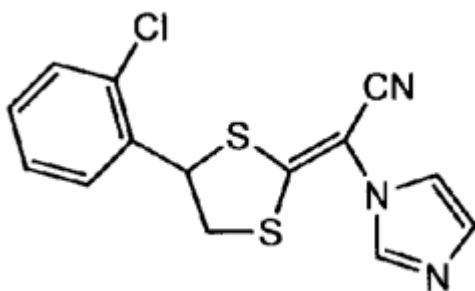
[0015]



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Luliconazole

[0016]



Lanoconazole

[0017]

[8] A method for amorphizing a compound represented by General Formula (1) and/or a salt thereof, the method comprising; a step of uniformly mixing the compound represented by General Formula (1) and/or the salt thereof with the amorphizing agent according to any one of [1] to [7] in an amount of 0.05 to 10 times the mass of the compound and/or the salt thereof, and solidifying the resulting mixture.

[9] An amorphous composition comprising a compound represented by General Formula (1) and/or a salt thereof and the amorphizing agent according to any one of

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[1] to [7] in an amount of 0.05 to 10 times the mass of the compound and/or the salt thereof.

[10] A method for producing a pharmaceutical composition comprising a compound represented by General Formula (1) and/or a salt thereof, the method comprising; a step of using the amorphous composition according to [9] as an intermediate product and dissolving the intermediate product.

[11] A composition comprising a compound represented by General Formula (1) and/or a salt thereof and the amorphizing agent according to any one of [1] to [7] in an amount of 0.05 to 10 times the mass of the compound and/or the salt thereof.

[12] The composition according to [11], further comprising a solvent to be evaporated.

[13] The composition according to [11] or [12], which is a pharmaceutical composition.

Advantageous Effects of Invention

[0018]

By the present invention, an amorphization technique for a compound represented by General Formula (1) and/or a salt thereof can be provided.

Brief Description of the Drawings

[0019]

Fig. 1 is a diagram (drawing substitute photographs) illustrating the process of formation of a coating by the composition of Example 1. LLCZ represents luliconazole, and PVP represents polyvinyl pyrrolidone. A of Fig. 1 is a photograph taken immediately after dropping; B of Fig. 1 is a photograph taken four hours after dropping; C of Fig. 1 is a photograph taken one day after dropping; and D of Fig. 1 is a photograph taken four days after dropping. In each of A to D of Fig. 1, a sample

containing no amorphizing agent (luliconazole solution) is shown in the left, and a sample containing an amorphizing agent (luliconazole + polyvinyl pyrrolidone solution) is shown in the right. In each of A to D of Fig. 1, the top row shows optical microscopic observation images, and the bottom row shows polarization
 5 microscopic observation images.

Fig. 2 is a diagram (drawing substitute photographs) illustrating the process of formation of a coating by the composition of Example 2. A photograph taken 0.5 minute after dropping is shown. Each leading line shows a micelle that has begun to appear.

10 Fig. 3 is a diagram (drawing substitute photographs) illustrating the process of formation of a coating by the composition of Example 2. A photograph taken 1 minute after dropping is shown. The photograph shows a structure in which micelles are dispersed.

Fig. 4 is a diagram (drawing substitute photographs) illustrating the process of formation of a coating by the composition of Example 2. A photograph taken 3
 15 minutes after dropping is shown. The photograph shows a coating in which amorphous bodies having a micelle-like structure are dispersed among continuous-phase-like amorphous bodies.

20 Description of Embodiments

[0020]

(1) Amorphizing Agent of Present Invention

The amorphizing agent of the present invention is an amorphizing agent for a compound represented by General Formula (1) and/or a salt thereof, and comprises
 25 one or more selected from the group consisting of water-soluble polymers and acids.

Preferred examples of the water-soluble polymer include water-soluble vinyl polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, and carboxyvinyl

polymers; water-soluble cellulose polymers such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose terephthalate, hydroxyethyl methylcellulose, and ethyl cellulose; and water-soluble polysaccharide polymers such as gum arabic, gum tragacanth, and xanthan gum. Preferred examples among these include water-soluble vinyl polymers and water-soluble cellulose polymers. Preferred examples of the vinyl polymers include polyvinyl pyrrolidone and carboxyvinyl polymers. Preferred examples of the water-soluble cellulose polymers include hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, methyl cellulose, and ethyl cellulose. One or more kinds of water-soluble polymers may be used.

