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(54) Title: INTRAORALLY DISINTEGRATING TABLET

(57) Abrégé/Abstract:
Disclosed is an orally disintegrating tablet which masks bitterness, dissolves well, and which permanently retains good oral disintegration properties immediately following manufacture. The disclosed orally disintegrating tablet is formed by compression-molding an organic acid together with particles comprising active ingredient-containing nuclear particles covered by a layer containing water-insoluble polymers and/or enteric polymers.

ABSTRACT

Disclosed is an orally disintegrating tablet which masks bitterness, dissolves well, and which permanently retains good oral disintegration properties immediately following manufacture. The disclosed orally disintegrating tablet is formed by compression-molding an organic acid together with particles comprising active ingredient-containing nuclear particles covered by a layer containing water-insoluble polymers and/or enteric polymers.

INTRAORALLY DISINTEGRATING TABLET

[TECHNICAL FIELD]

[0001]

The present invention relates to an intraorally disintegrating tablet comprising an organic acid as a disintegration accelerator.

[BACKGROUND ART]

[0002]

Intraorally disintegrating tablets containing organic acids such as ascorbic acids and citric acids are known. Specific examples thereof include, those containing ascorbic acid as an active ingredient (Patent Documents 1-3) and those illustrating the addition of an organic acid as a dissolution agent for an active ingredient in order to ensure absorptivity (Patent Documents 4 and 5). However, none of the above documents describe or suggest contributing to a disintegrating property of intraorally disintegrating tablets. As a technique intended for the disintegrating property thereof, the inclusion of a foaming disintegrant that requires combination with a carbonate is known (Patent Document 6).

[0003]

On the other hand, the problem of intraorally disintegrating tablets is to simultaneously attain an intraorally disintegrating property, a property of masking unpleasant tastes such as bitterness derived from the active ingredient and an irritating sensation, and a dissolution property intended for the intestinal tract (a dissolution property similar to an ordinary tablet, a controlled dissolution property such as sustained release, etc.), and

investigations therefor have been carried out.

[0004]

As an example thereof, an intraorally disintegrating tablet obtained by compression molding of an active ingredient-containing core particles with an ingredient such as a disintegrant, the particles being coated with a mixture in which a water insoluble polymer such as ethyl cellulose or an enteric polymer such as a methacrylic acid copolymer has been mixed with a disintegrant such as croscarmellose sodium and/or a water permeable ingredient such as hypromellose, is known (Patent Documents 7 and 8).

[0005]

While this technique provides a favorable bitterness-masking property and intra-intestinal dissolution property, a disintegrating property immediately after preparation is poor, and thus it was found to have a problem in terms of stable supply of a high quality formulation.

[RELATED ART DOCUMENTS]

[PATENT DOCUMENTS]

[0006]

[Patent Document 1] Japanese Unexamined Patent Publication (Kokai) No. 2009-161495

[Patent Document 2] Japanese Patent No. 3884056

[Patent Document 3] Japanese Unexamined Patent Publication (Kokai) No. 2002-121133

[Patent Document 4] Japanese National Patent Publication (Kohyo) No. 2003-512402

[Patent Document 5] Japanese Unexamined Patent Publication (Kokai) No. 2002-316923

[Patent Document 6] Japanese National Patent Publication (Kokai) No. H5-500956

[Patent Document 7] Japanese National Patent Publication (Kohyo) No. 2003-504324

[Patent Document 8] Japanese Unexamined Patent Publication (Kohyo) No. 2008-214334

[SUMMARY OF INVENTION]

[PROBLEMS TO BE SOLVED BY THE INVENTION]

[0007]

An object of the present invention is to provide an intraorally disintegrating tablet that has a property of masking bitterness and the like and a good dissolution property, and that constantly retains a good intraorally disintegrating property immediately after preparation.

