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(54) **Title**: EASILY DOSABLE SOLID PREPARATION

(54) 発明の名称 : 易服用性固形製剤

(57) **Abstract**: The object is to provide a preparation for oral administration having improved dosability, and/or a coating composition to be used in an easily dosable preparation, the coating composition not affecting elution properties. The object can be achieved by using a coating composition comprising a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate, a polyvalent metal compound, and a second thickener comprising at least one member selected from the group consisting of xanthan gum, guar gum and sodium alginate (provided that when the first thickener is sodium alginate, the second thickener is not sodium alginate), or a coating composition which comprises hydroxypropylmethylcellulose as a thickener and contains a sugar or sugar alcohol having a solubility at 20ºC of 30 or greater.

(57) 要約: 服用性が改善された経口投与製剤、及び／又は溶出性に影響を与えない易服用性製剤に用いるコーティング用組成物を提供すること。上記課題は、カルボキシビニルポリマーおよびアルギン酸ナトリウムからなる群から選択される第１の増粘剤、多価金属化合物、ならびにキサンタンガム、グアガムおよびアルギン酸ナトリウムからなる群から選択される少なくとも１種以上の第２の増粘剤（ただし、第１の増粘剤がアルギン酸ナトリウムである場合に、第２の増粘剤はアルギン酸ナトリウムではない）を含むコーティング用組成物、又は増粘剤にヒドロキシプロピルメチルセルロース及び２０℃の溶解度が３０以上の糖又は糖アルコールを含むコーティング用組成物を用いることにより解決される。

DESCRIPTION

TITLE OF INVENTION: EASILY DOSABLE SOLID PREPARATION

TECHNICAL FIELD

[0001]

The present invention relates to an easily administrable oral preparation having an improved administering property, and/or a coating composition used for an easily administrable preparation having an improved dissolution property.

BACKGROUND ART

[0002]

At present, orally-administered preparations have a high proportion of pharmaceutical preparations. Among such orally-administered preparations, solid preparations remain predominant. Such solid preparations include many high-dose solid preparations. When such a high-dose solid preparation is prepared as a single unit tablet, it becomes large in size. When it is prepared as a powder or a granule, it becomes a bulky preparation due to low density, and thus it is difficult for children and aged people whose swallowing function is low to take such bulky preparation in many cases.

A technique of producing an orally fast-disintegrating tablet has been developed to enhance the administering property of a tablet. However, since the content of a principal agent is small with respect to the total content of the tablet, this technique is not suitable for producing a preparation containing a large amount of principal agent. In a case in which an orally fast-disintegrating tablet is grown in size, it causes a great feeling of a foreign body in the oral cavity after disintegration of the tablet. Moreover, such an orally fast-disintegrating tablet is also problematic in that it is difficult to mask the taste when the principal agent thereof has an unpleasant taste such as a bitter taste.

Furthermore, preparations such as a liquid agent or a jelly agent have also been proposed as dosage forms having a good administering property. However, even in the case of these dosage forms, when the content of a principal agent is high, it is difficult to perform taste masking, and further, stability in water has not been achieved.

An example of a high-dose preparation is an anticholesteremic agent comprising, as an active ingredient, cholestimide that is an anion exchange resin. In order to reduce the preparation in size for easy administration, a multi-unit preparation

(a mini-tablet divided agent) has been developed and has been on the market. Japanese Patent No. 3883505 (Patent Literature 1) describes that, in order to improve the administering property of a multi-unit preparation (mini-tablet) of cholestimide, the drug is coated with a water-soluble polymer cellulose and is further coated with ethylcellulose, so as to prevent deterioration of the administering property due to disintegration and aggregation of the mini-tablet in the oral cavity. However, this publication does not describe a technique of improving the slipping property of the tablet to cause easy swallowing.

[0003]

In recent years, a method of making it easy to swallow a solid agent, a technique of using a gelling agent that causes a favorable slipping property on the mucosa has being developed. For example, JP Patent Publication (Kohyo) No. 2000-516222 A (Patent Literature 2) describes a preparation, in which a granule, a pellet or a mini-tablet is coated with a high-viscosity gelling agent as an inner layer and is coated with a low-viscosity gelling agent as an outer layer, so as to improve cohesiveness of the preparation in the oral cavity, the masking of a bitter taste and easy swallowability. However, the disclosed method is disadvantageous in that it takes a long time to form a gel and in that the formed gel highly adheres to the mucosa.

JP Patent Publication (Kokai) No. 2002-275054 A (Patent Literature 3) describes an easily swallowable tablet, which is coated with a coating solution, in which xanthan gum is used as a gelling agent and 40 parts or more of sugar alcohol is added to 100 parts of solid components. With regard to this coating, the tablet causes no slime or stickiness when it is placed in the oral cavity, and the slipping property on the mucosa is said to be favorable. However, a single use of xanthan gum as a gelling agent forms an excessively soft gel in the oral cavity, the masking of a bitter taste is insufficient, and it is desired to further improve its slipping property on the mucosa.

Japanese Patent No. 4267926 (Patent Literature 4) discloses a gelling film preparation. The publication describes that this film preparation is a sheet-like preparation formed by sandwiching a drug layer between carboxyvinyl polymer layers crosslinked by polyvalent metal salts, and that it rapidly turns into a gel in the oral cavity. It also describes that the film preparation is rarely stuck in the throat, and that a bitter taste can be masked. However, the publication does not describe the coating of a tablet or a granule. Since the carboxyvinyl polymer used in the present technique is subjected to a production process in the form of a solution having extremely high viscosity that has been crosslinked with polyvalent metal ions, it is considered difficult for the solution to be applied by spray-coating onto a tablet or a granule (see the

after-mentioned Reference Example 1). Thus, the preparation that can be produced by the present technique is a film dosage form, and it needs a special process called "application" and a special apparatus. When compared with the spray-coating of a tablet or a granule, a production cost tends to become high. Moreover, as described in the after-mentioned Reference Example 2, a coated mini-tablet produced by modifying the present technique such that the preparation can be applied by spray-coating could not achieve practically satisfactory, easy swallowability.

On the other hand, when coating is carried out using a gelling agent, there is a fear that diffusion of the drug will be suppressed by formation of a gel in the gastrointestinal tract, and a delay in dissolution will occur. JP Patent Publication (Kokai) No. 11-60472 A (1999) (Patent Literature 5) discloses that sugars are added to an easily swallowable coated tablet that has been coated with methylcellulose, so as to prevent a delay in dissolution. However, when a mini-tablet is produced from this coated tablet, cohesiveness in the oral cavity cannot be expected.

Hence, it is an important aspect to prevent a delay in dissolution of a drug from a preparation coated with a gelling agent.

The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification (including the claims) they are to be interpreted as specifying the presence of the stated features, integers, steps or components, but not precluding the presence of one or more other features, integers, steps or components, or group thereof.

CITATION LIST

PATENT LITERATURE

[0004]

Patent Literature 1: Japanese Patent No. 3883505

Patent Literature 2: JP Patent Publication (Kohyo) No. 2000-516222 A

Patent Literature 3: JP Patent Publication (Kokai) No. 2002-275054 A

Patent Literature 4: Japanese Patent No. 4267926

Patent Literature 5: JP Patent Publication (Kokai) No. 11-60472 A (1999)

SUMMARY OF INVENTION

[0005]

As described above, in the field of orally-administered preparations, and particularly, in the field of high-dose preparations such as large tablets, it has been desired to develop an easily producible coated preparation having the effect of masking an unpleasant taste such as a bitter taste and good swallowability. In addition, it has also been desired to develop a coated preparation with an improved dissolution property. It is an aspect of the present invention to provide a coated preparation having any one or more of, and preferably, all of the aforementioned properties, and a coating composition used to produce the coated preparation.

[0006]

Considering the above-mentioned aspect, the present inventors have conducted intensive studies for the purpose of improving the administering property of an oral preparation. As a result, the inventors have found that an orally-administered solid preparation, such as a tablet, is coated with a coating composition, which comprises a combination of a first thickener such as a carboxyvinyl polymer with a second thickener such as xanthan gum, and a small amount of polyvalent metal compound used as a viscosity adjuster, so that an unpleasant taste can be masked, so that the preparation can be easily swallowed because it easily slips on the mucosa, and so that the production thereof becomes easy. Moreover, the inventors have also found that hydroxypropylmethylcellulose and sugar or sugar alcohol having specific properties are added to the thickeners, so that the film of the preparation is disintegrated immediately after it has been swallowed, so as to prevent a delay in dissolution, thereby completing the present invention.

[0007]

Specifically, a first aspect of the present invention relates to the following coating composition.

[1-1] A coating composition comprising:

a first thickener that is a metal-crosslinked thickener, and preferably, a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate;

a polyvalent metal compound;

at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate; and

hydroxypropylmethylcellulose.

[1-1a] A coating composition comprising a carboxyvinyl polymer, a polyvalent metal compound and xanthan gum.

[1-1b] A coating composition comprising:

a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate;

a polyvalent metal compound;

at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate; and

hydroxypropylmethylcellulose.

[1-2] The coating composition according to [1-1] above, wherein the first thickener is a carboxyvinyl polymer or sodium alginate that is not substantially crosslinked by polyvalent metal ions.

[1-2a] The coating composition according to [1-1a] above, wherein the carboxyvinyl polymer is not substantially crosslinked.

[1-3] The coating composition according to any one of [1-1], [1-2], [1-1a] and [1-2a] above, which further comprises sugar or sugar alcohol having a solubility at 20°C of 30 or more.

[1-4] The coating composition according to any one of [1-1] to [1-3], [1-1a] and [1-2a] above, which further comprises hydroxypropylmethylcellulose.

[1-5] The coating composition according to [1-4] above, which is characterized in that the content of the first thickener is 3% to 15% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the second thickener is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

[1-5a] The coating composition according to [1-4] above, which is characterized in that the content of the carboxyvinyl polymer is 3% to 15% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the xanthan gum is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

[1-6] The coating composition according to any one of [1-1] to [1-5] above, which is characterized in that the content of the polyvalent metal compound is 5% to 15% by mass based on the content of the first thickener.

[1-6a] The coating composition according to any one of [1-1a], [1-2a], [1-3], [1-4] and [1-5a] above, which is characterized in that the content of the polyvalent metal compound is 5% to 15% by mass based on the content of the carboxyvinyl polymer.

[1-7] The coating composition according to any one of [1-1] to [1-6], [1-1a], [1-2a], [1-5a] and [1-6a] above, which is characterized in that it comprises alcohol as a solvent.

A coating composition comprising:

a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate;

a polyvalent metal compound;

at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate;

hydroxypropylmethylcellulose; and

at least one type of a sugar or sugar alcohol selected from the group consisting of erythritol, maltitol and trehalose,

wherein the content of the first thickener is 3% to 15% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the second thickener is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

An oral composition coated with the coating composition of the first aspect of the present invention has a favorable slipping property and favorable swallowability without adhesion to the mucosa. Otherwise, a sufficient effect of masking an unpleasant taste can be obtained. Preferably, the present oral composition has both of the two above effects. The coating composition in another preferred aspect has an improved drug-dissolution property. The coating composition in a further preferred aspect can be easily applied by spray-coating to a drug core, and it can also be easily dried.

[0008]

In addition, a second aspect of the present invention relates to the following oral composition.

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[2-1] An oral composition having:

a drug core containing an active ingredient; and

over the drug core,

a coating comprising

a first thickener that is a metal-crosslinked thickener, and preferably, a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate,

a polyvalent metal compound,

at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate; and

hydroxypropylmethylcellulose.

[2-1a] An oral composition having a drug core containing an active ingredient, and over the drug core, a coating comprising a carboxyvinyl polymer, a polyvalent metal compound and xanthan gum.

[2-1b] An oral composition having:

a drug core containing an active ingredient; and

over the drug core,

a coating comprising

a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate,

a polyvalent metal compound,

at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate, and

hydroxypropylmethylcellulose.

[2-2] The oral composition according to [2-1] above, wherein the first thickener is a carboxyvinyl polymer or sodium alginate that is not substantially crosslinked by polyvalent metal ions.

[2-2a] The oral composition according to [2-1a] above, wherein the carboxyvinyl polymer is not substantially crosslinked.

[2-3] The oral composition according to any one of [2-1], [2-2], [2-1a] and [2-2a] above, which further comprises sugar or sugar alcohol having a solubility at 20°C of 30 or more.

[2-4] The oral composition according to any one of [2-1] to [2-3], [2-1a] and [2-2a] above, which further comprises hydroxypropylmethylcellulose.

[2-5] The oral composition according to [2-4] above, which is characterized in that the content of the first thickener is 3% to 15% by mass (% by mass based on the total mass of all ingredients in the coating; the same applies below), the content of the second thickener is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

[2-5a] The oral composition according to [2-4] above, which is characterized in that the content of the carboxy vinyl polymer is 3% to 15% by mass (% by mass based on the total mass of all ingredients in the coating; the same applies below), the content of the xanthan gum is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

[2-6] The oral composition according to any one of [2-1] to [2-5] above, which is characterized in that the content of the polyvalent metal compound is 5% to 15% by mass based on the content of the first thickener.

