【DESCRIPTION】

【Disclosure Title】

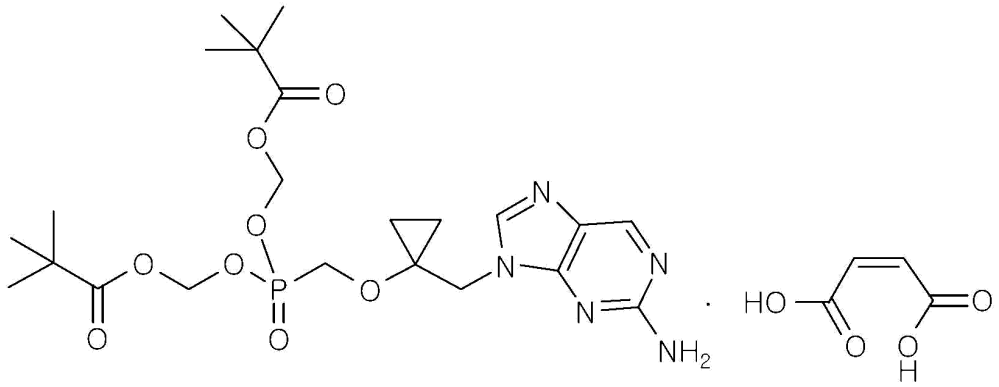
GRANULES CONTAINING BESIFOVIR DIPIVOXIL OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF, PHARMACEUTICAL COMPOSITION COMPRISING GRANULES, AND PREPARATION METHOD THEREFOR

【Technical Field】

• The present invention relates to granules which include besifovir dipivoxil or a pharmaceutical acceptable salt thereof and have improved properties in terms of masking of bitter taste and productivity, a pharmaceutical composition comprising the same, and a method of preparing the same.

【Background Art】

• Besifovir dipivoxil or a pharmaceutically acceptable salt thereof is a nucleotide-based antiviral drug that is mainly efficacious for chronic hepatitis B. The chemical name of besifovir dipivoxil is 3-[({1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methyl]-8,8-dimethyl]-3,7-dioxo-2,4,6-trioxa-3λ^5-phosphanon-1-yl] pivalate, and maleate thereof has a structure as follows:



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• This drug is very quickly metabolized in the body and the resulting metabolite is a phosphate nucleotide analogue of guanosine monophosphate. This metabolite is phosphorylated into diphosphate or triphosphate, thereby exhibiting antiviral activity and reaches maximum blood concentration in about 1.7 hours.

• In terms of pharmacology, besifovir dipivoxil or a pharmaceutically acceptable salt thereof has problems of strong bitter taste, poor fluidity in powder form, and stickiness upon compression molding, causing frequent failure in tableting. In order to overcome these problems, wet granulation using water or a solvent is generally employed. However, this method has limits in that besifovir dipivoxil or a pharmaceutically acceptable salt thereof is likely to be decomposed by moisture and a solvent.

• In addition, there also has been proposed a method of increasing density of granules using a pharmaceutical additive or a method of performing wet granulation of a main component using a relatively stable solvent. However, these methods cannot completely suppress sticky properties of granules since the main component is exposed to the surroundings upon processing. Further, a method of using various lubricants also has a problem in that significant suppression of sticky properties cannot be achieved even using an

excess of the lubricants. Generally, drugs having strong bitter taste are coated with a suitable coating agent for masking the bitter taste. However, this method has a problem in that further research is needed to secure physical strength of plain tablets for smooth progress of related processes and costs can increase due to increase in number of processes.

• Therefore, there is a need for a pharmaceutical composition for oral administration, which can prevent failure in tableting besifovir dipivoxil or a pharmaceutically acceptable salt thereof while providing masking of bitter taste of the besifovir dipivoxil or the pharmaceutically acceptable salt thereof.

【Disclosure】

【Technical Problem】

• Embodiments of the present invention provide a method, granules or composition which can prevent difficulty in production due to stickiness of besifovir dipivoxil or a pharmaceutically acceptable salt thereof upon compression molding while masking bitter taste and thus improving compliance to administration.

【Technical Solution】

• One aspect of the present invention relates to bitter taste-masked granules comprising besifovir dipivoxil or a pharmaceutically acceptable salt thereof, coated with a lipid excipient.

