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(54) **ORAL PREPARATIONS WITH FAVORABLE DISINTEGRATION CHARACTERISTICS**

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See application file for complete search history.

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(57) **ABSTRACT**

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.

11 Claims, No Drawings

ORAL PREPARATIONS WITH FAVORABLE DISINTEGRATION CHARACTERISTICS

This application is the national phase under 35 U.S.C. §371 of PCT International Application No. PCT/JP01/07983 which has an International filing date of Sep. 14, 2001, which designated the United States of America.

TECHNICAL FIELD

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

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 Feb. 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.

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

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.

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

The present invention will be explained in more detail hereinafter.

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, micro-crystalline cellulose, low substituted hydroxypropyl-cellulose, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, carboxymethyl starch sodium and crosspovidone.

(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 hydroxy-propyl-cellulose, hydroxypropylmethylcellulose, polyvinyl-pyrrolidone, 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 %, hereinafter 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 %, hereinafter 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.

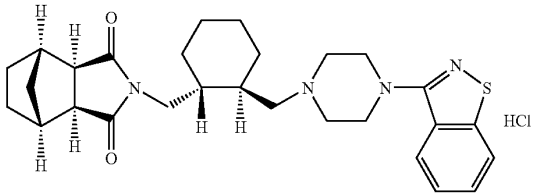
(38) A slightly water-soluble active ingredient-containing granule, which is obtained by adding a water-soluble polymer binder to a powdery mixture consisting of a water-soluble excipient, a first excipient and a slightly water-soluble active ingredient and combining them each other.

(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-tetramethylenebutyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2.2.1]heptanedicarboximide hydrochloride.

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.

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.

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 hydroxypropyl-cellulose, hydroxypropylmethylcellulose, polyvinyl-pyrrolidone, and polyvinyl alcohol (partially saponificated one). These water-soluble polymer binders may be used alone, or two or more thereof may be used together.

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.

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, cros-carmellose sodium, carboxymethyl starch sodium, cross-povidone, 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.

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.

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.

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.

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.

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.

Preparation Method 1

(1) Preparation of an aqueous solution of a water-soluble polymer binder:

A water-soluble polymer binder is dissolved in purified water, during which the temperature is, for example, in the range of about 20° C. to 90° C., preferably in the range of about 20° C. to 70° C. The amount of the water-soluble polymer binder is, for example, in the range of about 1 to 20% by weight, preferably in the range of about 2 to 8% by weight, to the weight of the purified water.

(2) Preparation of an aqueous suspension containing a water-soluble polymer binder and a slightly water-soluble active ingredient:

A slightly water-soluble active ingredient is dispersed and suspended in the aqueous water-soluble polymer binder solution obtained in the above (1), for example, at a temperature of about 20° C. to about 90° C., preferably at a temperature of about 20° C. to 40° C.

The amount of the water-soluble polymer binder is, for example, in the range of about 3 to about 200% by weight, preferably about 6 to about 80% by weight, to the weight of the slightly water-soluble active ingredient.

The slightly water-soluble active ingredient is preferably finely milled, and the average particle diameter thereof is, for example, in the range of about 0.5 to 5 μm.

(3) Mixing and granulation of the active ingredient-containing aqueous suspension with a first disintegrant:

A water-soluble excipient and a first disintegrant are charged into a fluid bed granulator, and thereto is sprayed the aqueous suspension containing a water-soluble polymer binder and a slightly water-soluble active ingredient obtained in the above (2), and the mixture is granulated.

This granulation step is carried out, for example, at a temperature for supplying air in the range of about 50° C. to 90° C., preferably about 60° C. to 80° C. The granulation is carried out, for example, for about 30 minutes to 180 minutes, preferably for about 40 minutes to 150 minutes.

The apparatus for granulation is, for example, ones classified into fluid bed granulation and roto granulation, and preferable one is a fluid bed granulator, a roto fluid bed granulator, etc.

The amount of the water-soluble excipient is, for example, in the range of about 200 to about 2000% by weight, preferably in the range of about 250 to about 1200% by weight, to the weight of the slightly water-soluble active ingredient.

The amount of the first disintegrant is in the range of about 5 to 300% by weight, preferably in the range of about 30 to 150% by weight, to the weight of the slightly water-soluble active ingredient.

(4) Drying of the granule:

The above granule containing a slightly water-soluble active ingredient and a first disintegrant is dried either under reduced pressure or under atmospheric pressure. The drying is carried out in such a manner that the loss on dry measured by infrared moisture meter is, for example, within about 3% by weight, preferably within 2% by weight.

(5) Mixing of the dried granule and a second disintegrant:

The granule containing a slightly water-soluble active ingredient and a first disintegrant dried in the above (4) is then mixed with a second disintegrant. The mixing apparatus is, for example, ones classified into diffusion mixers (tumble mixers). If necessary, after mixing with said mixer, the mixture is milled with a mill classified into impact mills. The diffusion mixers (tumble mixers) are, for example, tumble blender, V blender, double cone, bin tumbler, etc. The impact mills are, for example, a hammer conventional mill, etc.

The amount of the second disintegrant is, for example, in the range of 20 to 1200 w/w % (weight ratio) to the weight of the granule obtained by granulating with spraying the aqueous suspension of a slightly water-soluble active ingredient and a water-soluble polymer binder to a mixture of a first disintegrant and a water-soluble excipient.

(6) Blending of a lubricant:

The above mixture of the granule and the second disintegrant may be compressed without further components, but preferably compressed in admixture with a lubricant.

The lubricant may be blended by adding it into the mixture of the above (5). The mixing apparatus is, for example, ones classified into diffusion mixers (tumble mixers), such as tumble blender, V blender, double cone, bin tumbler, etc.

The lubricant is, for example, magnesium stearate, talc, hydrogenated oil, stearic acid, calcium stearate, glyceryl behenate, sodium stearylfumarate, etc.

The amount of the lubricant is, for example, in the range of 0.3 to 3% by weight, preferably in the range of about 0.5 to 1.5% by weight, to the total weight of the tablet.

(7) Compression:

The above mixture is compressed in a conventional manner to give tablets.

The compression apparatus is preferably ones classified into tablet press.

The compression hardness is, for example, in the range of about 50 to 200 N.

(8) Film Coating:

The tablets obtained above may be subjected to film coating, if necessary. The coating apparatus is ones classified into coating pans, preferably ones classified into perforated coating system.

The coating agent is, for example, a mixture of a base material (e.g., hydroxypropylmethylcellulose, hydropropylcellulose, polyvinylpyrrolidone, etc.) and a plasticizer (e.g., polyethylene glycol, propylene glycol, triacetine, triethyl cit-

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