[2-6a] The oral composition according to any one of [2-1a], [2-2a], [2-3], [2-4] and [2-5a] above, which is characterized in that the content of the polyvalent metal compound is 5% to 15% by mass based on the content of the carboxyvinyl polymer.

[2-7] The oral composition according to any one of [2-1] to [2-6], [2-1a], [2-2a], [2-5a] and [2-6a] above, which is characterized in that the drug core is a tablet core containing an active ingredient.

[2-8] The oral composition according to any one of [2-1] to [2-7] above, wherein the second thickener is at least one type of thickener selected from the group consisting of xanthan gum, guar gum, and sodium alginate that is not substantially crosslinked by polyvalent metal ions.

[2-9] The oral composition according to any one of [2-1] to [2-8], [2-1a], [2-2a], [2-5a] and [2-6a] above, which further has a seal coating between the drug core and the coating.

An oral composition having:

a drug core containing an active ingredient; and

over the drug core,

a coating comprising

a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate,

a polyvalent metal compound,

at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate,

hydroxypropylmethylcellulose, and

at least one type of a sugar or sugar alcohol selected from the group consisting of erythritol, maltitol and trehalose,

wherein the content of the first thickener is 3% to 15% by mass (% by mass based on the total mass of all ingredients in the coating; the same applies below), the content of the second thickener is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

The oral composition of the second aspect of the present invention has a favorable slipping property and favorable swallowability without adhesion to the mucosa. Otherwise, an effect of masking an unpleasant taste can be obtained. Preferably, the present oral composition has both of the two above effects. The oral composition in another preferred aspect has an improved drug-dissolution property.

[0009]

Moreover, a third aspect of the present invention relates to the following oral composition.

[3-1] An oral composition, which is obtained by spray-coating a drug core containing an active ingredient with a liquid that has been prepared by dispersing a first thickener that is a metal-crosslinked thickener, and preferably, a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate, and at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate, into an alcohol solution in which a polyvalent metal compound has been dissolved.

[3-1a] An oral composition, which is obtained by spray-coating a drug core containing an active ingredient with a liquid that has been prepared by dispersing a carboxyvinyl polymer and xanthan gum into an alcohol solution in which a polyvalent metal compound has been dissolved.

[3-2] The oral composition according to [3-1] above, wherein the first thickener is a carboxyvinyl polymer or sodium alginate that is not substantially crosslinked by polyvalent metal ions.

[3-2a] The oral composition according to [3-1a] above, wherein the carboxyvinyl polymer is not substantially crosslinked.

[3-3] The oral composition according to any one of [3-1], [3-2], [3-1a] and [3-2a] above, which is characterized in that sugar or sugar alcohol having a solubility at 20°C of 30 or more is further dispersed into the liquid used for the spray-coating.

[3-4] The oral composition according to any one of [3-1] to [3-3], [3-1a] and [3-2a] above, wherein the liquid used for the spray-coating further comprises hydroxypropylmethylcellulose.

[3-5] The oral composition according to [3-4] above, which is characterized in that, in the liquid used for the spray-coating, the content of the first thickener is 3% to 15% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the second thickener is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

[3-5a] The oral composition according to [3-4] above, which is characterized in that, in the liquid used for the spray-coating, the content of the carboxy vinyl polymer is 3% to 15% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the xanthan gum is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

[3-6] The oral composition according to any one of [3-1] to [3-5] above, which is characterized in that the content of the polyvalent metal compound is 5% to 15% by mass based on the content of the first thickener.

[3-6a] The oral composition according to any one of [3-1a], [3-2a], [3-3], [3-4] and [3-5a] above, which is characterized in that the content of the polyvalent metal compound is 5% to 15% by mass based on the content of the carboxyvinyl polymer.

[3-7] The oral composition according to any one of [3-1] to [3-6], [3-1a], [3-2a], [3-5a] and [3-6a] above, which is characterized in that the drug core is a tablet core containing an active ingredient.

[3-8] The oral composition according to any one of [3-1] to [3-7] above, wherein the second thickener is at least one type of thickener selected from the group consisting of xanthan gum, guar gum, and sodium alginate that is not substantially crosslinked by polyvalent metal ions.

[3-9] The oral composition according to any one of [3-1] to [3-8], [3-1a], [3-2a], [3-5a] and [3-6a] above, wherein the drug core, to which the spray coating is performed, is a drug core having a seal coating.

The oral composition of the third aspect of the present invention has a favorable slipping property and favorable swallowability without adhesion to the mucosa. Otherwise, a sufficient effect of masking an unpleasant taste can be obtained. Preferably, the present oral composition has both of the two above effects. The oral composition in another preferred aspect has an improved drug-dissolution property.

[0010]

Furthermore, a fourth aspect of the present invention relates to the following method for producing an oral composition.

[4-1] A method for producing an oral composition, which is characterized in that it comprises spray-coating a drug core containing an active ingredient with a liquid that has been prepared by dispersing a first thickener that is a metal-crosslinked thickener, and preferably, a first thickener selected from the group consisting of a carboxy vinyl polymer and sodium alginate, and at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate, into an alcohol solution in which a polyvalent metal compound has been dissolved.

[4-1a] A method for producing an oral composition, which is characterized in that it comprises spray-coating a drug core containing an active ingredient with a liquid that has been prepared by dispersing a carboxy vinylpolymer and xanthan gum into an alcohol solution in which a polyvalent metal compound has been dissolved.

[4-2] The method for producing an oral composition according to [4-1] above, wherein the first thickener is a carboxyvinyl polymer or sodium alginate that is not substantially crosslinked by polyvalent metal ions.

[4-2a] The method for producing an oral composition according to [4-1a] above, wherein the carboxyvinyl polymer is not substantially crosslinked.

[4-3] The method for producing an oral composition according to any one of [4-1], [4-2], [4-1a] and [4-2a] above, which is characterized in that sugar or sugar alcohol having a solubility at 20°C of 30 or more is further dispersed into the liquid used for the spray-coating.

[4-4] The method for producing an oral composition according to any one of [4-1] to [4-3], [4-1a] and [4-2a] above, wherein the liquid used for the spray-coating further comprises hydroxypropylmethylcellulose.

[4-5] The method for producing an oral composition according to [4-4] above, which is characterized in that, in the liquid used for the spray-coating, the content of the first thickener is 3% to 15% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the second thickener is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

[4-5a] The method for producing an oral composition according to [4-4] above, which is characterized in that, in the liquid used for the spray-coating, the content of the carboxyvinyl polymer is 3% to 15% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the xanthan gum is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

[4-6] The method for producing an oral composition according to any one of [4-1] to [4-5] above, which is characterized in that the content of the polyvalent metal compound is 5% to 15% by mass based on the content of the first thickener.

[4-6a] The method for producing an oral composition according to any one of [4-1a], [4-2a], [4-3], [4-4] and [4-5a] above, which is characterized in that the content of the polyvalent metal compound is 5% to 15% by mass based on the content of the carboxy vinyl polymer.

[4-7] The method for producing an oral composition according to any one of [4-1] to [4-6], [4-1a], [4-2a], [4-5a] and [4-6a] above, which is characterized in that the drug core is a tablet core containing an active ingredient.

[4-8] The method for producing an oral composition according to any one of [4-1] to [4-7] above, wherein the second thickener is at least one type of thickener selected from the group consisting of xanthan gum, guar gum, and sodium alginate that is not substantially crosslinked by polyvalent metal ions.

[4-9] The method for producing an oral composition according to any one of [4-1] to [4-8], [4-1a], [4-2a], [4-5a] and [4-6a] above, wherein the drug core, to which the spray coating is performed, is a drug core having a seal coating.

The method for producing an oral composition of the fourth aspect of the present invention can be easily applied by spray-coating to a drug core and it can also be easily dried. In addition, the oral composition obtained by the present production method has a favorable slipping property and favorable swallowability without adhesion to the mucosa. Otherwise, a sufficient effect of masking an unpleasant taste can be obtained. Preferably, the present oral composition has both of the two above effects. The oral composition obtained by the production method in another preferred aspect has

an improved drug-dissolution property.

[0011]

Furthermore, a fifth aspect of the present invention relates to the following coating composition.

[5-1] A coating composition comprising a thickener that turns into a gel when it is allowed to come into contact with water, sugar or sugar alcohol having a solubility at 20°C of 30 or more, and hydroxypropylmethylcellulose.

[5-2] The coating composition according to [5-1] above, wherein the thickener is at least one type selected from the group consisting of xanthan gum, guar gum and sodium alginate.

[5-2a] The coating composition according to [5-1] above, wherein the thickener comprises xanthan gum.

[5-3] The coating composition according to [5-1] above, wherein the thickener is selected from the group consisting of a carboxyvinyl polymer and sodium alginate.

[5-3a] The coating composition according to [5-1] above, wherein the thickener comprises a carboxyvinyl polymer.

[5-4] The coating composition according to [5-1] above, wherein the thickener comprises one type selected from the group consisting of a carboxyvinyl polymer and sodium alginate, and at least one type selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that a combination of the same substances is excluded.

[5-4a] The coating composition according to [5-1] above, wherein the thickener comprises a carboxyvinyl polymer and xanthan gum.

[5-5] The coating composition according to [5-3], [5-4], [5-3a] or [5-4a] above, which further comprises a polyvalent metal compound.

[5-6] The coating composition according to any one of [5-1] to [5-5] and [5-2a] to [5-4a] above, which is characterized in that the mixing ratio between the hydroxypropylmethylcellulose and the sugar or sugar alcohol is 1 : 1 to 1 : 4.

[5-7] The coating composition according to any one of [5-4] to [5-6] above, which is characterized in that the content of the hydroxypropylmethylcellulose is 5% to 35% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the sugar or sugar alcohol is 10% to 50% by mass, the content of the carboxy vinyl polymer is 3% to 15% by mass, and the content of at least one type selected from the group consisting of xanthan gum, guar gum and sodium alginate is 10% to 40% by mass.

[5-7a] The coating composition according to any one of [5-4a], [5-5] and [5-6] above,

which is characterized in that the content of the hydroxypropylmethylcellulose is 5% to 35% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the sugar or sugar alcohol is 10% to 50% by mass, the content of the carboxyvinyl polymer is 3% to 15% by mass, and the content of the xanthan gum is 10% to 40% by mass.

[5-8] The coating composition according to any one of [5-1] to [5-7], [5-2a] to [5-4a], and [5-7a] above, which comprises alcohol as a solvent.

[5-9] The coating composition according to any one of [5-1] to [5-8], [5-2a] to [5-4a], and [5-7a] above, wherein the sugar or sugar alcohol is selected from the group consisting of erythritol, maltitol and trehalose.

[5-10] The coating composition according to [5-9] above, wherein the sugar or sugar alcohol is erythritol.

The oral composition coated with the coating composition of the fifth aspect of the present invention exhibits a drug-dissolution property that is almost equivalent to that of an uncoated oral composition. Moreover, the coating composition in a preferred aspect has a favorable slipping property and favorable swallowability without adhesion to the mucosa. Otherwise, an effect of masking an unpleasant taste can be obtained. Preferably, the present coating composition has both of the two above effects. The coating composition in another preferred aspect can be easily applied by spray-coating to a drug core, and it can also be easily dried.

[0012]

Further, a sixth aspect of the present invention relates to the following oral composition.

[6-1] An oral composition having: a drug core containing an active ingredient; and a coating comprising a thickener that turns into a gel when it is allowed to come into contact with water, sugar or sugar alcohol having a solubility at 20°C of 30 or more, and hydroxypropylmethylcellulose.

[6-2] The oral composition according to [6-1] above, wherein the thickener is at least one type selected from the group consisting of xanthan gum, guar gum and sodium alginate.

[6-2a] The oral composition according to [6-1] above, wherein the thickener comprises xanthan gum.

[6-3] The oral composition according to [6-1] above, wherein the thickener is selected from the group consisting of a carboxyvinyl polymer and sodium alginate.

[6-3a] The oral composition according to [6-1] above, wherein the thickener comprises a carboxy vinyl polymer.

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[6-4] The oral composition according to [6-1] above, wherein the thickener comprises one type selected from the group consisting of a carboxyvinyl polymer and sodium alginate, and at least one type selected from the group consisting of xanthan gum, guar gum and sodium alginate with the proviso that a combination of the same substances is excluded.

[6-4a] The oral composition according to [6-1] above, wherein the thickener comprises a carboxyvinyl polymer and xanthan gum.

[6-5] The oral composition according to any one of [6-3], [6-4], [6-3a] and [6-4a] above, which further comprises a polyvalent metal compound.

[6-6] The oral composition according to any one of [6-1] to [6-5] and [6-2a] to [6-4a] above, which is characterized in that the mixing ratio between the hydroxypropylmethylcellulose and the sugar or sugar alcohol is 1 : 1 to 1 : 4.

