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(54) ORAL PREPARATIONS WITH FAVORABLE DISINTEGRATION CHARACTERISTICS

(57) The present invention provides oral preparations with good disintegration containing a slightly water-soluble active ingredient, which comprise a mixture of a solid formed product (e.g. a granule) and a second disintegrant wherein said solid formed product comprises a slightly water-soluble active ingredient, a first disintegrant and a water-soluble excipient which is formed by using a water-soluble polymer binder; or comprises a solid formed product prepared from a slightly water-soluble active ingredient, a disintegrant and a sugar alcohol by using a water-soluble polymer binder. When orally administered, these oral preparations exhibit excellent dissolution characteristics of the active ingredient in the digestive tract, and further, these preparations can show equivalent dissolution profile even at different amounts of the active ingredient, and thus enable the selection of the most suitable medicament for each patient, which makes these preparations highly useful in the clinical field.

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Description

TECHNICAL FIELD

[0001] The present invention relates to an oral preparation with good disintegration, which comprises a slightly water-soluble component as an active ingredient. More particularly, the present invention relates to pharmaceutical preparations for oral administration, especially tablets, containing a slightly water-soluble component as an active ingredient, which have equivalent dissolution profile of the active ingredient even at different contents of the active ingredient. Further, the present invention relates to a pharmaceutical preparation for oral administration, especially tablets, containing a slightly water-soluble component as an active ingredient, which show a rapid dissolution of the active ingredient even though the amount of the active ingredient therein is varied in the range of several mg to several tens of mg, for example, in the range of 5 mg to 20 mg or in the range of 5 mg to 40 mg, and further these preparations show equivalent dissolution profile in the same ratio of components.

BACKGROUND ART

[0002] In order to secure the bioequivalence when a pharmaceutical preparation having different amounts is administered at the same dose, there was issued "Guideline for Bioequivalence testing of Oral Solid Dosage Forms with Different Content" (Notification No. 64 of the Evaluation and Licensing Division, PMSD dated February 14, 2000), by which it has been required that a pharmaceutical preparation having different amounts should be equivalent in dissolution profile in test solutions such as buffers of pH 1.2, 3.0 to 5.0 and 6.8 (which correspond to the pH values of the stomach, the intestine and the oral cavity, respectively), water, and saline solution, etc.

[0003] For medicaments showing a good solubility in water, it is easy to prepare such a preparation having equivalent dissolution profile even in different amounts due to their water solubility. On the contrary, for medicaments containing as an active ingredient a slightly water-soluble compound, it has been difficult to prepare a pharmaceutical preparation having equivalent dissolution profile even in different amounts, because such an active ingredient shows low affinity to water, etc.

DISCLOSURE OF INVENTION

[0004] An object of the present invention is to provide a pharmaceutical preparation for oral administration containing as an active ingredient a slightly water-soluble compound, which can rapidly release the active ingredient therefrom and can show equivalent dissolution profile even in different amounts of said active ingredient. Especially, the object of the present invention is to provide a pharmaceutical preparation for oral administration with increased amount of the active ingredient, which can show equivalent dissolution profile to that when multiple tablets having a low content of the active ingredient are administered, and can release a slightly water-soluble active ingredient therefrom at a desired concentration.

[0005] The present inventor has intensively studied in order to achieve the above objects, and has found that pharmaceutical preparations prepared by the following processes showed a good disintegration, and can show a rapid dissolution profile regardless of the contents of the active ingredient, by releasing the active ingredient therefrom at a desired concentration, and further can show equivalent dissolution profile, and found that such pharmaceutical preparations meet the desired purposes, and finally has accomplished the present invention.

(1) A process of making a preparation comprising a step of preparing a solid formed product (e.g., granule) from a slightly water-soluble active ingredient and a mixture of a first disintegrant and a water-soluble excipient with a water-soluble polymer binder, and a step of mixing the resultant with a second disintegrant.

(2) A process of making a preparation comprising a step of preparing a solid formed product from a mixture of a slightly water-soluble active ingredient, a first disintegrant and a water-soluble excipient with a water-soluble polymer binder, and a step of mixing the resultant with a second disintegrant.

(3) A process of making a preparation comprising a step of preparing a solid formed product from a slightly water-soluble active ingredient and a mixture of a first disintegrant and a sugar alcohol with a water-soluble polymer binder.

(4) A process of making a preparation comprising a step of preparing a solid formed product from a mixture of a slightly water-soluble active ingredient, a first disintegrant and a sugar alcohol with a water-soluble polymer binder.

BEST MODE FOR CARRYING OUT THE INVENTION

[0006] The present invention will be explained in more detail hereinafter.

[0007] According to the present invention, oral preparations in the following various embodiments are provided.