• Another aspect of the present invention relates to a method of preparing bitter taste-masked granules comprising besifovir dipivoxil or a pharmaceutically acceptable salt thereof, the method comprising: melting a lipid excipient through heating to a temperature higher than or equal to a melting point of the lipid excipient; mixing the melt with solid state besifovir dipivoxil or the pharmaceutically acceptable salt thereof ; and cooling the mixture.

• A further aspect of the present invention relates to a pharmaceutical composition comprising: bitter taste-masked granules comprising besifovir dipivoxil or a pharmaceutically acceptable salt thereof, coated with a lipid excipient; and a pharmaceutically acceptable additive.

• Yet another aspect of the present invention relates to a method of preparing a pharmaceutical agent, comprising: mixing a pharmaceutically acceptable additive with bitter taste-masked granules comprising besifovir dipivoxil or a pharmaceutically acceptable salt thereof, coated with a lipid excipient; and forming the mixture into an oral pharmaceutical agent.

【Advantageous Effects】

• Granules or pharmaceutical compositions comprising besifovir dipivoxil or a pharmaceutically acceptable salt thereof according to the present invention can suppress intrinsic stickiness of the drug, thereby increasing productivity and can effectively mask bitter taste of the drug, thereby improving compliance to administration.

• A preparation method according to the present invention can prevent failure in tableting due to stickiness of a drug upon compression molding, thereby allowing continuous compression molding.

• A preparation method according to the present invention can eliminate a need to use water or a solvent, thereby preventing decomposition of a drug and thus improving stability of the drug.

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【Description of Drawings】

• FIG. 1 is a 100x magnification image of bitter taste-masked granules prepared in Example 1 according to present invention.
• FIG. 2 is a 100x magnification image of bitter taste-masked granules prepared in Example 2 according to present invention.
• FIG. 3 is a 100x magnification image of bitter taste-masked granules prepared in Example 3 according to present invention.
• FIG. 4 is a 100x magnification image of bitter taste-masked granules prepared in Example 4 according to present invention.
• FIG. 5 is a 100x magnification image of bitter taste-masked granules prepared in Example 5 according to present invention.
• FIG. 6 is a 100x magnification image of particles of Comparative Example 1.
• FIG. 7 is a 100x magnification image of particles of Comparative Example 2.
• FIG. 8 is a 100x magnification image of particles of Comparative Example 3.
• FIG. 9 is a 100x magnification image of particles of Comparative Example 4.
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【Mode for Invention】

• In accordance with one aspect of the present invention, there is provided bitter taste-masked granules comprising besifovir dipivoxil or a pharmaceutically acceptable salt thereof, coated with a lipid excipient. The granules can have improved flowability or fluidity.
• The granules may be prepared by heating the lipid excipient to a temperature higher than or equal to a melting point of the lipid excipient to melt the lipid excipient, mixing the melt with the besifovir dipivoxil or the pharmaceutically acceptable salt thereof in a solid state, and cooling the mixture.
• Examples of the pharmaceutically acceptable salt of besifovir dipivoxil may include maleate, hydrochloride, sulfate, phosphate, mesylate, methanesulfonic acid, p-toluenesulfonic acid, fumaric acid, tartaric acid, and citric acid. Preferably, the pharmaceutically acceptable salt of besifovir dipivoxil is maleate.
• The granules may have a particle size of 1 μm to 2,000 μm, specifically a particle size d(0.9) of 50 μm to 1,500 μm, more specifically a particle size d(0.9) of 100 μm to 1,200 μm.
• The granules can have masked bitter taste and exhibit improved flowability and fluidity upon compression molding by being coated with the lipid excipient in a specific weight ratio. Thus, the granules are useful for preparation of a pharmaceutical agent containing besifovir dipivoxil or a pharmaceutically acceptable salt thereof.
• The lipid excipient may include a lipid excipient having a melting point of 40°C to 90°C, and examples thereof may include waxes, fatty acids, fatty acid esters, and fatty acid alcohols. Preferably, the lipid excipient includes fatty acid esters such as glycerol distearate, glyceryl stearate, glyceryl oleate, glyceryl myristate, cetyl palmitate, cetyl caprate, stearyl palmitate, and stearyl stearate, more preferably glycerol distearate.
• The lipid excipient may be melted by being heated to a temperature higher than or equal to a melting point thereof, that is, in the range of greater than 40°C to greater than 90°C, for example, in the range of 45°C to 100°C. Then, the besifovir dipivoxil or the pharmaceutically acceptable salt thereof in a solid state may be mixed with and dispersed in