[6-7] The oral composition according to any one of [6-4] to [6-6] above, which is characterized in that the content of the hydroxypropylmethylcellulose is 5% to 35% by mass (% by mass based on the total mass of all ingredients in the coating; the same applies below), the content of the sugar or sugar alcohol is 10% to 50% by mass, the content of one type selected from the group consisting of a carboxyvinyl polymer and sodium alginate is 3% to 15% by mass, and the content of at least one type selected from the group consisting of xanthan gum, guar gum and sodium alginate is 10% to 40% by mass.

[6-7a] The oral composition according to any one of [6-4a], [6-5] and [6-6] above, which is characterized in that the content of the hydroxypropylmethylcellulose is 5% to 35% by mass (% by mass based on the total mass of all ingredients in the coating; the same applies below), the content of the sugar or sugar alcohol is 10% to 50% by mass, the content of the carboxyvinyl polymer is 3% to 15% by mass, and the content of the xanthan gum is 10% to 40% by mass.

[6-8] The oral composition according to any one of [6-1] to [6-7], [6-2a] to [6-4a], and [6-7a] above, wherein the drug core is a drug core having a seal coating.

[6-9] The oral composition according to any one of [6-1] to [6-8], [6-2a] to [6-4a], and [6-7a] above, wherein the sugar or sugar alcohol is selected from the group consisting of erythritol, maltitol and trehalose.

[6-10] The oral composition according to [6-9] above, wherein the sugar or sugar alcohol is erythritol.

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The oral composition of the sixth aspect of the present invention exhibits a drug-dissolution property that is almost equivalent to that of an uncoated oral composition, although it is coated with a thickener. Moreover, the oral composition

in a preferred aspect has a favorable slipping property and favorable swallowability without adhesion to the mucosa. Otherwise, a sufficient effect of masking an unpleasant taste can be obtained. Preferably, the present oral composition has both of the two above effects.

[0013]

Further, a seventh aspect of the present invention relates to the following oral composition.

[7-1] An oral composition, which is obtained by spray-coating a drug core containing an active ingredient with a liquid that has been prepared by dispersing a thickener that turns into a gel when it is allowed to come into contact with water, sugar or sugar alcohol having a solubility at 20°C of 30 or more, and hydroxypropylmethylcellulose, into an alcohol solution.

[7-2] The oral composition according to [7-1] above, wherein the thickener is at least one type selected from the group consisting of xanthan gum, guar gum and sodium alginate.

[7-2a] The oral composition according to [7-1] above, wherein the thickener comprises xanthan gum.

[7-3] The oral composition according to [7-1] above, wherein the thickener is selected from the group consisting of a carboxyvinyl polymer and sodium alginate.

[7-3a] The oral composition according to [7-1] above, wherein the thickener comprises a carboxyvinyl polymer.

[7-4] The oral composition according to [7-1] above, wherein the thickener comprises one type selected from the group consisting of a carboxyvinyl polymer and sodium alginate, and at least one type selected from the group consisting of xanthan gum, guar gum and sodium alginate with the proviso that a combination of the same substances is excluded.

[7-4a] The oral composition according to [7-1] above, wherein the thickener comprises a carboxyvinyl polymer and xanthan gum.

[7-5] The oral composition according to [7-3], [7-4], [7-3a] or [7-4a] above, wherein the liquid used for the spray-coating further comprises a polyvalent metal compound.

[7-6] The oral composition according to any one of [7-1] to [7-5] and [7-2a] to [7-4a] above, which is characterized in that the mixing ratio between the hydroxypropylmethylcellulose and the sugar or sugar alcohol in the liquid used for the spray-coating is 1 : 1 to 1 : 4.

[7-7] The oral composition according to any one of [7-4] to [7-6] above, which is characterized in that, in the liquid used for the spray-coating, the content of the

hydroxypropylmethylcellulose is 5% to 35% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the sugar or sugar alcohol is 10% to 50% by mass, the content of the carboxyvinyl polymer is 3% to 15% by mass, and the content of at least one type selected from the group consisting of xanthan gum, guar gum and sodium alginate is 10% to 40% by mass.

[7-7a] The oral composition according to any one of [7-4a], [7-5] and [7-6] above, which is characterized in that, in the liquid used for the spray-coating, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the sugar or sugar alcohol is 10% to 50% by mass, the content of the carboxyvinyl polymer is 3% to 15% by mass, and the content of the xanthan gum is 10% to 40% by mass.

[7-8] The oral composition according to any one of [7-1] to [7-7], [7-2a] to [7-4a], and [7-7a] above, wherein the drug core to be spray-coated is a drug core having a seal coating.

[7-9] The oral composition according to any one of [7-1] to [7-8], [7-2a] to [7-4a], and [7-7a] above, wherein the sugar or sugar alcohol is selected from the group consisting of erythritol, maltitol and trehalose.

[7-10] The oral composition according to [7-9] above, wherein the sugar or sugar alcohol is erythritol.

The oral composition of the seventh aspect of the present invention is obtained by spray-coating a drug core with an alcohol solution and then drying it. Thus, it is easy to produce the present oral composition. Moreover, the oral composition of the seventh aspect of the present invention exhibits a drug-dissolution property that is almost equivalent to that of an uncoated oral composition, although it is coated with a thickener. Furthermore, the oral composition in a preferred aspect has a favorable slipping property and favorable swallowability without adhesion to the mucosa. Otherwise, a sufficient effect of masking an unpleasant taste can be obtained. Preferably, the present oral composition has both of the two above effects.

[0014]

Still further, an eighth aspect of the present invention relates to the following method for producing an oral composition.

[8-1] A method for producing an oral composition, which is characterized in that it comprises spray-coating a drug core containing an active ingredient with a liquid that has been prepared by dispersing a thickener that turns into a gel when it is allowed to come into contact with water, sugar or sugar alcohol having a solubility at 20°C of 30 or more, and hydroxypropylmethylcellulose, into an alcohol solution in which a polyvalent

metal compound has been dissolved.

[8-2] The method for producing an oral composition according to [8-1] above, wherein the thickener is at least one type selected from the group consisting of xanthan gum, guar gum and sodium alginate.

[8-2a] The method for producing an oral composition according to [8-1] above, wherein the thickener comprises xanthan gum.

[8-3] The method for producing an oral composition according to [8-1] above, wherein the thickener is selected from the group consisting of a carboxyvinyl polymer and sodium alginate.

[8-3a] The method for producing an oral composition according to [8-1] above, wherein the thickener comprises a carboxyvinyl polymer.

[8-4] The method for producing an oral composition according to [8-1] above, wherein the thickener comprises one type selected from the group consisting of a carboxyvinyl polymer and sodium alginate, and at least one type selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that a combination of the same substances is excluded.

[8-4a] The method for producing an oral composition according to [8-1] above, wherein the thickener comprises a carboxy vinyl polymer and xanthan gum.

[8-5] The method for producing an oral composition according to any one of [8-1] to [8-4] and [8-2a] to [8-4a] above, which is characterized in that the mixing ratio between the hydroxypropylmethylcellulose and the sugar or sugar alcohol in the liquid used for the spray-coating is 1 : 1 to 1 : 4.

[8-6] The method for producing an oral composition according to [8-4] or [8-5] above, which is characterized in that, in the liquid used for the spray-coating, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the sugar or sugar alcohol is 10% to 50% by mass, the content of one type selected from the group consisting of a carboxyvinyl polymer and sodium alginate is 3% to 15% by mass, and the content of at least one type selected from the group consisting of xanthan gum, guar gum and sodium alginate is 10% to 40% by mass.

[8-6a] The method for producing an oral composition according to [8-4a] or [8-5] above, which is characterized in that, in the liquid used for the spray-coating, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the sugar or sugar alcohol is 10% to 50% by mass, the content of the carboxyvinyl polymer is 3% to 15% by mass, and the content of the xanthan gum is

10% to 40% by mass.

[8-7] The method for producing an oral composition according to any one of [8-1] to [8-6], [8-2a] to [8-4a], and [8-6a] above, which is characterized in that the drug core is a tablet core containing an active ingredient.

[8-8] The method for producing an oral composition according to any one of [8-1] to [8-7], [8-2a] to [8-4a], and [8-6a] above, wherein the drug core to be spray-coated is a drug core having a seal coating.

[8-9] The method for producing an oral composition according to any one of [8-1] to [8-8], [8-2a] to [8-4a], and [8-7a] above, wherein the sugar or sugar alcohol is selected from the group consisting of erythritol, maltitol and trehalose.

[8-10] The method for producing an oral composition according to [8-9] above, wherein the sugar or sugar alcohol is erythritol.

The method for producing an oral composition of the eighth aspect of the present invention can be easily applied by spray-coating to a drug core and it can also be easily dried. In addition, the oral composition obtained by the present production method exhibits a drug-dissolution property that is almost equivalent to that of an uncoated oral composition, although it is coated with a thickener. Moreover, the coating composition obtained by the production method in a preferred aspect has a favorable slipping property and favorable swallowability without adhesion to the mucosa. Otherwise, a sufficient effect of masking an unpleasant taste can be obtained. Preferably, the coating composition has both of the two above effects.

[0015]

Still further, a ninth aspect of the present invention relates to the following oral composition.

[9-1] An oral composition having:

a drug core containing an active ingredient; and

over the drug core,

a coating comprising

a gelatinous substance selected from the group consisting of a carboxyvinyl polymer and sodium alginate, which are crosslinked by polyvalent metal ions when water is present, and

at least one type of a thickener selected from the group consisting of xanthan gum and guar gum.

[9-2] The oral composition according to [9-1] above, which further comprises sugar or sugar alcohol having a solubility at 20°C of 30 or more.

[9-3] The oral composition according to [9-1] or [9-2] above, which further

comprises hydroxypropylmethylcellulose.

[9-4] The oral composition according to any one of [9-1] to [9-3] above, which is characterized in that the content of the gelatinous substance is 3% to 15% by mass (% by mass based on the total mass of all ingredients in the coating; the same applies below), the content of the thickener is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

The oral composition of the ninth aspect of the present invention is equivalent to the oral composition of the second aspect of the present invention, which is generated by water contents present in the oral cavity, such as saliva. That is to say, the oral composition of the ninth aspect of the present invention has a favorable slipping property and favorable swallowability without adhesion to the mucosa. Otherwise, an effect of masking an unpleasant taste can be obtained. Preferably, the present oral composition has both of the two above effects. The oral composition in a further preferred aspect has an improved drug-dissolution property.

ADVANTAGEOUS EFFECTS OF INVENTION

[0016]

In the case of a composition having the preferred coating of the present invention, the surface layer of a tablet rapidly turns into a gel in the presence of a small amount of water or saliva. At the same time, a first thickener that is a metal crosslinked thickener, and preferably, a first thickener such as a carboxyvinyl polymer and/or sodium alginate is crosslinked by polyvalent metal ions generated from a polyvalent metal compound, and viscosity thereby increases. As a result, a relatively hard jelly-like gel is formed, so that the tablet easily slips on the mucosa, and its swallowability is improved. Moreover, since the gelatinous coating film suppresses short-term drug dissolution before the swallowing of the tablet, it can be anticipated that the effect of masking an unpleasant taste can be obtained. Furthermore, a composition having the preferred coating of the present invention can be anticipated to have an improved dissolution property in that it is rapidly disintegrated and thus it does not affect the dissolution of a drug after it has been swallowed. The coating composition of the present invention has at least one of, and preferably, all of the above-described preferred properties. When a high-dose preparation is produced, a more preferred coating composition of the present invention can be used to produce a preparation having an improved administering property, without affecting drug dissolution.

Further, using a preferred coating composition of the present invention, a

coated preparation can be easily obtained according to a common coating technique.

[Description of Embodiments]

[0017]

The present invention will be described in detail below.

The first thickener used in the present invention is a metal-crosslinked thickener. The metal-crosslinked thickener means a substance, which is crosslinked by polyvalent metal ions that are generated from a polyvalent metal compound in the presence of a small amount of water, and which is not crosslinked in the absence of water (in the presence of an alcohol solvent or the like) because polyvalent metal ions are not generated from the polyvalent metal compound. The type of the metal-crosslinked thickener is not particularly limited, as long as it exhibits the aforementioned properties. Specific examples of such a metal-crosslinked thickener include a carboxyvinyl polymer, sodium alginate, polyacrylic acid, polymethacrylic acid, pectin, carboxymethylcellulose, glucomannan, and carmellose sodium. Preferred examples include a carboxyvinyl polymer and sodium alginate, a carboxyvinyl polymer is more preferable. As a result of this crosslinking formation, viscosity increases, and a relatively hard jelly-like gel is formed. Thereby, it can be anticipated that the preparation easily slips on the mucosa upon administration and swallowability is improved, and that the effect of masking an unpleasant taste can be obtained by suppressing short-term drug dissolution before the swallowing of the preparation, as described later.