[0021]

Preferred examples of the acid include organic acids and inorganic acids, and preferred examples of the organic acids include hydroxy acids such as citric acid, lactic acid, and gluconic acid; dibasic acids such as oxalic acid, tartaric acid, and adipic acid; and carboxylic acids such as formic acid and acetic acid. Hydroxy acids and dibasic acids are especially preferred. Among these, lactic acid is preferred as a hydroxy acid, and tartaric acid is especially preferred as a dibasic acid. Preferred examples of the inorganic acids include mineral acid. One or more kinds of acids may be used.

[0022]

A single kind of water-soluble polymer or acid may be used, or two or more kinds of water-soluble polymer and/or acid may be used in combination. In a preferred mode, a water-soluble polymer and an acid are used in combination.

[0023]

The amorphizing agent of the present invention is used, for example, preferably in an amount of 0.05 to 10 times, more preferably in an amount of 0.5 to 5 times, still more preferably in an amount of 0.7 to 3 times the total mass of the

compound represented by General Formula (1) and/or a salt thereof. This is because sufficient amorphization cannot be achieved in some cases where the amount is too small, and limitation in the formulation occurs when the amount is too large. In cases where a water-soluble polymer and an acid are used in combination, their mass ratio is set such that the water-soluble polymer is contained in an amount of preferably 1 to 15% by mass, more preferably 4 to 10% by mass, with respect to the acid.

[0024]

Regarding the amorphizing agent of the present invention, in cases where luliconazole is used as the compound represented by General Formula (1), the amorphizing agent is preferably the combination of lactic acid and polyvinyl pyrrolidone. In cases where lanoconazole is used, the amorphizing agent is preferably the combination of hydroxypropyl cellulose, tartaric acid, and lactic acid.

[0025]

(2) Compound Represented by General Formula (1) and/or Salt Thereof

The compound to which the amorphizing agent of the present invention is to be applied is represented by General Formula (1).

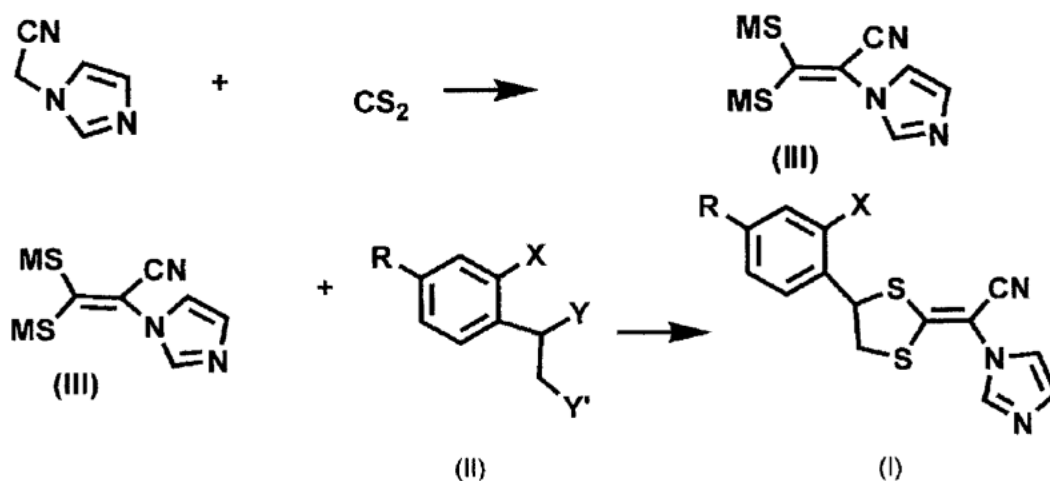
In General Formula (1), each group represented by R_1 or R_2 is a hydrogen atom or a halogen atom, and preferred examples of the halogen atom include a chlorine atom, bromine atom, fluorine atom, and iodine atom. A hydrogen atom or a chlorine atom is especially preferred.

[0026]

Among the compounds represented by General Formula (1) and/or salts thereof, luliconazole ($R_1 = R_2 = Cl$; (R)-(-)-(E)-[4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-1-imidazolylacetonitrile) and lanoconazole ($R_1 = Cl$, $R_2 = H$; 4-(2-chlorophenyl)-1,3-dithiolan-2-ylidene-1-imidazolylacetonitrile) are especially preferred. Luliconazole is especially preferred.

These compounds can be synthesized according to, for example, the method described in JP 60-218387 A. More specifically, the compounds can be synthesized by the method described in the following formulae. That is, 1-cyanomethylimidazole is reacted with carbon disulfide to obtain a compound (III), which is then reacted with a compound of General Formula (II) having leaving groups, to thereby obtain a compound represented by General Formula (I). Preferred examples of the leaving groups include methanesulfonyloxy, benzenesulfonyloxy, p-toluenesulfonyloxy, and halogen atoms. In the following formulae, R and X each represent a halogen atom or a hydrogen atom.