the melt. Here, the lipid excipient may be present in an amount of 10 parts by weight to 70 parts by weight, for example, 10 parts by weight to 60 parts by weight or 10 parts by weight to 50 parts by weight, relative to 100 parts by weight of the besifovir dipivoxil or the pharmaceutically acceptable salt thereof. Within this range, the lipid excipient can effectively mask bitter taste of the besifovir dipivoxil or the pharmaceutically acceptable salt thereof and can improve flowability or fluidity of the granules upon compression molding, thereby reducing stickiness of the granules upon tableting.

• Then, the mixture or dispersion may be cooled to a temperature of 40°C or less, specifically in the range of 10°C to 40°C, more specifically in the range of 20°C to 30°C. Upon cooling, the lipid excipient can condense on surfaces of particles of the besifovir dipivoxil or the pharmaceutically acceptable salt thereof, whereby granules coated with the lipid excipient can be prepared.

• Optionally, the prepared granules may be allowed to pass through a sieve of a certain size to adjust particle size. For example, the prepared granules may be pulverized or may be allowed to pass through a sieve of a size of 1.18 mm or less (USP sieve No. 16).

• As used herein, the expression 'bitter taste-masked' means that intrinsic bitter taste of the besifovir dipivoxil or the pharmaceutically acceptable salt thereof is not sensed until more than 10 seconds have elapsed after putting a pharmaceutical agent containing the besifovir dipivoxil or the pharmaceutically acceptable salt thereof in the mouth without drinking any beverage or water.

• As used herein, the expression 'coated with the lipid excipient' may mean that the lipid excipient is present on at least a portion of a solid surface of the besifovir dipivoxil or the pharmaceutically acceptable salt thereof. As used herein, the term 'coating' may refer to melt coating. Herein, melt coating refers to melting the lipid excipient through heating to a temperature higher than the melting point thereof and coating the melt onto the besifovir dipivoxil or the pharmaceutically acceptable salt thereof.

• In one embodiment, coating of the besifovir dipivoxil or the pharmaceutically acceptable salt thereof can be ascertained by observing that an intrinsic needle-like portion of the besifovir dipivoxil or the pharmaceutically acceptable salt thereof has been at least partially covered with the lipid excipient.

• As used herein, the expression 'stickiness or sticky properties' refers to properties of the granules by which the granules stick to an upper or lower surface of a punch upon continuous tablet production for 10 minutes or more using a tablet press, causing formation of tablets having rough surfaces.

• Another aspect of the present invention relates to a pharmaceutical composition comprising: bitter taste-masked granules comprising besifovir dipivoxil or a pharmaceutically acceptable salt thereof, coated with a lipid excipient; and a pharmaceutically acceptable additive.

• The granules may include the granules described above relating to the above aspect of the present invention. The granules may be present in an amount of 20 wt% to 70 wt%, specifically 30 wt% to 60 wt% in the pharmaceutical composition.

• Examples of the pharmaceutically acceptable additive may include a pharmaceutically acceptable excipient, disintegrant, binder, or lubricant.

• Examples of the excipient may include cellulose derivatives and starches, such as Microcelac, microcrystalline cellulose, pregelatinized starch, starch, lactose, white sugar, mannitol, sorbitol, glucose, calcium monohydrogen phosphate, methyl cellulose, ethyl cellulose, hydroxypropyl methylcellulose, and carboxymethylcellulose sodium, without being

limited thereto. Here, the excipient may be present in an amount of 5 wt% to 60 wt% based on the total weight of the pharmaceutical composition.