The type of the carboxyvinyl polymer used in the present invention is not particularly limited. A carboxy vinyl polymer having an indicated viscosity of 4000 to 60000 mPa•s (0.5%, 25°C, 20 rpm) can be preferably used. A carboxyvinyl polymer having an indicated viscosity of 4000 to 40000 mPa•s is more preferable because it hardly causes a delay in dissolution. More specific examples of such a carboxyvinyl polymer that can be used herein include commercially available products such as Carbopol 971P (trade name) (Lubrizol Advanced Material Inc.; indicated viscosity: 6420 mPa•s), Carbopol 974P (trade name) (Lubrizol Advanced Material Inc.; indicated viscosity: 32850 mPa•s), HIVISWAKO 103 (trade name) (Wako Pure Chemical Industries, Ltd.; indicated viscosity: 15000 mPa•s), HIVISWAKO 104 (trade name) (Wako Pure Chemical Industries, Ltd.; indicated viscosity: 26000 mPa•s), and HIVISWAKO 105 (trade name) (Wako Pure Chemical Industries, Ltd.; indicated viscosity: 4000 mPa•s).

The type of the sodium alginate used in the present invention is not particularly

limited. Sodium alginate having an indicated viscosity of 600 mPa•s or more (1%/1% KCl solution, 25°C) can be preferably used. Sodium alginate having an indicated viscosity of 800 to 1600 mPa•s is more preferable. More specific examples of such sodium alginate that can be used herein include commercially available products such as Kimica Algin I-8 (KIMICA Corporation; indicated viscosity, 800 to 900 mPa•s (1%, 20°C)) and Duck Algin (trade name) (Kibun Food Chemifa Co., Ltd.; indicated viscosity: 850 mPa•s).

The first thickener such as a carboxyvinyl polymer or sodium alginate is a metal-crosslinked thickener, which is crosslinked by polyvalent metal ions generated from the after-mentioned polyvalent metal compound in the presence of water, and as a result, the viscosity of the first thickener increases, thereby forming a relatively hard jelly-like gel. Preferably, the carboxyvinyl polymer and the sodium alginate contained in the composition of the present invention are not substantially crosslinked by polyvalent metal ions. The content of such a carboxyvinyl polymer or sodium alginate is preferably 3% to 15% by mass, and more preferably 10% to 13% by mass, based on the total mass of all ingredients excluding a solvent in the coating composition of the present invention. The ratio of such a carboxyvinyl polymer or sodium alginate based on the total mass of all ingredients in the coating used for the oral composition of the present invention (hereinafter referred to as a coating film at times) is the same as described above.

In the present specification, the polyvalent metal compound means pharmaceutically acceptable water-soluble salts of polyvalent metals such as calcium magnesium, aluminum and zinc. Specific examples of such a polyvalent metal compound include calcium chloride, magnesium chloride, aluminum chloride, aluminum sulfate, aluminum potassium sulfate, aluminum ferric chloride, ammonium alum, ferric sulfate, aluminum hydroxide, aluminum silicate, aluminum phosphate, iron citrate, magnesium oxide, calcium oxide, zinc oxide, zinc sulfate, and a hydrate thereof. Preferred examples include calcium chloride and a hydrate thereof. A calcium chloride dihydrate is more preferable. Specific examples of polyvalent metal ions generated from such a polyvalent metal compound include calcium ions, magnesium ions, aluminum ions, divalent or trivalent iron ions, and zinc ions. Calcium ions are preferable.

The polyvalent metal compound used in the present invention is preferably mixed at a mass percentage of 5% to 15%, and more preferably 9% to 11%, based on the mass of the first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate.

The type of the xanthan gum used in the present invention is not particularly limited. Xanthan gum having an indicated viscosity of 600 mPa•s or more (1%/1% KCl solution, 25°C) can be preferably used. Xanthan gum having an indicated viscosity of 800 to 1600 mPa•s is more preferable. More specific examples of such xanthan gum that can be used herein include commercially available products such as Keltrol CG-T (trade name) (Sansho Co., Ltd.; indicated viscosity: 1555 mPa•s), and San-Ace (trade name) (San-Ei Gen F. F. I., Inc.; indicated viscosity: 1600 mPa•s).

The type of the guar gum used in the present invention is not particularly limited. Guar gum having an indicated viscosity of 600 mPa•s or more (1%/1% KCl solution, 25°C) can be preferably used. Guar gum having an indicated viscosity of 800 to 1600 mPa•s (1%/1% KCl solution, 25°C) is more preferable. More specific examples of such guar gum that can be used herein include commercially available products such as guar gum RG100 (trade name) (MRC Polysaccharide Co., Ltd.; indicated viscosity: 1100 mPa•s). In addition, VIS TOP D-2029 (trade name) (San-Ei Gen F. F. I., Inc.; indicated viscosity: approximately 450 mPa•s (0.5%)) can also be used.

Xanthan gum, guar gum and sodium alginate are second thickeners. By adding such a second thickener, a moderate adhesive property is generated among tablets, and it causes good cohesiveness of tablets in the oral cavity, so that the tablets can be easily swallowed. The content of at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate in the coating film can be appropriately adjusted depending on the composition of other ingredients. In order to obtain a good administering property, the content of the second thickener is preferably 10% to 40% by mass, and more preferably 20% to 30% by mass.
[0018]

Examples of a combination of the first thickener with the second thickener in the coating composition and oral composition of the present invention will be given below, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate:

(1) a combination of the first thickener: a carboxyvinyl polymer with the second thickener: xanthan gum;

(2) a combination of the first thickener: a carboxyvinyl polymer with the second thickener: guar gum;

(3) a combination of the first thickener: a carboxyvinyl polymer with the second thickener: sodium alginate;

(4) a combination of the first thickener: a carboxyvinyl polymer with the second

thickener: xanthan gum and guar gum;
(5) a combination of the first thickener: a carboxyvinyl polymer with the second thickener: xanthan gum and sodium alginate;
(6) a combination of the first thickener: a carboxyvinyl polymer with the second thickener: guar gum and sodium alginate;
(7) a combination of the first thickener: a carboxyvinyl polymer with the second thickener: xanthan gum, guar gum and sodium alginate;
(8) a combination of the first thickener: sodium alginate with the second thickener: xanthan gum;
(9) a combination of the first thickener: sodium alginate with the second thickener: guar gum; and
(10) a combination of the first thickener: sodium alginate with the second thickener: xanthan gum and guar gum.
[0019]

Examples of the combination of the first thickener with the second thickener in a preferred aspect of the present invention will be given below:
(1) a combination of the first thickener: a carboxyvinyl polymer with the second thickener: xanthan gum;
(2) a combination of the first thickener: a carboxyvinyl polymer with the second thickener: guar gum;
(3) a combination of the first thickener: a carboxy vinyl polymer with the second thickener: sodium alginate;
(4) a combination of the first thickener: sodium alginate with the second thickener: xanthan gum; and
(5) a combination of the first thickener: sodium alginate with the second thickener: guar gum.
[0020]

The combination of the first thickener with the second thickener in a more preferred aspect of the present invention is (1) a combination of the first thickener: a carboxyvinyl polymer with the second thickener: xanthan gum.
[0021]

The surface layer of an oral composition (e.g. a tablet, etc.), which is coated with a coating composition comprising a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate, a polyvalent metal compound, and at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, rapidly turns into a gel in the

presence of a small amount of water or saliva. At the same time, the carboxyvinyl polymer and/or the sodium alginate are crosslinked by polyvalent metal ions generated from the polyvalent metal compound, and as a result, viscosity increases and a relatively hard jelly-like gel is thereby formed. Thus, the oral composition easily slips on the mucosa, and swallowability is improved. Simultaneously, the gelled film suppresses short-term drug dissolution before the swallowing of the oral composition, so as to exhibit an unpleasant taste-masking effect. When the oral composition is used for the after-mentioned multi-unit, cohesiveness of tablets in the oral cavity becomes better, and swallowability is further improved.

[0022]

The sugar or sugar alcohol that can be used in the present invention has a solubility at 20°C of 30 or more, and preferably of 50 or more. The solubility means the largest mass (g) of a solute dissolved in 100 g of water. Examples of preferred sugar or sugar alcohol that can be used in the present invention include trehalose, maltose, erythritol, and maltitol. Erythritol and maltitol that cause a moderate sweet taste when they are placed in the mouth are preferable in terms of good sensation upon administration. In addition, erythritol, maltitol and trehalose have low moisture absorbency, and thus, they are particularly preferable in terms of the preservation stability of a preparation. The content of the sugar or sugar alcohol in the coating film is preferably 10% to 50% by mass, and more preferably 30% to 40% by mass.

The sugar or sugar alcohol having a solubility at 20°C of 30 or more that can be used in the present invention accelerates the swelling of the gel by the thickener. It is considered that the sugar or sugar alcohol also promotes the disintegration of the gel and exhibits the effect of improving a drug-dissolution property.

The type of the hydroxypropylmethylcellulose (HPMC) used in the present invention is not particularly limited. HPMC having a viscosity of 100 mPa•s or less is preferable, and HPMC having a viscosity of 10 mPa•s or less is more preferable. More specific examples of such hydroxypropylmethylcellulose that can be used herein include commercially available products such as TC-5E (trade name) (Shin-Etsu Chemical Co., Ltd.; indicated viscosity: 3mPa•s) and TC-5R (trade name) (Shin-Etsu Chemical Co., Ltd.; indicated viscosity: 6mPa•s).

The content of the hydroxypropylmethylcellulose in the coating film is preferably 5% to 35% by mass, more preferably 10% to 30% by mass, and further preferably 14% to 25% by mass.

A combined use of the HPMC with the sugar or sugar alcohol having a solubility at 20°C of 30 or more in the oral cavity promotes the disintegration of the gel,

as compared with a single use of the sugar or sugar alcohol. Thereby, when the gel needs to be rapidly disintegrated, a simple increase in the amount of the sugar or sugar alcohol can be avoided.

As described above, a combined use of the HPMC with the sugar or sugar alcohol having a solubility at 20°C of 30 or more brings on a synergistic effect, and it promotes the disintegration of the gel. Thereby, when the drug core is coated with the gel, a drug-dissolution property is effectively improved. The mixing ratio between the HPMC and the sugar or sugar alcohol is preferably 1 : 1 to 1 : 4, and more preferably 1 : 2 to 1 : 3.

[0023]

The thickener used in the fifth to eighth aspects of the present invention means a substance that turns into a gel when it is allowed to come into contact with water. The type of the thickener is not particularly limited, as long as it has such a property. Examples of such a thickener include the metal-crosslinked thickeners and second thickeners, which are described in the first to fourth aspects of the present invention. More specific examples of such a thickener include a carboxyvinyl polymer, xanthan gum, starch and a derivative thereof, agar, sodium alginate, arabinogalactan, galactomannan, cellulose and a derivative thereof, carrageenan, dextran, tragacanth, gelatin, pectin, hyaluronic acid, guar gum, gellan gum, collagen, and casein.

The thickener may be used singly or in combination of several types. A combination of two or more types of thickeners including a metal-crosslinked thickener is preferable. A preferred example of the combination of two or more types of thickeners including a metal-crosslinked thickener is a combination of one or more types selected from the group consisting of a carboxy vinyl polymer and sodium alginate, used as metal-crosslinked thickener(s), with one or more types selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that a combination of the same substances is excluded.

The coating composition of the present invention and the oral composition of the present invention having the coating may also comprise hydroxypropylcellulose and the like. Since hydroxypropylcellulose provides appropriate viscosity when it is dissolved in alcohol, it is able to suppress rapid sedimentation of particles, when the coating composition is dispersed into ethanol and spray-coating is then performed. Thus, the use of such hydroxypropylcellulose is advantageous in order to maintain uniformity. Moreover, hydroxypropylcellulose acts as a binder to help adhesion of particles to the surface of a tablet, so as to enhance coating efficiency, and it also acts to form a smooth film. For such reasons, addition of a certain amount of

hydroxypropylcellulose to the coating composition is advantageous for the production of an oral composition having the coating.

The type of the hydroxypropylcellulose that can be used in the present invention is not particularly limited. Hydroxypropylcellulose having low viscosity is preferable, and hydroxypropylcellulose having a viscosity of 10mPa•s (2%, 20°C) or less is more preferable. More specific examples of such hydroxypropylcellulose include commercially available products such as HPC-L (trade name) (Nippon Soda Co., Ltd.; indicated viscosity: 6.0 to 10 mPa•s), and HPC-SL (trade name) (Nippon Soda Co., Ltd.; indicated viscosity: 3.0 to 5.9 mPa•s). The content of the hydroxypropylcellulose in the coating film is preferably 0% to 15% by mass, and more preferably 0% to 10% by mass. The content of the hydroxypropylcellulose in the coating composition (coating solution) of the present invention used for spray-coating is 0% to 5% by mass, preferably 0% to 3% by mass, and more preferably 0% to 1.5% by mass, based on the total mass of the coating solution.

[0024]

As a solvent that can be used to prepare the coating composition of the present invention, water, alcohol, a mixed solvent of water and alcohol, or the like can be used. Of these, alcohol is preferable. As such alcohol, ethanol or dehydrated ethanol is preferable. Herein, the term "ethanol" means a substance containing 95.1 to 96.9 vol % or more of ethanol (C_2H_6O), and the term "dehydrated ethanol" means a substance containing 99.5 vol % or more of ethanol. Preferably, it is 95.1 to 96.9 vol % or more of ethanol.