[0027]



(In the formulae, Y and Y' represent leaving groups, and M represents an alkali metal.)

[0028]

The compound represented by General Formula (1) to which the amorphizing agent of the present invention is to be applied may be used as a physiologically acceptable salt formed with sulfuric acid, hydrochloric acid, nitric acid, phosphoric acid, or the like. In such a case, the salt is a salt that can be stably present in the presence of the amorphizing agent.

[0029]

(3) Amorphous Composition of Present Invention

The amorphous composition of the present invention comprises as essential constituents the amorphizing agent of the present invention and the compound represented by the General Formula (1) and/or a salt thereof. The amorphous composition of the present invention can be obtained by uniformly mixing the compound represented by General Formula (1) and/or a salt thereof with the amorphizing agent in an amount of 0.05 to 10 times the mass of the compound and/or the salt thereof, and solidifying the resulting mixture by evaporation of the solvent. A composition obtained by uniformly mixing a compound represented by General Formula (1) and/or a salt thereof with an amorphizing agent in an amount of 0.05 to 10 times the mass of the compound and/or the salt thereof is a composition of the present invention. The composition of the present invention may include a solvent in addition to the compound represented by General Formula (1) and/or the salt thereof and the amorphizing agent. Since the compound represented by General Formula (1) and/or a salt thereof has/have an antifungal effect, the composition of the present invention may be a pharmaceutical composition. The compound and/or the salt is/are preferably an antifungal pharmaceutical composition, more preferably an antifungal pharmaceutical composition for nails. The composition of the present invention may be a composition for preparation of a pharmaceutical product, that is, an intermediate product for production of a pharmaceutical product.

Since the compound represented by General Formula (1) and/or a salt thereof has/have an antifungal effect, the amorphous composition of the present invention may also be a pharmaceutical composition. The composition is preferably an antifungal pharmaceutical composition, more preferably an antifungal pharmaceutical composition for nails.

The formulation of the pharmaceutical composition is preferably a coating-forming formulation. The mode of use may be appropriately selected in

consideration of the body weight, age, sex, symptoms, and the like of the patient.

For an adult human, the compound represented by General Formula (I) and/or a salt thereof is usually preferably administered at 0.01 to 1 g per day. One may also refer to doses of compounds represented by General Formula (1) and/or salts thereof that are normally used for diseases caused by fungi.

For example, an appropriate amount of the composition may be applied to an affected area once or several times per day, and such treatment is preferably carried out every day.

[0030]

The composition may contain, in addition to the essential components, an arbitrary component used for a pharmaceutical composition or the like. Preferred examples of such an arbitrary component include excipients, dispersants, correctives, coloring agents, and surfactants. The ratio of the arbitrary component in the composition of the present invention is not limited as long as the amorphous form can be maintained. The upper limit of the ratio is preferably about 50% by mass with respect to the total amorphous composition. That is, the composition may contain the amorphizing agent and the compound represented by General Formula (1) and/or a salt thereof in an amount of from more than 50% by mass to 100% by mass with respect to the total amorphous composition. The blend ratio between the amorphizing agent and the compound represented by General Formula (1) and/or a salt thereof is the same as the blend ratio described in “(1) Amorphizing Agent of Present Invention”.

[0031]

The present invention also relates to a method for amorphization of a compound represented by General Formula (1) and/or a salt thereof using the amorphizing agent of the present invention. The amorphization method of the present invention comprises a step of uniformly mixing the compound represented by

General Formula (1) and/or a salt thereof with an amorphizing agent in an amount of 0.05 to 10 times the mass of the compound and/or the salt thereof, and solidifying the resulting mixture. Examples of the method of uniformly mixing the compound represented by General Formula (1) and/or a salt thereof with an amorphizing agent include a method in which the compound represented by General Formula (1) and/or the salt thereof is/are dissolved in a solvent, and then the amorphizing agent is added thereto, followed by mixing the resulting mixture. Examples of the method of solidification include a method in which the mixture is stored at room temperature, and then the solvent is removed.

[0032]

The present invention also relates to a method for producing a pharmaceutical composition comprising a compound represented by General Formula (1) and/or a salt thereof, the method comprising a step of using the amorphous composition of the present invention as an intermediate product and dissolving the intermediate product.

The amorphous composition of the present invention provided as the intermediate product is a readily soluble, stable intermediate product. By the use of such an intermediate product, a method for producing a pharmaceutical composition comprising the compound represented by General Formula (1) and/or a salt thereof, which method hardly causes production of analogs, can be provided.