- In one embodiment, the pregelatinized starch may be present in an amount of 5 wt% to 15 wt% based on the total weight of the pharmaceutical composition. In one embodiment, the microcrystalline cellulose may be present in an amount of 10 wt% to 30 wt% based on the total weight of the pharmaceutical composition. In one embodiment, Microcelac may be present in an amount of 10 wt% to 30 wt% based on the total weight of the pharmaceutical composition.
- Examples of the disintegrant may include: low-substituted hydroxypropylcellulose; and pharmaceutically acceptable croscarmellose sodium, crospovidone, sodium glycolate starch, and carboxymethylcellulose calcium, without being limited thereto. The disintegrant may be present in an amount of 5 wt% to 20 wt% based on the total weight of the pharmaceutical composition.
- Examples of the binder may include hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, methylcellulose, and carboxymethylcellulose, without being limited thereto. The binder may be present in an amount of 5 wt% to 20 wt% based on the total weight of the pharmaceutical composition.
- Examples of the lubricant may include: hardened oils; and pharmaceutically acceptable alkali metal salts or amine salts, colloidal silicon dioxide, silicates, and talc, without being limited thereto. The lubricant may be present in an amount of 0.2 wt% to 10 wt% based on the total weight of the pharmaceutical composition.
- The pharmaceutical composition is useful as a preventive or therapeutic agent for viral infection. Specifically, the pharmaceutical composition may be used as a preventive or therapeutic agent for hepatitis B or as a preventive or therapeutic agent for human immunodeficiency virus infection. An effective amount of the besifovir dipivoxil or the pharmaceutically acceptable salt thereof may vary depending on various factors such as the sex, age, progression of disease, and nutritional status of a patient, and can be easily determined on a clinical basis by those skilled in the art.
- Another aspect of the present invention relates to a method of preparing a pharmaceutical agent, comprising: mixing a pharmaceutically acceptable additive with bitter taste-masked granules comprising besifovir dipivoxil or a pharmaceutically acceptable salt thereof, coated with a lipid excipient; and forming the mixture into an oral pharmaceutical agent.
- Here, the granules and the pharmaceutically acceptable additive may be the same with the granules and pharmaceutically acceptable additive described above relating to the above aspect of the present invention.
- In this method, mixing may include mixing the aforementioned components in powder or granular form, and forming the mixture into the oral pharmaceutical agent may comprising formulating the mixture into tablets, granules, dried syrup, or suspended syrup. Particularly, tablets are preferred in terms of ease of administration and patient compliance. Thus, forming the mixture into the oral pharmaceutical agent may include preparing tablets by directly tableting the mixture.
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- Next, the present invention will be described in more detail with reference to examples. However, it should be noted that these examples are provided for illustration only and should not be construed in any way as limiting the disclosure.
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- **Examples 1 to 5**: Preparation of coated granules of besifovir dipivoxil maleate and

glycerol distearate

• Glycerol distearate was melted in a high-speed mixer at 80°C and then besifovir dipivoxil maleate was added to and mixed with the melted glycerol distearate, followed by cooling the mixture at room temperature, wherein the weight ratio of besifovir dipivoxil maleate to glycerol distearate was as listed in Table 1. Thereafter, the cooled mixture was milled using a 1.18 mm sieve (USP sieve No. 16), thereby preparing granules of Examples 1 to 5.

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• **Comparative Examples 1 to 2**: Besifovir dipivoxil maleate or glycerol distearate particles

• Powder containing only besifovir dipivoxil maleate particles was used as Comparative Example 1 and powder containing only glycerol distearate particles (Precirol® ATO5, Gattefosse, S.A., France) was used as Comparative Examples 2.

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• **Comparative Examples 3 to 4**: Preparation of granules of besifovir dipivoxil maleate and glycerol distearate

• Granules of Comparative Examples 3 to 4 were prepared in the same manner as in Examples 1 to 5 except that the weight ratio of besifovir dipivoxil maleate to glycerol distearate was changed as listed in Table 1

• Table 1

	Example 1	Example 2	Example 3	Example 4	Example 5	Comp. Example 1	Comp. Example 2	Comp. Example3	Comp. Example 4
Besifovir dipivoxil maleate	100	100	100	100	100	100	0	100	100
Glycerol distearate	10	15	20	30	50	0	100	2	5

• **Examples 6 to 10**: Preparation of tablets containing coated granules of besifovir dipivoxil maleate and glycerol distearate

• Each of the granules prepared in Examples 1 to 5 was mixed with the components shown in Table 2 in amount ratios as listed in Table 2 and then the mixture was compressed into circular tablets using a rotary tablet press (PKT-30, Pharmatech Korea), thereby preparing tablets of Examples 6 to 10.