Glycerin may be added to prepare the coating composition of the present invention. It is considered that glycerin acts as a plasticizer in the coating composition, and that it has the effect of promoting the swelling of a gel when the coating film is allowed to come into contact with water. The type of the glycerin used in the composition of the present invention is not particularly limited. It is preferable to use concentrated glycerin containing 98.0% or more of glycerin with respect to a dehydration product converted during assay. The content of glycerin is 0.1% to 5% by mass, preferably 0.5% to 3% by mass, and more preferably 0.5% to 1% by mass, based on the total mass of the coating composition including a solvent.

It is to be noted that, in the preparation of the coating composition, an aqueous solvent such as water or a mixed solvent of water and alcohol can be used depending on the type or amount of a thickener used. When an aqueous solvent is used to prepare the coating composition of the present invention, if the concentration of the coating composition is set at high, viscosity becomes high, resulting in poor operability in some

cases. Thus, it is necessary to select a coating method, as appropriate, depending on the properties of the coating composition.

As a method of preparing the coating composition of the first aspect of the present invention, constitutional gradients of the coating composition of the present invention may be dissolved in or uniformly dispersed into water, alcohol, a mixed solvent of water and alcohol, or the like. There is preferably applied a method of uniformly dispersing constitutional ingredients other than a polyvalent metal compound into an alcohol solution in which the polyvalent metal compound has been dissolved. Specifically, the coating composition may be prepared by uniformly dispersing fine powders comprising at least one second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate (preferably, xanthan gum) and a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate (preferably, a carboxyvinyl polymer), with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate, into an alcohol solution in which a polyvalent metal compound has been dissolved, and preferably, by uniformly dispersing the aforementioned fine powders further comprising hydroxypropylmethylcellulose and/or sugar or sugar alcohol having a solubility at 20°C of 30 or more into an alcohol solution in which a polyvalent metal compound has been dissolved. More preferably, ethanol is used as a solvent.

Further preferably, fine powders comprising: at least one second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate (more preferably, xanthan gum); a first thickener that is a metal-crosslinked thickener (more preferably, a thickener selected from the group consisting of a carboxy vinyl polymer and sodium alginate, and further preferably, a carboxyvinyl polymer), with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate; hydroxypropylmethylcellulose; and sugar or sugar alcohol having a solubility at 20°C of 30 or more, are uniformly dispersed in a mixed solution of ethanol and glycerin, so as to prepare a suspension, separately. Then, a solution formed by dissolving a polyvalent metal compound in ethanol is added to the thus obtained suspension, so as to prepare a coating solution.

[0025]

As a method of preparing the coating composition of the fifth aspect of the present invention, fine powders comprising hydroxypropylmethylcellulose and sugar or sugar alcohol having a solubility at 20°C of 30 or more are dissolved in or uniformly dispersed into a suspension or solution, in which thickeners have been dispersed or dissolved, so as to prepare a coating solution. As described above, alcohol is

preferably used as a solvent. Ethanol is more preferably used.

In order to obtain a suspension in which the coating composition of the present invention has been uniformly dispersed, the particle diameter of constitutional ingredients is preferably reduced using a mill such as a jet mill, as necessary. With regard to particle diameter, a median diameter (D50: the diameter causing that, when powders are divided into two portions based on a certain particle diameter, the amount of the greater portion becomes equal to the amount of the smaller portion) is preferably 35 μm or less, more preferably 25 μm or less, and further preferably 10 μm or less.

As a method of coating a drug core or an orally-administered solid with the coating composition of the present invention, a previously described coating technique can be applied. Thus, the coating method is not particularly limited. Examples of a coating device that can be applied herein include a pan coating device, a fluidized bed coating device, and a vented rotating-drum coating device. A vented rotating-drum coating device is particularly suitable for the after-mentioned coating of mini-tablets. Spray-coating or powder-coating is carried out using these devices, so that a drug core or an orally-administered solid can be coated with the present coating composition. A preferred coating method is spray-coating. It is particularly preferable to continuously supply the present coating composition using a spray nozzle. A drug core or an orally-administered solid can be coated by a single coating operation. However, the number of coating operations is not limited to one, but coating operations may be carried out several times.

As with the above-described preferred example, if alcohol is used as a solvent, the first thickener such as a carboxyvinyl polymer or sodium alginate is not substantially crosslinked by polyvalent metal ions, and as a result, a coating composition having low viscosity can be obtained. Thus, spray-coating can be easily carried out using such a coating composition having low viscosity. In addition, since the used solvent is an alcohol solution, a drying operation can be carried out in a short time after completion of the coating operation, and thus it is advantageous for production.

When the oral composition of the second aspect of the present invention is obtained with the use of the above-described coating using alcohol as a solvent, the first thickener contained in the coating film, such as a carboxyvinyl polymer or sodium alginate, is not substantially crosslinked by polyvalent metal ions, if the film is not allowed to come into contact with water.

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It is also possible to produce an oral composition using water as a solvent. When water is used as a solvent, the first thickener such as a carboxyvinyl polymer or

sodium alginate is substantially crosslinked by polyvalent metal ions, and as a result, a coating composition having high viscosity can be obtained. Thus, when a drug core or an orally-administered solid is coated with this coating composition having high viscosity, the oral composition of the ninth aspect of the present invention, which comprises a gelatinous substance selected from the group consisting of a carboxyvinyl polymer crosslinked by polyvalent metal ions, sodium alginate crosslinked by polyvalent metal ions, and the like, can be produced.

The amount of the solid ingredients of the coating composition of the present invention is preferably 5% to 30% by mass, and more preferably 5% to 15% by mass, based on the mass of the drug core or orally-administered solid to be coated. The thickness of the coating film of the thus coated oral composition is 10 μm to 100 μm, and preferably 40 μm to 70 μm.

[0026]

The content of the first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate of the coating composition (coating solution) of the present invention used for spray-coating is, for example, 0.5% to 5% by mass, preferably 0.5% to 3% by mass, and more preferably 0.5% to 2% by mass, based on the total mass of the coating solution.

The content of at least one type of the second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate is, for example, 1% to 5% by mass, preferably 1% to 4% by mass, and more preferably 3% to 4% by mass, based on the total mass of the coating solution.

The total content of the thickeners is, for example, 1.5% to 10% by mass, preferably 1.5% to 7% by mass, and more preferably 3.5% to 6% by mass, based on the total mass of the coating solution.

The content of the hydroxypropylmethylcellulose is, for example, 1% to 10% by mass, preferably 1% to 5% by mass, and more preferably 1.5% to 3.5% by mass, based on the total mass of the coating solution.

The content of the sugar or sugar alcohol having a solubility at 20°C of 30 or more is 1% to 10% by mass, preferably 1% to 6% by mass, and more preferably 3% to 6% by mass, based on the total mass of the coating composition (coating solution) of the present invention used for spray-coating.

The coating composition of the present invention includes: a kit comprising a combination of ingredients to be contained in the coating composition; and a combination or kit of compositions, in which ingredients to be contained in the coating composition are divided into two or more groups. An example of such a combination

or kit is a combination of a coating composition (A) comprising a first thickener, a second thickener, and as necessary, hydroxypropylmethylcellulose and sugar or sugar alcohol having a solubility at 20°C of 30 or more, with a coating composition (B) comprising a polyvalent metal compound. Other examples of such a combination or kit include: a kit, in which the above-described coating composition (A) is combined with a polyvalent metal compound (C); and a kit, in which a combined composition (D) of the first thickener and the second thickener, a coating composition (E) comprising hydroxypropylmethylcellulose and sugar or sugar alcohol having a solubility at 20°C of 30 or more, and a polyvalent metal compound (C) are combined.

A drug core or an orally-administered solid may be coated as described above, with the combined one of ingredients contained in such a combination or kit. Also, a drug core or an orally-administered solid may be successively coated with each coating composition that has been dissolved in or uniformly dispersed into an alcohol solvent or water. During the coating operations, the solvents may be changed. In the aforementioned example, the drug core or the orally-administered solid may be first coated with the composition (A) that has been dissolved in or uniformly dispersed into an alcohol solvent, and may be then coated with the composition (B) that has been dissolved in water. In this case, the oral composition of the ninth aspect of the present invention comprising a coating, in which the first thickener is partially crosslinked by polyvalent metal ions, is produced at the boundary between the composition (A) and the composition (B).

[0027]

The oral composition of the second aspect of the present invention can be obtained by coating a drug core with the coating composition of the first aspect of the present invention. However, the method for producing the oral composition of the second aspect of the present invention is not limited thereto. Any oral composition, which has a first thickener such as a carboxyvinyl polymer or sodium alginate, a polyvalent metal compound, and a second thickener such as xanthan gum, guar gum or sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate,, over the surface of a drug core, is included in the oral composition of the second aspect of the present invention.

The oral composition of the sixth aspect of the present invention can be obtained by coating a drug core with the coating composition of the fifth aspect of the present invention. However, the method for producing the oral composition of the sixth aspect of the present invention is not limited thereto. Any oral composition, which has thickeners, sugar or sugar alcohol having a solubility at 20°C of 30 or more,

and hydroxypropylmethylcellulose over the surface of a drug core, is included in the oral composition of the sixth aspect of the present invention.

Examples of the drug core containing an active ingredient used in the oral composition of the present invention include solid preparations such as a tablet core, a pill core, a capsule core, a pellet core and a granule core. The type of the orally-administered solid is not particularly limited, as long as it is a solid product that contains a drug core as a solid and is used for oral administration. In the case of a high-dose preparation, in order to prevent the preparation from growing in size, a mini-tablet, in which the content of a drug per tablet can be decreased and the bulk is reduced to the minimum, is preferably applied as a drug core. Such a mini-tablet can be produced in ordinary equipment.

The mini-tablet used in the present specification is a form of a tablet, and it is referred to as a granular solid preparation having a diameter and a thickness, each of which is 6 mm or less. In the case of a high-dose active ingredient, if the diameter of a tablet is 3 to 4 mm, the number of tablets for a single administration may be approximately 20 to 100. In the present specification, a single administration of an oral preparation, in which the number of tablets for the single administration is 10 or more, is referred to as a multi-unit. It is preferably a granular tablet having a diameter and a thickness, each of which is 0.5 to 5 mm, and more preferably 2 to 4 mm.

[0028]

In the oral composition of the present invention, a seal coating may be established between a drug core or orally-administered solid containing an active ingredient and a coating. The oral composition of the present invention having such a seal coating can be obtained, for example, by coating a drug core having a seal coating with the coating composition of the present invention.

It is anticipated that the seal coating of a drug core is useful to prevent the phenomenon whereby the ingredients of the drug core are moved to the coating layer during preservation and incompatibility thereby occurs between the ingredients of the drug core and the ingredients of the coating layer, or to prevent the phenomenon whereby unpleasant taste ingredients contained in the drug core are moved to the coating layer during preservation and the unpleasant taste-masking effect of the coating is thereby attenuated upon administration, or to enhance the unpleasant taste-masking effect of the coating upon administration.

The present seal coating is obtained by coating a drug core containing an active ingredient with a seal coating composition according to a previously described coating

technique. The type of such a seal coating composition is not particularly limited, as long as it is able to prevent ingredients contained in the drug core from moving to the coating during preservation of the oral composition. An example of such a seal coating composition is a composition comprising at least one selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, polyvinylpyrrolidone, Pullulan, an acrylate-methacrylate copolymer, and the like.

As a solvent that can be used to prepare the seal coating composition, water, alcohol, a mixed solvent of water and alcohol, etc. can be used.

The amount of solid ingredients contained in the seal coating composition is preferably 1% to 10% by mass, and more preferably 2% to 5% by mass, based on the mass of the drug core or orally-administered solid to be coated. The thickness of the seal coating film of the oral composition comprising the thus obtained seal coating is 10 to 80 μm, and preferably 20 to 40 μm.

[0029]

The drug core or orally-administered solid used in the present invention is prepared by mixing a desired drug serving as an active ingredient with pharmaceutical carriers commonly used in the technical field of pharmaceutical preparations. As such pharmaceutical carriers, carriers recognized in the technical field of pharmaceutical preparations can be widely used. Examples of such pharmaceutical carriers include: excipients such as lactose, saccharose, mannitol, sodium chloride, glucose, starch, calcium carbonate, kaoline, crystalline cellulose and filler such as silicate, water, ethanol, simple syrup, dextrose solution, starch solution, gelatin solution, carboxymethylcellulose, sodium carboxymethylcellulose, shellac, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinyl alcohol, gelatin, dextrin and Pullulan; pH adjusters such as citric acid, anhydrous citric acid, sodium citrate, sodium citrate dihydrate, anhydrous sodium monohydrogen phosphate, anhydrous sodium dihydrogen phosphate, sodium hydrogen phosphate and anhydrous sodium dihydrogen phosphate; disintegrators such as carmellose calcium, low substituted hydroxypropylcellulose, carmellose, croscarmellose sodium, partially pregelatinized starch, dry starch, sodium carboxymethyl starch, crospovidone and polysorbate 80; absorption promoters such as sodium lauryl sulfate; and lubricants such as purified talc, stearate, polyethylene glycol and colloidal silica.