[0033]

The amorphous composition of the present invention can be used also as a final coating of a pharmaceutical product, or an intermediate product for production of a pharmaceutical product.

[0034]

The amorphous composition of the present invention can be an intermediate product (also referred to as “production intermediate” or “intermediate”) for obtaining a pharmaceutical composition stably comprising a compound represented

by General Formula (1) and/or a salt thereof. By the use of such an intermediate product, production of analogs during the production process of a pharmaceutical composition can be reduced.

[0035]

5 The amorphous composition of the present invention may be a coating-forming preparation as a product, or may be a coating finally generated when a pharmaceutical composition is administered to a target site. By such amorphization, penetration of the compound represented by General Formula (1) and/or a salt thereof into the skin can be improved, and the high concentration in the tissue can be
10 maintained for a long period. This is because the amorphous has the function as a reservoir. Such amorphization of a film as a final preparation is also within the scope of the right of the present invention as long as the film has a property as an amorphous film.

[0036]

15 The coating as a final product may be used, for example, as a coating of an effective component formed on a carrier such as a granule, or may be used as a coating of a pharmaceutical composition formed on the skin or a nail. With such a coating of an amorphous composition, bioavailability of the compound represented by General Formula (1) and/or a salt thereof as an effective component can be
20 increased. This is due to the reservoir effect described above.

Examples

[0037]

25 The present invention is described below in more detail by way of Examples, but the present invention is not limited to these Examples as long as the spirit of the present invention is not spoiled.

[0038]

<Example 1>

A solution containing 1% by mass luliconazole in ethanol and a solution containing 1% by mass luliconazole and 0.1% by mass polyvinyl pyrrolidone in ethanol were prepared, and each solution was dropped onto a slide glass. The properties of each solution were observed under the microscope immediately after the dropping, after four hours of storage at room temperature after the dropping, after one day of storage at room temperature after the dropping, and after four days of storage at room temperature after the dropping. The microscopic observation was carried out using both a normal optical microscope and a polarization microscope. The results are shown in Fig. 1. From the results, it can be seen that the amorphizing agent of the present invention caused a difference in the crystallization, and that polyvinyl pyrrolidone acted as an amorphizing agent. Thus, also in cases where crystals and amorphous bodies coexist, when inclusion of the amorphizing agent of the present invention caused the coexistence with the amorphous bodies (caused the appearance of the amorphous structure) while only crystals should be present in the original state, the amorphizing agent of the present invention is judged to be effective.

[0039]

<Example 2>

With pharmaceutical composition 1 having the following composition, a coating-forming preparation was produced according to the following procedure.

[0040]

Table 1

Component	% by mass
Luliconazole	5
N-methyl-2-pyrrolidone	8
Benzyl alcohol	4
Diisopropyl adipate	10
Lactic acid	4
Polyvinyl pyrrolidone	0.5

Ethanol	Remainder
Total	100

[0041]

Luliconazole and ethanol were combined together, and heated at 70°C with stirring to allow solubilization. Subsequently, lactic acid and polyvinyl pyrrolidone were added to the mixture, and the resulting mixture was heated at 70°C with stirring. After confirmation of solubilization, the remaining solvent components were added thereto to dilute the mixture, and the resulting dilution was solubilized with stirring. After confirmation of the solubilization, the liquid was cooled to room temperature with stirring, to obtain pharmaceutical composition 1.

[0042]

<Coating-forming Process of Pharmaceutical Composition 1 Produced>

Into a tube, 1 mL of pharmaceutical composition 1 was placed, and 100 µL of a liquid prepared by dissolving 10 mg of neutral red in 200 µL of methanol was added thereto, followed by stirring the resulting mixture well. Thereafter, the mixture was dropped onto a slide glass, followed by solvent evaporation and observation of the coating-forming process under the microscope (× 400) at room temperature. The observed process is shown in Figs. 2 to 4. Micelle-like structures began to appear in a uniform phase (Fig. 2), and then the micelle structures increased (Fig. 3), resulting in appearance of an amorphous film having the micelle-like structures uniformly dispersed in a continuous-phase-like structure (Fig. 4). By this, an amorphization effect of polyvinyl pyrrolidone and lactic acid as an amorphizing agent of the present invention could be confirmed.

[0043]

<Example 3>

According to the procedure shown in Example 2, pharmaceutical compositions 2 and 3 (coating-forming preparations) having the compositions shown in Table 2 were produced. According to the method described in Example 2, the

coating-forming process was observed under the microscope ($\times 400$). Similarly to pharmaceutical composition 1, pharmaceutical compositions 2 and 3 showed amorphous films in which micelle-like structures are uniformly dispersed in a continuous-phase-like structure. Thus, an amorphization effect could be observed.