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• **Comparative Examples 5 to 7**: Tablets containing besifovir dipivoxil maleate particles or glycerol distearate particles

• The particles of Comparative Example 1 or each of the granules of Comparative Examples 3 and 4 were mixed with the components shown in Table 2 in amount ratios as listed in Table 2 and then the mixture was compressed into circular tablets using a rotary tablet press (PKT-30, Pharmatech Korea), thereby preparing tablets of Comparative Examples 5 to 7.

• Table 2

	Example 6	Example 7	Example 8	Example 9	Example 10	Comp. Example 5	Comp. Example 6	Comp Example 7
Example 1	50.3	-	-	-	-	-	-	-
Example 2	-	51.4	-	-	-	-	-	-
Example 3		-	52.5	-	-	-	-	-

Example 4	-	-	-	54.5	-	-	-	-
Example 5	-	-	-	-	58.0	-	-	-
Comparative Example 1	-					47.9	-	-
Comparative Example 3	-					-	48.4	-
Comparative Example 4	-	-	-	-	-		-	49.2
Pregelatinized starch	6.8	6.6	6.5	6.2	5.7	7.1	7.0	6.9
Microcrystalline cellulose	13.4	13.1	12.8	12.3	11.4	14.1	13.9	13.7
Microcelac 100	20.0	19.6	19.1	18.3	16.9	21.0	20.8	20.5
Low-substituted hydroxypropyl cellulose	9.0	8.8	8.6	8.2	7.6	9.4	9.4	9.2
Hardened oil	0.5	0.5	0.5	0.5	0.4	0.5	0.5	0.5
Total	100	100	100	100	100	100	100	100

- *Unit: wt%
- **Experimental Example 1**
- The granules and particles of Examples 1 to 5 and Comparative Examples 1 to 4 were observed under a microscope (Eclipse te2000-u, Nikon), and changes in particle appearance are shown in FIG. 1 to FIG. 9, respectively.
- It can be seen that the degree of surface coating of crystalline particles increased with increasing amount of glycerol distearate with respect to Comparative Example 1.
- In particular, beginning in Example 1, in which glycerol distearate was present in an amount of 10 parts by weight, a distinct change in particle appearance was observed. Therefore, it was confirmed that coating of surfaces of crystalline besifovir dipivoxil maleate particles can be observed with the naked eye when glycerol distearate is present in an amount of 10 parts by weight or more relative to 100 parts by weight of besifovir dipivoxil maleate.
- For Comparative Examples 3 and 4, in which glycerol distearate was present in an amount of 2 or 5 parts by weight relative to 100 parts by weight of besifovir dipivoxil maleate, it can be seen that coating of crystalline particles was only partially achieved in that needle-like structures were still observed as in Comparative Example 1.
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- **Experimental Example 2**
- Each of the mixture compositions prepared in Examples 6 to 10 and Comparative Examples 5 to 7 (see Table 2) was subjected to compression molding using a rotary tablet press (PKT-30, Pharmatech Korea), thereby performing continuous production of tablets for 10 minutes or more. When an abnormality was found on surfaces of the tablets during continuous production, the tablet press was stopped to check whether granules had stuck to upper and lower surfaces of a punch. Results are shown in Table 3.
- Table 3

	Example 6	Example 7	Example 8	Example 9	Example 10	Comp. Example 5	Comp. Example 6	Comp. Example 7
Degree of stickiness of granules	-	-	-	-	-	+++	+++	++
+++: Within 10 minutes after the start of tableting, most prepared tablets had unsmooth surfaces, and severe sticking of granules to the surface of the punch occurred, causing difficulty in continuous								

production.

++: Within 10 minutes after the start of tableting, some of the prepared tablets had unsmooth surfaces, and partial sticking of granules to the surface of the punch occurred, causing difficulty in continuous production.

+: Even after 10 minutes from the start of tableting, some defective tablets were observed, but sticking of granules to the surface of the punch was not observed after completion of tableting.

-: Even after 10 minutes from the start of tableting, no defective tablets were observed, and sticking of granules to the surface of the punch was not observed after completion of tableting.

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• From the results shown in Table 3, it can be seen that the mixture compositions of Examples 6 to 10 could suppress stickiness of granules upon compression molding, thereby allowing efficient continuous production of tablets. Therefore, it was confirmed that efficient continuous production of tablets is possible when glycerol distearate is present in an amount of 10 parts by weight or more relative to 100 parts by weight of besifovir dipivoxil maleate.