When a coated preparation is produced using a mini-tablet and it is then administered in the form of a multi-unit, the surface layer of each tablet turns into a gel after it has been

allowed to come into contact with water. At the same time, the first thickener such as a carboxyvinyl polymer and/or sodium alginate is crosslinked by polyvalent metal ions generated from the polyvalent metal compound, so that viscosity

increases and a relatively hard jelly-like gel can be formed. As a result, tablets obtain a good slipping property, and good cohesiveness among tablets causes good swallowability. Moreover, since the formed gel layer suppresses the release of the drug in a short time, a higher effect of masking an unpleasant taste is exhibited.

The methods for producing an oral composition of the fourth and eighth aspects of the present invention are as described above.

In addition, the oral compositions of the third and seventh aspects of the present invention can be obtained by the above-described production methods. The oral composition of the third aspect of the present invention can be produced by spray-coating a drug core containing an active ingredient with a liquid that is prepared by dispersing a first thickener such as a carboxyvinyl polymer or sodium alginate (preferably, a carboxyvinyl polymer) and a second thickener such as xanthan gum, guar gum or sodium alginate (preferably, xanthan gum), with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate, into an alcohol solution in which a polyvalent metal compound has been dissolved. Thus, as described above, the first thickener such as a carboxyvinyl polymer contained in the coating film is not substantially crosslinked by polyvalent metal ions, if the film is not allowed to come into contact with water. Moreover, the coating can be easily washed away from the oral composition of the present invention by the used alcohol solvent. On the other hand, in the case of the oral composition that has been coated using, as a solvent, a solution other than alcohol, such as an aqueous solution, since the first thickener such as a carboxyvinyl polymer contained in the coating film is substantially crosslinked by polyvalent metal ions, it is not easy to wash away the coating from the oral composition.

[0030]

The easy swallowability of the oral composition according to the present invention can be specifically expressed in the form of the maximum stress that is required for the movement (rate: 8 mm/sec; up and down movement distance: 40 mm) of a probe (a ball having a diameter of 6 mm) inserted into a tube used to the filled oral composition, by the test method described in the after-mentioned Test Example 1, namely, in an evaluation using a vertically fixed silicon tube with a length of 5 cm (8 × 12), the bottom portion of which is sealed with absorbent cotton (25-30mg). With regard to the oral composition of the present invention, the above-described maximum stress is preferably 41 g or less, more preferably 30 g or less, and further preferably 20 g or less. Moreover, the area under the stress-distance curve is preferably 600 g•mm or less, more preferably 400 g•mm or less, and further preferably 200 g•mm or less.

The unpleasant taste-masking effect in the present invention can be specifically expressed in the form of the concentration of the active ingredient contained in a liquid discharged from a syringe, by the test method described in the after-mentioned Test Example 2, namely, by the method comprising: placing an oral composition containing an active ingredient in a vertically fixed 2-mL plastic syringe in the same manner as that in Test Example 2; adding dropwise water heated to 37°C to the syringe at a rate of 2 mL/min for a predetermined time, such as 30 seconds or 2minutes; and measuring the concentration of the active ingredient contained in a liquid discharged from the port of the syringe. If the measured concentration becomes the threshold concentration or less of the unpleasant taste of the active ingredient after completion of the dropwise addition of water for 30 seconds in the aforementioned test, the oral composition of the present invention is determined to be sufficiently masked for practical use. For example, a levofloxacin hydrate having a levofloxacin concentration of 1,000 μg/mL or less after completion of the dropwise addition of water for 30 seconds is considered to have a high unpleasant taste-masking effect, and thus it is preferable. Even in the case of a preparation that is administered without using water, if the concentration of the active ingredient becomes the threshold concentration or less of the unpleasant taste of the active ingredient after completion of the dropwise addition of water for 30 seconds or 2 minutes in the aforementioned test, the preparation is determined to be sufficiently masked for practical use. In the case of a levofloxacin hydrate, for example, the concentration after completion of the dropwise addition of water for 30 seconds is 100 μg/mL or less, preferably 50 μg/mL or less, more preferably 10 μg/mL or less, and further preferably 3 μg/mL or less.

The dissolution property in the present invention can be specifically expressed in the form of an dissolution rate measured 30 minutes after initiation of a test, namely, in an evaluation using Japanese Pharmacopoeia disintegration test solution 1 and the number of rotations that is 50, by Japanese Pharmacopoeia dissolution test paddle method, the test example described in the after-mentioned Test Example 3. The above-described dissolution rate of the oral composition of the present invention is preferably 80% or more, more preferably 90% or more, and further preferably 95% or more. It does not cause a substantial delay in dissolution, and it satisfies the dissolution specification of a quick-release tablet.

[0031]

The type of the active ingredient contained in the drug core used in the oral composition of the present invention is not particularly limited. Taking into consideration the purpose of the present invention, a drug that is administered at a high

dose for a single administration is particularly preferable. Examples of such a drug include: antibiotics such as amoxicillin, cefuroxime axetil, cephalexin, fosfomycin, ceftazidime, ampicillin, cyclacillin, lenampicillin, cefotiam hexetil, sultamicillin, vancomycin, polymyxin B, erythromycin, clarithromycin, telithromycin, azithromycin, josamycin, midecamycin, rokitamycin, roxithromycin, kanamycin, ceftibuten, chloramphenicol, cycloserine and rifabutin; synthetic antibacterial agents such as ofloxacin, enoxacin, levofloxacin, ciprofloxacin, norfloxacin, moxifloxacin, garenoxacin, lomefloxacin, nalidixic acid and linezolid; sulfa drugs such as salazosulfapyridine; antifungal agents such as voriconazole and itraconazole; antiviral agents such as aciclovir, valacyclovir, famciclovir, valganciclovir, nelfinavir, raltegravir, lamivudine, emtricitabine, ritonavir, ribavirin, abacavir, efavirenz, nelfinavir, tenofovir, disoproxil, darunavir and atazanavir; antihyperlipidemic drugs such as probucol, clofibrate, colestimide and cholestyramine; anthelminthics such as praziquantel and albendazole; antiprotozoal drugs such as tinidazole and metronidazole; agents against hepatic diseases, such as a branched chain amino acid; antidotes such as activated carbon; agents for digestive organs, such as 5-aminosalicylic acid and polycarbophil calcium; anticancer agents such as imatinib mesylate; immunosuppressive agents such as mycophenolate mofetil; and other agents such as inosine pranobex. Moreover, examples of the drug are not limited thereto. The coating composition of the present invention can also be applied to Chinese medicines, OTC medicines, and health food.

EXAMPLES

[0032]

The present invention will be more specifically described in the following examples and comparative examples. However, these examples are not intended to limit the scope of the present invention.

[0033]

(1) Production of placebo mini-tablet (uncoated tablet P):

The following ingredients were weighed, mixed, and then subjected to tableting, so as to obtain 2 kg of placebo mini-tablets, each having a diameter of 3.1 mm and a thickness of 3.1 mm (approximately 25 mg/tablet; approximately 80,000 tablets).

Lactose	2.050 kg
Crystalline cellulose	0.519 kg
Magnesium stearate	0.026 kg

[0034]

(2) Production of levofloxacin hydrate mini-tablet:

Levofloxacin hydrate or valacyclovir hydrochloride was selected as a high water-soluble model drug having a bitter taste, and levofloxacin hydrate-containing mini-tablets A to C (uncoated tablets A to C) and a valacyclovir hydrochloride-containing mini-tablet (uncoated tablet D) were then produced.

(i) Production of levofloxacin hydrate-containing mini-tablet A (uncoated tablet A):

The following ingredients were weighed, and they were placed in a stirring/mixing granulator (Powrex VG-25) and were then mixed. Then, 1760 g of a 8 w/w% hydroxypropylcellulose aqueous solution was added as a binder to the mixture, followed by granulation.

Levofloxacin hydrate	4.100 kg
Crystalline cellulose	0.364 kg
Carmellose	0.392 kg
Sodium stearyl fumarate	0.108 kg

The granulated product was dried using a fluidized bed dryer (Powrex MP-01), and it was then sized. Thereafter, 0.087 kg of sodium stearyl fumarate was added to 4.277 kg of the obtained powders, and they were mixed and were then subjected to tableting, so as to obtain 3.612 kg of levofloxacin hydrate mini-tablets, each having a diameter of 3.1 mm and a thickness of 3.1 mm (approximately 24 mg/tablet; approximately 150,500 tablets).

[0035]

(ii) Production of levofloxacin hydrate-containing mini-tablet B (uncoated tablet B):

The following ingredients were weighed, and were then placed in a stirring/mixing granulator (high-speed mixer), followed by mixing. Thereafter, water was added thereto, followed by granulation.

Levofloxacin hydrate	205.0 g
Crystalline cellulose	18.2 g
Pregelatinized starch (SWELSTAR PD-1; Asahi Kasei Corp.)	19.6 g
Pregelatinized starch (SWELSTART WB-1; Asahi Kasei Corp.)	9.0 g
Sodium stearyl fumarate	5.4 g

The granulated product was dried using a fluidized bed dryer (Powrex MP-01), and it was then sized. Thereafter, 4.9 g of sodium stearyl fumarate was added to 239.9 g of the obtained powders, and they were mixed and were then subjected to tableting, so as to obtain approximately 220 g of levofloxacin hydrate mini-tablets, each having a diameter of 3.1 mm and a thickness of 3.1 mm (approximately 24 mg/tablet; approximately 9,200 tablets).

[0036]

(iii) Production of levofloxacin hydrate-containing mini-tablet C (uncoated tablet C):

The following ingredients were weighed, and were then placed in a stirring/mixing granulator (high-speed mixer), followed by mixing. Thereafter, 1 kg of a 5 w/w% pregelatinized starch (SWELSTAR WB-1; Asahi Kasei Corporation) aqueous solution used as a binder and 2.5 kg of water were added to the mixture, followed by granulation.

Levofloxacin hydrate	2.471 kg
Crystalline cellulose	0.220 kg
Carboxymethyl starch sodium (Primogel)	0.627 kg
Pregelatinized starch (SWELSTAR WB-1; Asahi Kasei Corp.)	0.048 kg
Sodium stearyl fumarate	0.065 kg

The granulated product was dried using a fluidized bed dryer (Powrex MP-01), and it was then sized. Thereafter, 0.058 kg of sodium stearyl fumarate was added to 3.095 kg of the obtained powders, and they were mixed and were then subjected to tableting, so as to obtain approximately 3 kg of levofloxacin hydrate mini-tablets, each having a diameter of 3.1 mm and a thickness of 3.1 mm (approximately 24 mg/tablet; approximately 125,000 tablets).

[0037]

(iv) Production of valacyclovir hydrochloride-containing mini-tablet (uncoated tablet D):

The following ingredients were weighed, and were then placed in a stirring/mixing granulator (high-speed mixer), followed by mixing. Thereafter, 100 g of a 6.4 w/w% pregelatinized starch (SWELSTAR WB-1; Asahi Kasei Corporation) aqueous solution was added as a binder to the mixture, followed by granulation.

Valacyclovir hydrochloride	178.0 g
Crystalline cellulose	10.2 g
Carboxymethyl starch sodium (Primogel)	32.0 g
Sodium stearyl fumarate	4.3 g

The granulated product was dried using a fluidized bed dryer (Powrex MP-01), and it was then sized. Thereafter, 3.6 g of sodium stearyl fumarate was added to 197.6 g of the obtained powders, and they were mixed and were then subjected to tableting, so as to obtain approximately 177.7 g of valacyclovir hydrochloride mini-tablets, each having a diameter of 3.1 mm and a thickness of 3.1 mm (approximately 24 mg/tablet; approximately 7,400 tablets).

[0038]

The compositioins of the uncoated tablets A-D (wherein each numelarl value

indicates the amount of each gradient per 500mg of the active ingredient) are shown in Table 1.

[Table 1]

Ingredient	Uncoated tablet A	Uncoated tablet B	Uncoated tablet C	Uncoated tablet D
Levofloxacin hydrate	512.5	512.5	512.5	
Valacyclovir hydrochloride				556
Crystalline cellulose	45.5	45.5	45.5	32.0
Carmellose	49.0			
Pregelatinized starch (SWELSZTAR PD-1)		130.0		
Carboxymethyl starch sodium (Primogel)			130.0	100.0
HPC-L	20.0			
Pregelatinized starch (SWELSTAR WB-1)		20.0	20.0	20.0
Sodium stearyl fumarate	27.0	27.0	27.0	27.0

[0039]
Examples 1 and 2

Concentrated glycerin was mixed into ethanol, and hydroxypropylcellulose (HPC-L; Nippon Soda Co., Ltd.; indicated viscosity: 6 to 10 mPa•s) was then added to and dissolved in the solution. Thereafter, hydroxypropylmethylcellulose (HPMC (TC-5E); Shin-Etsu Chemical Co., Ltd.; indicated viscosity: 3 mPa•s) and a carboxyvinyl polymer (Carbopol 971P; Lubrizol Advanced Material Inc.; indicated viscosity: 6420 mPa•s) were successively added to the mixed solution, and they were then uniformly dispersed therein. Thereafter, erythritol (Mitsubishi Shoji Foodtech Co., Ltd.) and xanthan gum (Keltrol CG-T; Sansho Co., Ltd.; indicated viscosity: 1555 mPa•s) were micronized using a jet mill (Seishin Enterprise Co., Ltd.; SJ-3), and then, they were successively added to the solution, so that they were uniformly dispersed therein. Finally, a calcium chloride dihydrate dissolved in ethanol was added to the solution, and they were uniformly dispersed therein, so as to prepare a coating solution. This coating solution (mass ratio to the mini-tablets: approximately 10%) was applied by spray-coating onto the above-described uncoated tablet A, using a coater (Powrex Dria-Coater 200), so as to obtain a coated mini-tablet. 140 g of uncoated tablets (approximately 5,833 tablets) were coated by a single coating operation.