(1) An oral preparation with good disintegration, which comprises a mixture of a granule and a second disintegrant, said granule being obtained by granulating with spraying an aqueous suspension containing a slightly water-soluble active ingredient and a water-soluble polymer binder to a mixture of a water-soluble excipient and a first disintegrant.

(2) The oral preparation with good disintegration according to the above (1), which is in the form of a tablet.

(3) An oral preparation with good disintegration, which comprises a mixture of an active ingredient-containing layered composite and a second disintegrant, said layered composite being made by setting a slightly water-soluble active ingredient-containing layer onto an internal layer consisting of a water-soluble excipient and a first disintegrant via a layer of a water-soluble polymer binder.

(4) An oral preparation with good disintegration, which comprises a mixture of a granule and a second disintegrant, said granule being obtained by granulating with spraying an aqueous solution of a water-soluble polymer binder to a mixture of a slightly water-soluble active ingredient, a water-soluble excipient and a first disintegrant.

(5) The oral preparation with good disintegration according to the above (4), which is in the form of a tablet.

(6) An oral preparation with good disintegration, which comprises a mixture of an active ingredient-containing granule and a second disintegrant, said granule being obtained by combining a slightly water-soluble medicament, a water-soluble excipient and a first disintegrant each other by a water-soluble polymer binder.

(7) An oral preparation with good disintegration, which comprises a granule obtained by granulating with spraying an aqueous suspension containing a slightly water-soluble active ingredient and a water-soluble polymer binder to a mixture of a sugar alcohol and a first disintegrant.

(8) The oral preparation with good disintegration according to the above (7), which is in the form of a tablet.

(9) An oral preparation with good disintegration, which comprises an active ingredient-containing layered composite, said layered composite being made by setting a slightly water-soluble active ingredient-containing layer onto the internal layer consisting of a sugar alcohol and a first disintegrant via a layer of a water-soluble polymer binder.

(10) An oral preparation with good disintegration, which comprises a granule obtained by granulating with spraying an aqueous solution of a water-soluble polymer binder to a mixture of a slightly water-soluble active ingredient, a sugar alcohol and a first disintegrant.

(11) The oral preparation with good disintegration according to the above (10), which is in the form of a tablet.

(12) An oral preparation with good disintegration, which comprises an active ingredient-containing granule, said granule being obtained by combining a slightly water-soluble medicament, a sugar alcohol and a first disintegrant each other by a water-soluble polymer binder.

(13) The oral preparation with good disintegration according to any one of the above (1) to (12), wherein the slightly water-soluble active ingredient has a solubility of not more than 0.1 mg/ml at either pH 1.0, 3.0 to 5.0, or 6.8.

(14) The oral preparation with good disintegration according to any one of the above (1) to (12), wherein the average particle diameter of the slightly water-soluble active ingredient is in the range of about 0.5 to 5 μm.

(15) The oral preparation with good disintegration according to any one of the above (1), (2), (3), (4), (5) and (6), wherein the water-soluble excipient is a saccharide or a sugar alcohol.

(16) The oral preparation with good disintegration according to any one of the above (1), (2), (3), (4), (5) and (6), wherein the water-soluble excipient is a sugar alcohol.

(17) The oral preparation with good disintegration according to any one of the above (1), (2), (3), (4), (5) and (6), wherein the water-soluble excipient is a saccharide and a sugar alcohol.

(18) The oral preparation with good disintegration according to any one of the above (1), (2), (3), (4), (5) and (6), wherein the water-soluble excipient is one or more members selected from lactose, sucrose, fructo-oligosaccharide, paratinose, glucose, maltose, hydrogenated maltose, maltotetraose, fructose, isomerized lactose, lactitol, honey sugar, D-sorbitol, D-mannitol, maltitol, erythritol, and xylitol.

(19) The oral preparation with good disintegration according to any one of the above (1), (2), (3), (4), (5) and (6), wherein the water-soluble excipient is one or more members selected from D-sorbitol, D-mannitol, erythritol, and xylitol.

(20) The oral preparation with good disintegration according to any one of the above (7), (8), (9), (10), (11) and (12), wherein the sugar alcohol is one or more members selected from D-sorbitol, D-mannitol, erythritol, and xylitol.

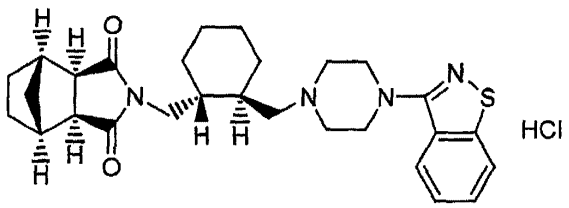
(21) The oral preparation with good disintegration according to any one of the above (1), (2), (3), (4), (5) and (6), which comprises one or more water-soluble excipients selected from D-sorbitol, D-mannitol, erythritol, and xylitol, and further comprises one or more water-soluble excipients selected from lactose, sucrose, fructo-oligosaccharide, paratinose, glucose, maltose, hydrogenated maltose, maltotetraose, fructose, lactulose, lactitol and honey sugar.