5 [0044]

Table 2

Component	Pharmaceutical composition 2	Pharmaceutical composition 3 % by mass
Luliconazole	5	5
N-methyl-2-pyrrolidone	8	8
Benzyl alcohol	4	4
Diisopropyl adipate	10	10
Lactic acid	8	6
Polyvinyl pyrrolidone	1	0.5
Ethanol	Remainder	Remainder
Total	100	100

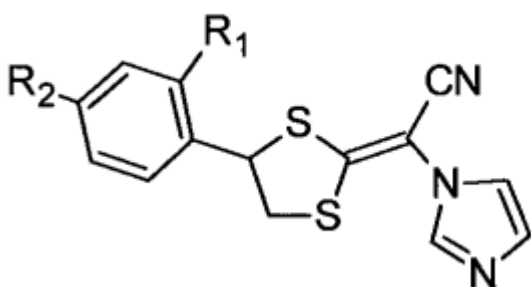
Industrial Applicability

[0045]

10 The present invention is applicable to pharmaceutical products and production of pharmaceutical products.

CLAIMS

1. An amorphizing agent for a compound represented by the following General Formula (1) and/or a salt thereof, the amorphizing agent comprising one or more selected from the group consisting of water-soluble polymers and acids:



General Formula (1)

(wherein R₁ and R₂ each independently represent a hydrogen atom or a halogen atom).

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2. The amorphizing agent according to claim 1, wherein the water-soluble polymer is a water-soluble vinyl polymer or a water-soluble cellulose polymer.

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3. The amorphizing agent according to claim 2, wherein the water-soluble vinyl polymer is polyvinyl pyrrolidone or a carboxyvinyl polymer.

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4. The amorphizing agent according to claim 2, wherein the water-soluble cellulose polymer is hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, methyl cellulose, or ethyl cellulose.

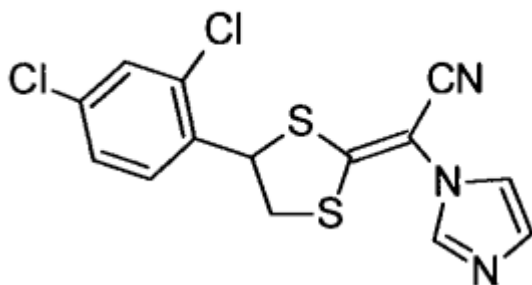
5. The amorphizing agent according to any one of claims 1 to 4, wherein

the acid is an organic acid.

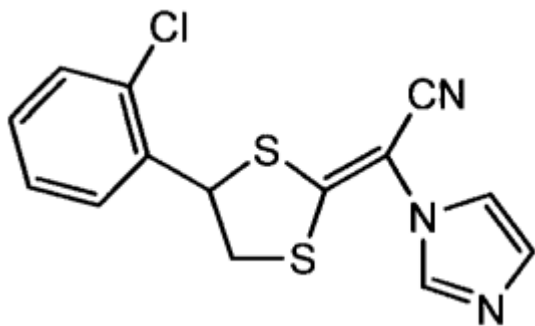
6. The amorphizing agent according to any one of claims 1 to 5, comprising a water-soluble polymer and an acid.

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7. The amorphizing agent according to any one of claims 1 to 6, wherein the compound represented by General Formula (1) is luliconazole or lanoconazole:



Luliconazole



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Lanoconazole.

8. A method for amorphizing a compound represented by General Formula (1) and/or a salt thereof, the method comprising;

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a step of uniformly mixing the compound represented by General Formula (1) and/or the salt thereof with the amorphizing agent according to any one of claims 1 to 7 in an amount of 0.05 to 10 times the mass of the compound and/or the salt thereof,

and solidifying the resulting mixture.

9. An amorphous composition comprising a compound represented by General Formula (1) and/or a salt thereof and the amorphizing agent according to any one of claims 1 to 7 in an amount of 0.05 to 10 times the mass of the compound and/or the salt thereof.

10. A method for producing a pharmaceutical composition comprising a compound represented by General Formula (1) and/or a salt thereof, the method comprising;

a step of using the amorphous composition according to claim 9 as an intermediate product and dissolving the intermediate product.

11. A composition comprising a compound represented by General Formula (1) and/or a salt thereof and the amorphizing agent according to any one of claims 1 to 7 in an amount of 0.05 to 10 times the mass of the compound and/or the salt thereof.

12. The composition according to claim 11, further comprising a solvent to be evaporated.

13. The composition according to claim 11 or 12, which is a pharmaceutical composition.