Moreover, as Examples 1-P and 2-P, coated mini-tablets (140 g of uncoated tablets; approximately 5,833 tablets) were obtained by the same preparation methods as those of Examples 1 and 2, respectively, with the exception that uncoated tablets P were used instead of the uncoated tablets A.

[0040]
Example 3

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 1, with the exception that HPC-L was not added in the method for preparing a coating solution of Example 1.

[0041]
Example 4

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 1, with the exception that Carbopol 974 P (Lubrizol Advance Material Inc.; indicated viscosity: 32850 mPa•s) was used instead of Carbopol 971P in the method for preparing a coating solution of Example 2.

[0042]
Example 1-1

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 1, with the exception that mannitol (mannit P; Mitsubishi Shoji Foodtech Co., Ltd.) micronized with a jet mill was used instead of erythritol in the method for preparing a coating solution of Example 1.

[0043]
Example 1-2

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 1, with the exception that HPMC was not used in the method for preparing a coating solution of Example 1.

[0044]
Example 1-3

Coated mini-tablets were obtained by a preparation method equivalent to that

of Example 1, with the exception that HPMC was not used and the amount of erythritol was increased in the method for preparing a coating solution of Example 1.

[0045]

Example 1-4

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 1, with the exception that the amount of Carbopol 971P was increased and the amount of erythritol was decreased in the method for preparing a coating solution of Example 1.

[0046]

Example 1-5

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 1, with the exception that erythritol was not used and the amount of HPMC was increased in the method for preparing a coating solution of Example 1.

[0047]

Example 2-1

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 1, with the exception that Carbopol 971P was not used in the method for preparing a coating solution of Example 1.

[0048]

Example 2-2

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 1, with the exception that xanthan gum was not used in the method for preparing a coating solution of Example 1.

[0049]

Comparative Example 1

As Comparative Example 1, uncoated tablets A obtained as a result of the above-described production of levofloxacin hydrate mini-tablets were used.

[0050]

Comparative Example 2

Ordinary film coated mini-tablets were prepared for the purpose of light-shielding or the masking of a bitter taste. HPMC and macrogol 6000 (Wako Pure Chemical Industries, Ltd.) were dissolved in water, and thereafter, talc (Matsumura Sangyo Co.) and titanium oxide (Freund) were uniformly dispersed therein, so as to prepare a coating solution. Thereafter, the above-described uncoated tablets P or uncoated tablets A were coated with this coating solution (mass ratio to the mini-tablets: approximately 10%), using a coater (Powrex Dria-Coater 200), so as to obtain coated mini-tablets.

[0051]

Comparative Example 3

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 1, with the exception that neither HPMC nor calcium chloride dihydrate was used and mannitol (mannit P; Mitsubishi Shoji Foodtech Co., Ltd.) crushed with a jet mill was used instead of erythritol micronized with a jet mill in the method for preparing a coating solution of Example 1.

[0052]

The composition of the coating solution of each of Examples 1 to 4 and 1-1 to 2-2, and Comparative Examples 2 and 3 is shown in Table 2 (wherein each numerical

value indicates the amount (g) of each ingredient coated to 100 g of uncoated tablets).
[0053]

[Table 2]

Ingredient	Example											Comp. Ex.	
	1	2	3	4	1-1	1-2	1-3	1-4	1-5	2-1	2-2	2	3
Uncoated tablet	A	A	A	A	A	A	A	A	A	A	A	A	A
Carbopol 974P				1.00									
Carbopol 971P	1.50	0.50	1.50		1.50	1.50	1.50	2.00	1.50		1.50		1.50
Xantham gum (jet mill crushing) Particle diameter (D_{50}): 13.3 μm	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00			3.00
HPC-L	1.20	1.20			1.20	1.20	1.20	1.20	1.20	1.20	1.20		1.20
HPMC	1.80	1.80	3.00	3.00	1.80			1.80	4.20	1.80	1.80	4.62	
Mannit (jet mill crushing) Particle diameter (D_{50}): 5.7 μm					4.20								4.20
Erythritol (jet mill crushing) Particle diameter (D_{50}): 3.8 μm	4.20	5.30	4.20	4.75		4.20	6.00	3.70		4.20	4.20		
Calcium chloride dihydrate	0.15	0.05	0.15	0.10	0.15	0.15	0.15	0.15	0.15		0.15		
Macrogol 6000												0.92	
Talc												1.38	
Titanium oxide												3.08	
Concentrated glycerin	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60		0.60
Ethanol	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	81.00	80.00	80.0		81.0
Water												90.00	

[0054]
Example 5

140 g of the above-described uncoated tablets C were spray-coated with a seal coating solution (mass ratio to the mini-tablets: approximately 4.2%) prepared by dissolving macrogol 6000 (Sanyo Chemical Industries, Ltd.) in water and then dissolving hydroxypropylmethylcellulose (HPMC (TC-5R); Shin-Etsu Chemical Co., Ltd.; indicated viscosity: 6mPa•s) therein, using a coater (Powrex Dria Coater 200), so as to obtain seal coated mini-tablets. Subsequently, hydroxypropylcellulose (HPC-L; Nippon Soda Co., Ltd.; indicated viscosity: 6 to 10 mPa•s) was added to and dissolved in ethanol. Thereafter, hydroxypropylmethylcellulose (HPMC (TC-5E); Shin-Etsu Chemical Co., Ltd.) and a carboxyvinyl polymer (Carbopol 971P; Lubrizol Advanced Material Inc.; indicated viscosity: 6420 mPa•s) were successively added to the solution, and they were uniformly dispersed therein. Thereafter, erythritol (Mitsubishi Shoji Foodtech Co., Ltd.) and xanthan gum (Keltrol CG-T; Sansho Co., Ltd.; indicated viscosity: 1555 mPa•s) were micronized with a jet mill (Seishin Enterprise Co., Ltd.; SJ-3), and thereafter, they were successively added to the solution and were then uniformly dispersed therein. Finally, a solution prepared by dissolving calcium chloride dihydrate in ethanol was added to the solution, and it was uniformly dispersed therein, so as to prepare an over-coating solution. The above-described seal coated mini-tablets were spray-coated with this over-coating solution (mass ratio to the mini-tablets: approximately 8.2%), using a coater (Powrex Dria Coater 200), so as to obtain coated mini-tablets.

[0055]
Example 6

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 5, with the exception that maltitol (Amalty MR-100; Mitsubishi Shoji Foodtech Co., Ltd.) micronized with a jet mill was used instead of erythritol in the method for preparing an over-coating solution of Example 5.

[0056]
Example 7

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 5, with the exception that trehalose (trehalose S; Asahi Kasei Chemicals Corporation) micronized with a jet mill was used instead of erythritol in the method for preparing an over-coating solution of Example 5.

[0057]
Example 8

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 5, with the exception that guar gum (guar gum RG-100; MRC Polysaccharide Co., Ltd.; indicated viscosity: 1100 mPa•s) micronized with a jet mill was used instead of xanthan gum in the method for preparing an over-coating solution of Example 5.

[0058]
Example 9-1

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 5, with the exception that sodium alginate (Kimica Algin I-8; KIMICA Corporation) micronized with a jet mill was used instead of xanthan gum in the method for preparing an over-coating solution of Example 5.

[0059]
Example 9-2

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 5, with the exception that sodium alginate (Kimica Algin I-8; KIMICA Corporation) micronized with a jet mill was used instead of the carboxy vinyl polymer in the method for preparing an over-coating solution of Example 5.

[0060]
Example 10

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 5, with the exception that uncoated tablets A were used instead of uncoated tablets C in Example 5.

[0061]
Example 11

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 5, with the exception that uncoated tablets B were used instead of uncoated tablets C in Example 5.

[0062]
Example 12

Coated mini-tablets were obtained by a preparation method equivalent to that of Example 5, with the exception that uncoated tablets D were used instead of uncoated tablets C in Example 5.

[0063]
Comparative Example 4

The above-described uncoated tablets C were used as Comparative Example 4.

[0064]
Comparative Example 5

The seal coated mini-tablets prepared in Example 5 were used as Comparative Example 5.

[0065]
Comparative Example 6

The uncoated tablets D were used as Comparative Example 6.

[0066]

The uncoated tablets and the compositions of over-coating solutions used in Examples 5-8, 9-1, 9-2, and 10 to 12, and Comparative Examples 4 to 6, are shown in Table 3 (wherein each numerical value indicates the amount (g) of each ingredient coated to 100 g of uncoated tablets).

[0067]

[Table 3]

Ingredient	Example									Comparative Example		
	5	6	7	8	9-1	9-2	10	11	12	4	5	6
Uncoated tablet	C	C	C	C	C	C	A	B	D	C	C	D
Seal coating	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Carbopol 974P	1.05	1.05	1.05	1.05	1.05		1.05	1.05	1.05			
Xantham gum (jet mill crushing) Particle diameter (D_{50}): 13.3 μm	2.10	2.10	2.10			2.10	2.10	2.10	2.10			
Guar gum (jet mill crushing) Particle diameter (D_{50}): 27.3 μm				2.10								
Sodium alginate (jet mill crushing) Particle diameter (D_{50}): 31.3 μm					2.10	1.05						
HPC-L	0.84	0.84	0.84	0.84	0.84	0.84	0.84	0.84	0.84	Over-	Over-	Over-
HPMC	1.26	1.26	1.26	1.26	1.26	1.26	1.26	1.26	1.26	coating:	coating:	coating:
Erythritol (jet mill crushing) Particle diameter (D_{50}): 3.8 μm	2.94			2.94	2.94	2.94	2.94	2.94	2.94	No	No	No
Maltitol (jet mill crushing) Particle diameter (D_{50}): 2.5 μm		2.94										
Trehalose (jet mill crushing) Particle diameter (D_{50}): 5.3 μm			2.94									
Calcium chloride	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04			
Ethanol	49.00	49.0	49.0	49.0	49.00	49.00	49.00	49.00	49.00			

[0068]
Reference Example 1

A solution was prepared according to liquid A described in Production Example 1 of Patent Literature 4. Specifically, 3.0 g of hydrolyzed polyvinyl alcohol (Wako Pure Chemical Industries, Ltd.) was slowly added to 55.0 g of purified water, while stirring. Thereafter, while heating to 70°C, the obtained mixture was stirred for approximately 1 hour, so that it was completely dissolved in the purified water. Likewise, 1.0 g of Carbopol 974P was slowly added to 45.0 g of purified water, while stirring, and the obtained mixture was then stirred for approximately 30 minutes, so that it was completely dissolved in the purified water. The thus obtained two types of solutions were gathered, and the mixed solution was then fully stirred. Since the solution obtained at this time point did not contain calcium chloride, it had extremely high viscosity although it was not crosslinked by polyacrylic acid. Thus, the solution could not used for spray-coating using the spray-coater described in Example 1. Accordingly, it was assumed that it would be difficult to carry out spray-coating, using a solution prepared by adding calcium chloride to the aforementioned solution so that the resultant solution would be crosslinked by polyacrylic acid with the action of calcium ions generated as a result of the electrolytic dissociation of the added calcium chloride.

[0069]
Reference Example 2

An inner coating solution was prepared in the same manner as that of Reference Example 1, with the exception that 0.33 g of glycerin was added to the prescription of Reference Example 1 and the total amount of purified water added was set at 250 g. At the same time, while stirring, 1.0 g of glycerin, 3.5 g of polyvinylpyrrolidone (PVP K-90, ISP Japan Ltd.), 0.5 g of calcium chloride and 0.5 g of xanthan gum (Keltrol CG-T; Sansho Co., Ltd.; indicated viscosity: 1555 mPa•s) were slowly added to 170 g of purified water. Thereafter, while heating to 70°C, the obtained mixture was stirred for approximately 30 minutes, so that the aforementioned substances were completely dissolved in the purified water, thereby preparing an outer coating solution.

The above-described uncoated tablets P were spray-coated with the inner coating solution, using a coater (Powrex Dria Coater 200), and they were then dried. Thereafter, the tablets were also spray-coated with the outer coating solution in the same manner as described above, so as to obtain coated mini-tablets. Even though coating operations were carried out twice, the mass ratio of the inner and outer coating films to the mini-tablets remained at approximately 4.3%.