(22) The oral preparation with good disintegration according to any one of the above (7), (8), (9), (10), (11) and (12), which comprises one or more sugar alcohols selected from D-sorbitol, D-mannitol, erythritol, and xylitol, and further comprises one or more water-soluble excipients selected from lactose, sucrose, fructo-oligo-saccharide,

paratinose, glucose, maltose, hydrogenated maltose, maltotetraose, fructose, lactulose, lactitol and honey sugar.
(23) The oral preparation with good disintegration according to any one of the above (1), (2), (3), (4), (5) and (6), wherein the water-soluble excipient has an average particle diameter in the range of about 10 μm to 150 μm.
(24) The oral preparation with good disintegration according to any one of the above (7), (8), (9), (10), (11) and (12), wherein the sugar alcohol has an average particle diameter in the range of about 10 μm to 150 μm.
(25) The oral preparation with good disintegration according to any one of the above (1) to (12), wherein the first disintegrant is selected from corn starch, microcrystalline cellulose, low substituted hydroxypropylcellulose, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, carboxymethyl starch sodium and crospovidone.
(26) The oral preparation with good disintegration according to any one of the above (1) to (12), wherein the water-soluble polymer binder is selected from hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, agar, starch, dextrin and gelatin.
(27) The oral preparation with good disintegration according to any one of the above (1), (2), (3), (4), (5) and (6), wherein the second disintegrant is one or more members selected from lactose, anhydrous dibasic calcium phosphate, dibasic calcium phosphate, microcrystalline cellulose, low substituted hydroxypropylcellulose, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, carboxymethyl starch sodium and crosspovidone.
(28) The oral preparation with good disintegration according to any one of the above (2), (5), (8) and (11), wherein the compression hardness is in the range of about 50 to 200 N.
(29) The oral preparation with good disintegration according to the above (1) or (2), wherein the second disintegrant is contained in a ratio of 20 to 1200 w/w % (by weight) to the weight of the granule obtained by granulating with spraying an aqueous suspension containing a slightly water-soluble active ingredient and a water-soluble polymer binder to a mixture of an excipient and a first disintegrant.
(30) The oral preparation with good disintegration according to the above (4) or (5), wherein the second disintegrant is contained in a ratio of 20 to 1200 w/w (by weight) to the weight of the granule obtained by granulating with spraying an aqueous solution of a water-soluble polymer binder to a mixture of a slightly water-soluble active ingredient, an excipient and a first disintegrant.
(31) The oral preparation with good disintegration according to any one of the above (1), (2), (3), (4), (5) and (6), wherein the amount of the water-soluble excipient is in the range of about 250 to 2000 % by weight (w/w %, hereinafer the same) to the weight of the slightly water-soluble active ingredient.
(32) The oral preparation with good disintegration according to any one of the above (7), (8), (9), (10), (11) and (12), wherein the amount of the sugar alcohol is in the range of about 250 to 2000 % by weight (w/w %, hereinafer the same) to the weight of the slightly water-soluble active ingredient.
(33) The oral preparation with good disintegration according to any one of the above (1) to (12), wherein the amount of the first disintegrant is in the range of about 5 to 300 % by weight to the weight of the slightly water-soluble active ingredient.
(34) The oral preparation with good disintegration according to any one of the above (1) to (12), wherein the amount of the water-soluble polymer binder is in the range of about 6 to 80 % by weight to the weight of the slightly water-soluble active ingredient.
(35) The oral preparation with good disintegration according to any one of the above (1) to (12), wherein the amount of the water-soluble polymer binder is in the range of about 1 to 10 % by weight to the total weight of said preparation.
(36) The oral preparation with good disintegration according to any one of the above (1) to (12), wherein the amount of the water-soluble polymer binder is in the range of about 1 to 5 % by weight to the total weight of said preparation.
(37) A granule, which is obtained by granulating with spraying an aqueous suspension containing a slightly water-soluble active ingredient and a water-soluble polymer binder to a mixture of a water-soluble excipient and a first disintegrant.
(38) A slightly water-soluble active ingredient-containing granule, which is obtained by adding a water-soluble polymer binder to a powdery mixture consisting of a water-soluble excipient, a first excipient and a slightly water-soluble active ingredient and combining them each other.
(39) A granule, which is obtained by granulating with spraying an aqueous suspension containing a slightly water-soluble active ingredient and a water-soluble polymer binder to a mixture of a sugar alcohol and a first disintegrant.
(40) A slightly water-soluble active ingredient-containing granule, which is obtained by adding a water-soluble polymer binder to a powdery mixture consisting of a sugar alcohol, a first disintegrant and a slightly water-soluble active ingredient and combining them each other.
(41) The oral preparation with good disintegration according to any one of the above (1) to (40), wherein the slightly water-soluble active ingredient is N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetra-methylenebutyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2.2.1]-heptanedicarboximide hydrochloride.