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• **Experimental Example 3**

• Each of the tablets prepared in Examples 6 to 10 and Comparative Examples 5 to 7 was evaluated as to a degree of masking of bitter taste.

• For healthy adult volunteers, one tablet containing 183 mg of besifovir dipivoxil maleate was put into the mouth without drinking any water or beverage. When bitter taste was not sensed until more than 10 seconds elapsed, the tablet was rated as +; when bitter taste was sensed within more than 5 to 10 seconds, the tablet was rated as ++; and when bitter taste was sensed in 5 seconds, the tablet was rated as +++. Results are shown in Table 4.

• Table 4

	Example 6	Example 7	Example 8	Example 9	Example 10	Comp. Example 5	Comp. Example 6	Comp. Example 7
Degree of bitter taste	+	+	+	+	+	+++	+++	++

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• From the results shown in Table 4, it can be seen that the tablets prepared in Examples 6 to 10 succeeded in masking bitter taste of besifovir dipivoxil maleate. Therefore, it was confirmed that significant suppression of bitter taste of besifovir dipivoxil maleate can be achieved when glycerol distearate is present in an amount of 10 parts by weight or more relative to 100 parts by weight of besifovir dipivoxil maleate.

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【CLAIMS】

【Claim 1】

Bitter taste-masked granules comprising besifovir dipivoxil or a pharmaceutically acceptable salt thereof, and being coated with a lipid excipient.

【Claim 2】

The bitter taste-masked granules according to claim 1, wherein the lipid excipient is present in an amount of 10 parts by weight to 70 parts by weight relative to 100 parts by weight of the besifovir dipivoxil or the pharmaceutically acceptable salt thereof.

【Claim 3】

The bitter taste-masked granules according to claim 1, wherein the lipid excipient comprises waxes, fatty acids, fatty acid esters, or fatty acid alcohols having a melting point of 40°C to 90°C.

【Claim 4】

The bitter taste-masked granules according to claim 3, wherein the lipid excipient is at least one fatty acid ester selected from the group consisting of glycerol distearate, glyceryl stearate, glyceryl oleate, glyceryl myristate, cetyl palmitate, cetyl caprate, stearyl palmitate, and stearyl stearate.

【Claim 5】

The bitter taste-masked granules according to claim 1, wherein intrinsic bitter taste of the besifovir dipivoxil or the pharmaceutically acceptable salt thereof is not sensed until more than 10 seconds have elapsed after putting an agent containing the besifovir dipivoxil or the pharmaceutically acceptable salt thereof in the mouth without any beverage or water.

【Claim 6】

A method of preparing bitter taste-masked granules comprising besifovir dipivoxil or a pharmaceutically acceptable salt thereof, and being coated with a lipid excipient, the

method comprising:

melting the lipid excipient through heating to a temperature higher than or equal to a melting point of the lipid excipient;

mixing the melt with the besifovir dipivoxil or the pharmaceutically acceptable salt thereof in a solid state; and

cooling the mixture.

【Claim 7】

The method according to claim 6, wherein the lipid excipient comprises waxes, fatty acids, fatty acid esters, or fatty acid alcohols having a melting point of 40°C to 90°C.

【Claim 8】

The method according to claim 6, wherein cooling the mixture comprises cooling the mixture to a temperature of 10°C to 40°C.

【Claim 9】

The method according to claim 6, further comprising:

sieving the cooled mixture after cooling the mixture.

【Claim 10】

A pharmaceutical composition comprising:

the bitter taste-masked granules according to any one of claims 1 to 5; and

a pharmaceutically acceptable additive.

【Claim 11】

The pharmaceutical composition according to claim 10, wherein the bitter taste-masked granules are present in an amount of 20 wt% to 70 wt% based on the total weight of the pharmaceutical composition.

【Claim 12】

The pharmaceutical composition according to claim 10, wherein the pharmaceutical

composition is a tablet obtained by directly tableting a mixture of the bitter taste-masked granules and the pharmaceutically acceptable additive.

【Claim 13】

A method of preparing a pharmaceutical agent, comprising:

mixing a pharmaceutically acceptable additive with bitter taste-masked granules comprising besifovir dipivoxil or a pharmaceutically acceptable salt thereof and being coated with a lipid excipient; and

forming the mixture into an oral pharmaceutical agent.

【Claim 14】

The method according to claim 13, wherein the pharmaceutical agent is prepared by directly tableting the mixture.