[0070]
Test Example 1 (evaluation of slipping property)

A silicon tube (8 ×12; inner diameter: 8 mm, outer diameter: 12 mm) was cut into a length of 5 cm, and it was then vertically fixed on an aluminum block, using an adhesive tape. The bottom portion thereof was sealed with absorbent cotton (25 to 30 mg), and 20 mini-tablets were then placed therein from the upper portion, followed by tapping. Using a syringe, 5 mL of water was supplied into the silicon tube. Immediately after the water had been discharged, a probe (a ball-type probe with a diameter of 6 mm) set into a texture analyzer (TA-XT-Plux) manufactured by Stable Micro Systems was inserted into the tube, and it was then moved 40 mm from the top to

the bottom at a rate of 8 mm/sec. The stress required at that time was measured.
[0071]
Test Example 2 (evaluation of bitter taste-masking)

A 2.5-mL plastic syringe was vertically placed, and it was then filled with approximately 27 to 30 coated mini-tablets containing levofloxacin hydrate or valacyclovir hydrochloride (500 mg of levofloxacin or valacyclovir). Thereafter, from above, water heated to 37°C was added dropwise to the syringe at a flow rate of 2 mL/min for 30 seconds or 2 minutes. A liquid discharged from the port of the syringe was gathered, and the concentration of levofloxacin hydrate or valacyclovir hydrochloride contained therein was then measured.
[0072]
Test Example 3 (evaluation of dissolution property)

Approximately 27 to 30 coated mini-tablets containing levofloxacin hydrate or valacyclovir hydrochloride (500 mg of levofloxacin or valacyclovir) were tested according to the Japanese Pharmacopoeia dissolution test paddle method (test solution: Japanese Pharmacopoeia disintegration test solution 1; the number of rotations: 50). The dissolution rate at 30 minutes after initiation of the test was measured.

The test results are shown in Tables 4 and 5.
[0073]

[Table 4]

Test Example	Evaluation item	Example											Comparative Example		
		1	2	3	4	1-1	1-2	1-3	1-4	1-5	2-1	2-2	1	2	3
1	Maximum stress (g)	10.3	29.3	26.3	36.9	28.9	23.0	24.6	40.6	29.8	46.0	85.3	1135	125.8	132.5
	Area under the stress-distance curve (g•mm)	133	472	386	516	347	323	297	516	501	801	1624	20806	2779	974
2	Concentration of liquid discharged for 2 minutes (μg/mL)	0.652	0.831	2.33	0.737	0.579	0.249	0.577	0.477	0.764	3.69	4.89	10033	677	0.148
3	dissolution rate (%) for 30 minutes Test solution: pH 1.2	86.1	88.7	92.8	82.2	42.4	47.3	52.1	66.2	30.0	81.2	74.0	102.0	97.8	61.5

[Table 5]

Test Example	Evaluation item	Example									Comparative Example		
		5	6	7	8	9-1	9-2	10	11	12	4	5	6
1	Maximum stress (g)	17.3	22.5	20.4	25.2	24.0	31.1	17.1	19.4	17.3			
	Area under the stress-distance curve (g•mm)	164	220	326	399	408	426	308	306	164			
2	Concentration of liquid discharged for 30 seconds (μg/mL)	17.4	18.9	47.9	40.6	42.1	29.6	23.2	25.3	17.4	2494.3	124.7	6306.0
3	dissolution rate (%) for 30 minutes Test solution: pH 1.2	103.5	104.5	105.4	105.5	105.0	106.0	106.4	110.5	103.5			

[0074]
Evaluation results of Test Example 1 (evaluation of slipping property)

In Comparative Example 1 (uncoated tablets A), Comparative Example 2 (uncoated tablets A subjected to common film coating), and Comparative Example 3, in which a carboxyvinyl polymer and xanthan gum were used but polyvalent metal salts were not used, the maximum stress and the area under the stress-distance curve showed great values, and thus, it was assumed that the tablets had a poor slipping property on the mucosa and could be hardly swallowed. In Comparative Example 3, since polyvalent metal ions were not generated by water, the carboxy vinyl polymer was not crosslinked by the polyvalent metal ions. In Examples 1 to 4 and 1-1 to 1-5, in which a carboxy vinyl polymer, polyvalent metal salts and xanthan gum were used, the stress was 41 g or less, the area under the stress-distance curve was 516 g•mm or less. Thus, it was assumed that the tablets could be easily swallowed.

Also, in Examples 6 and 7 in which maltitol or trehalose was used instead of erythritol, in Examples 8 and 9-1 in which guar gum or sodium alginate was used instead of xanthan gum, and in Example 9-2 in which sodium alginate was used instead of a carboxy vinyl polymer, the values of the maximum stress and the area under the stress-distance curve were small, and thus, it was assumed that they could be easily swallowed.

Moreover, the slipping property of Examples 1-P and 2-P was equivalent to that of Examples 1 and 2. From this result, it was confirmed that, even if the compositions of uncoated tablets are different, if the shapes of the uncoated tablets are the same and the coating of the present invention is applied, the same level of slipping property can be obtained.

Furthermore, slight gelation of the coated mini-tablets obtained in Reference Example 2 was observed as a result of addition of water. However, the maximum stress (62.7 g) and the area under the stress-distance curve (786 g•mm) of Reference Example 2 were both greater than those of the Examples of the present invention. Hence, it was assumed that the tablets had a poor slipping property on the mucosa and could be hardly swallowed.

[0075]
Evaluation of Test Example 2 (evaluation of bitter taste-masking)

The concentration of levofloxacin hydrate in the discharged liquid obtained after dropwise addition of water for 2 minutes was significantly higher in both Comparative Example 1 (uncoated tablets A) and Comparative Example 2 (uncoated tablets A subjected to common film coating) than in other examples. The concentration levofloxacin hydrate in Comparative Example 2 was lower than that of Comparative Example 1, but its masking effect was considered to be insufficient. In Examples 1-4 and 1-1 to 1-5 in which a carboxy vinyl polymer, polyvalent metal salts and xanthan gum were used, the concentration of the eluted solution after dropwise addition of water for 2 minutes was 3 μg/mL or less, and thus, the tablets are considered to have a high bitter taste-masking effect. From these results, it became clear that a combination of a carboxy vinyl polymer with xanthan gum achieves a high bitter taste-masking effect.

Further, in Example 5 and the subsequent examples, the amount of the over-coating solution was decreased for the studies. In these examples, the concentration of the eluted solution after dropwise addition of water for 30 seconds was

found to be 50 μg/mL or less. In Examples 5 to 9-2 in which levofloxacin hydrate-containing uncoated tablets C were subjected to over-coating, the concentration of the drug in the discharged solution was low, and it was about one-seventh to one-third of that of Comparative Example 5 (uncoated tablets C subjected to only seal coating). In Example 12 in which valacyclovir hydrochloride-containing uncoated tablets D were subjected to over-coating, the concentration of the drug in the discharged solution was lower (about 1/360) than that of Comparative Example 6 (uncoated tablets D subjected to only seal coating). Thus, it was confirmed that each over-coating operation provided a practically sufficient masking effect.

The concentrations of the drugs in the discharged solutions in Comparative Examples 2 and 5, in which uncoated tablets were subjected to only seal coating, were lower than Comparative Examples 1 and 4 (about 1/15 and about 1/20, respectively) that were the uncoated tablets of Comparative Examples 2 and 5 before subjecting to seal coating. From these results, it was supposed that a combination of the over-coating of the present invention with the seal coating of the present invention exhibited the effect of enhancing the unpleasant taste-masking effect upon administration and/or the effect of preventing ingredients contained in a drug core, such as an unpleasant taste ingredient, from moving to an over-coating layer during preservation, so as to prevent the incompatibility between the ingredients of the drug core ingredient and the ingredients of the over-coating layer or attenuation of the masking effect.

[0076]

Evaluation results of Test Example 3

The dissolution rate of the drug was extremely high in Comparative Examples 1 and 2. In Examples 1 to 4 in which HPMC and sugar alcohol were used, and in Example 2-1 in which Carbopol was not used, but xanthan gum, HPMC and erythritol were used, the dissolution rate was 80% or more for 30 minutes, and thus, they exhibited an excellent dissolution property. In Example 2-2 in which only Carbopol was used as a thickener, an dissolution rate of 70% or more could be obtained. From the results of Example 1 and Example 1-4, it was found that the content of Carbopol in the film that was 12% did not cause a delay in dissolution, but that if the content reached 16% by mass, dissolution was slightly delayed.

From the results of Examples 5 to 7, it was found that even if erythritol is replaced with maltitol or trehalose, an excellent dissolution property is exhibited in any case.

In Example 5 and the subsequent examples, the amount of the over-coating solution was decreased for the studies. In all cases in Example 5 and the subsequent examples, high dissolution rates were exhibited, and neither difference in the compositions of uncoated tablets nor influence by seal coating was found.

[0077]

As stated above, in the case of the oral composition of the present invention, the surface layer of a tablet promptly turns into a gel in the presence of a small amount of water or saliva, resulting in good cohesiveness of tablets. Thus, the tablets can easily slip on the mucosa and can be easily swallowed. In addition, the gelated coating film suppresses short-term drug dissolution before it is swallowed, and thus it exhibits an unpleasant taste-masking effect. After it has been swallowed, the film thereof is rapidly disintegrated, so that it does not affect drug efflux.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A coating composition comprising:

a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate;

a polyvalent metal compound;

at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate; and

hydroxypropylmethylcellulose.

2. The coating composition according to claim 1, which further comprises sugar or sugar alcohol having a solubility at 20°C of 30 or more.

3. The coating composition according to claim 2, wherein the sugar or sugar alcohol is selected from the group consisting of erythritol, maltitol and trehalose.

4. The coating composition according to any one of claims 1-3, wherein the content of the first thickener is 3% to 15% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the second thickener is 10% to 40% by mass, and the content of the hydroxypropylmethylcellulose is 5% to 35% by mass.

5. The coating composition according to any one of claims 2-4, wherein the mixing ratio between the hydroxypropylmethylcellulose and the sugar or sugar alcohol is 1:1 to 1:4.

6. A coating composition comprising:

a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate;

a polyvalent metal compound;

at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate;

hydroxypropylmethylcellulose; and

at least one type of a sugar or sugar alcohol selected from the group consisting of erythritol, maltitol and trehalose,

wherein the content of the first thickener is 3% to 15% by mass (% by mass based on the total mass of all ingredients excluding a solvent; the same applies below), the content of the second thickener is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

7. The coating composition according to any one of claims 1-6, wherein the content of the polyvalent metal compound is 5% to 15% by mass based on the content of the first thickener.

8. The coating composition according to any one of claims 1-7, wherein it comprises alcohol as a solvent.

9. The coating composition according to any one of claims 1-8, wherein the first thickener is a carboxyvinyl polymer or sodium alginate that is not substantially crosslinked by polyvalent metal ions.

10. An oral composition having:

a drug core containing an active ingredient; and

over the drug core,

a coating comprising

a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate,

a polyvalent metal compound,

at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate, and

hydroxypropylmethylcellulose.

11. The oral composition according to claim 10, which further comprises sugar or sugar alcohol having a solubility at 20°C of 30 or more.

12. The oral composition according to claim 11, wherein the sugar or sugar alcohol is selected from the group consisting of erythritol, maltitol and trehalose.

13. The oral composition according to any one of claims 10-12, wherein the content of the first thickener is 3% to 15% by mass (% by mass based on the total mass of all ingredients in the coating; the same applies below), the content of the second thickener is 10% to 40% by mass, and the content of the hydroxypropylmethylcellulose is 5% to 35% by mass.

14. The oral composition according to any one of claims 11-13, wherein the mixing ratio between the hydroxypropylmethylcellulose and the sugar or sugar alcohol is 1:1 to 1:4.

15. An oral composition having:

a drug core containing an active ingredient; and

over the drug core,

a coating comprising

a first thickener selected from the group consisting of a carboxyvinyl polymer and sodium alginate,

a polyvalent metal compound,

at least one type of a second thickener selected from the group consisting of xanthan gum, guar gum and sodium alginate, with the proviso that when the first thickener is sodium alginate the second thickener is not sodium alginate,

hydroxypropylmethylcellulose, and

at least one type of a sugar or sugar alcohol selected from the group consisting of erythritol, maltitol and trehalose,

wherein the content of the first thickener is 3% to 15% by mass (% by mass based on the total mass of all ingredients in the coating; the same applies below), the content of the second thickener is 10% to 40% by mass, the content of the hydroxypropylmethylcellulose is 5% to 35% by mass, and the content of the sugar or sugar alcohol is 10% to 50% by mass.

16. The oral composition according to any one of claims 10-15, wherein the content of the polyvalent metal compound is 5% to 15% by mass based on the content of the first thickener.

17. The oral composition according to any one of claims 10-16, wherein the first thickener is a carboxyvinyl polymer or sodium alginate that is not substantially crosslinked by polyvalent metal ions.

18. The oral composition according to any one of claims 10-17, wherein the drug core is a tablet core containing an active ingredient.

19. A composition according to any one of claims 1, 6, 10 and 15, substantially as hereinbefore described, with reference to any one of the examples; excluding comparative examples.