[0008] The "slightly water-soluble active ingredient" includes slightly soluble compounds having a low solubility in

water, especially compounds having a solubility of not more than about 0.1 mg/ml at pH 1.0, 3.0-5.0 and 6.8, these pH values corresponding to the pH values of the stomach, the intestine and the oral cavity, respectively. A concrete example thereof is N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylenebutyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2.2.1]heptanedicarboximide hydrochloride of the following formula:



(hereinafter, referred to as Compound 1) (cf. Japanese Patent No. 2800953). Compound 1 has been known to exhibit a psychotropic effect, and it is useful as an agent for treatment of schizophrenia, etc.

[0009] In addition, these slightly water-soluble active ingredients are preferably finely milled, and the average particle diameter thereof is, for example, in the range of about 0.5 to 5 μm.

[0010] The "water-soluble polymer binder" includes, for example, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, polyvinyl alcohol (partially saponificated one), pullulan, starch, dextrin, gelatin, etc., and preferable ones are hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, and polyvinyl alcohol (partially saponificated one). These water-soluble polymer binders may be used alone, or two or more thereof may be used together.

[0011] The "first disintegrant" includes, for example, corn starch, microcrystalline cellulose, low substituted hydroxypropylcellulose, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, carboxymethyl starch sodium, crosspovidone, etc. These first disintegrants may be used alone or two or more thereof may be used together. The average particle diameter of these first disintegrants is, for example, in the range of about 5 to about 75 μm, and preferable first disintegrant is ones having an average particle diameter in the range of about 5 to about 75 μm, wherein the ratio of particles having a particle diameter of more than 75 μm is not more than 5 % to the total.

[0012] The "second disintegrant" includes, for example, lactose, anhydrous dibasic calcium phosphate, dibasic calcium phosphate, microcrystalline cellulose, magnesium aluminometasilicate, synthesized hydrotalcite, synthesized aluminum silicate, low substituted hydroxypropyl cellulose, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, carboxymethyl starch sodium, crosspovidone, etc. Preferable second disintegrant is, for example, lactose, anhydrous dibasic calcium phosphate, dibasic calcium phosphate, microcrystalline cellulose, low substituted hydroxypropyl cellulose, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, carboxymethyl starch sodium, and crosspovidone. These second disintegrants may be used alone, or two or more thereof may be used together.

[0013] The average particle diameter of the second disintegrant is, for example, in the range of about 5 to about 500 μm, preferably in the range of about 30 to 350 μm.

[0014] The "water-soluble excipient" includes, for example, a sugar alcohol and a saccharide. Specific examples are saccharides such as lactose, sucrose, fructo-oligo-saccharide, paratinose, glucose, maltose, hydrogenated maltose, maltotetraose, fructose, lactulose, lactitol, honey sugar, and sugar alcohols such as D-sorbitol, D-mannitol, maltitol, erythritol, and xylitol. These water-soluble excipients may be used alone, or one or more thereof may be used together.

[0015] Even when the amount of the slightly water-soluble active ingredient is substantially changed, for example, even when it is changed within the range of 5 mg to 40 mg, the oral preparation shall show a rapid dissolution of said active ingredient as well as equivalent dissolution profile, and the water-soluble excipients preferable for preparing such oral preparation are, for example, sugar alcohols such as D-sorbitol, D-mannitol, erythritol, xylitol, etc. In these cases, a saccharide such as lactose, sucrose, fructo-oligosaccharide, paratinose, glucose, maltose, hydrogenated maltose, maltotetraose, fructose, lactulose, lactitol, honey sugar, etc. may simultaneously be contained in said oral preparation.

[0016] When orally administered, the oral preparation of the present invention can release a slightly water-soluble active ingredient rapidly and can show equivalent dissolution profile regardless of the amounts of the active ingredient therein to give a desired serum concentration thereof. The oral preparations of the present invention may include various dosage forms such as pills, granules, fine granules, tablets, capsules, etc.

[0017] The oral preparations of the present invention may be prepared by a conventional method depending on desired dosage forms. For instance, the present preparations may be prepared by the following processes.

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