[MEANS FOR SOLVING THE PROBLEMS]

[0008]

In view of the above object, the present inventors conducted diligent studies and, as a result, have found that by compression molding of an active ingredient-containing core particle coated with a water insoluble polymer or an enteric polymer together with an organic acid such as ascorbic acid and citric acid to a formulation, a property of masking bitterness and the like and a good dissolution property can be obtained and good intraorally disintegrating property can be constantly retained immediately after preparation, and thereby have attained the present invention.

[0009]

That is, the present invention relates to an intraorally disintegrating tablet, in which an active ingredient-containing core particle coated with a coating layer comprising a water insoluble polymer and/or an enteric polymer has been compression molded together with an organic

acid.

[EFFECTS OF THE INVENTION]

[0010]

In accordance with the present invention, an intraorally disintegrating tablet having a property of masking bitterness and the like and a good dissolution property and retaining a good intraorally disintegrating property immediately after preparation is provided.

[DESCRIPTION OF EMBODIMENTS]

[0011]

The present invention relates to an intraorally disintegrating tablet, in which an active ingredient-containing core particle coated with a coating layer comprising a water insoluble polymer and/or an enteric polymer was compression molded together with an organic acid.

[0012]

As used herein an intraorally disintegrating tablet means a tablet capable of being taken by a patient, wherein the tablet disintegrates in the oral cavity, within 60 seconds, preferably within 30 seconds, with only saliva in the oral cavity or with a small amount of water.

[0013]

The intraorally disintegrating tablet of the present invention may preferably have a practical hardness of 29 N or more, and more preferably of 49 N or more. The preferred dissolution properties of the tablet of the invention are represented by a 60-min dissolution rate of 80% or more, as measured according to the Japanese Pharmacopoeia Paddle method at 50 revolutions per minute, using a pH 6.0 McIlvaine buffer solution.

[0014]

The core particle in the present invention may contain a fluidizer, such as light anhydrous silicic acid, talc, stearic acid or a metal salt thereof, or the like in addition to the active ingredient.

The particle diameter of the core particle in the present invention is usually 1 to 50 μm, and preferably 3 to 30 μm, as a median diameter as measured by a laser diffraction technique.

[0015]

The core particle in the present invention is coated with a coating agent containing a water insoluble polymer, an enteric polymer, or a mixture thereof. Examples of the water insoluble polymer include ethyl cellulose, aminoalkyl methacrylate copolymer RS and ethyl acrylate/methyl methacrylate copolymer, and examples of the enteric polymer include methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, hydroxypropyl methyl cellulose phthalate, and hydroxypropyl methyl cellulose acetate succinate, etc. Such a coating agent may contain, in addition to the above, a plasticizer such as macrogol, triethyl citrate, acetylated monoglyceride, triacetin, polysorbate 80, and propylene glycol, an anti-adhesive such as talc, titanium oxide, stearic acid or a metal thereof, sucrose fatty acid ester, and sodium fumarate, a disintegrant such as croscarmellose sodium, low-substituted hydroxypropyl cellulose, and crospovidone, and a dissolution rate-controlling substance such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, polyvinyl alcohol, and polyvinyl pyrrolidone.

[0016]

The methacrylic acid copolymer for use in the present invention includes, but not particularly limited to, methacrylic acid copolymer LD (for example, trade name: EUDRAGIT L30D55, Evonik), methacrylic acid copolymer L (for example, trade name: EUDRAGIT L100, Evonik), methacrylic acid copolymer S (for example, trade name: EUDRAGIT S100, Evonik), etc.

[0017]

The content (coating rate) of the coating layer containing these water insoluble polymer and enteric polymer may be usually 2-100 wt%, preferably 5-80 wt%, and more preferably 10-60 wt%, of the core particle.

[0018]

Examples of the organic acids for use in the present invention include ascorbic acids such as ascorbic acid, sodium ascorbate, potassium ascorbate and ascorbic acid 2-glucoside, citric acid and citrate (collectively referred to as "citric acids", the same hereinafter), fumaric acid and fumarate (fumaric acids), malic acid and malate (malic acids), and tartaric acid and tartrate (tartaric acids), and among them ascorbic acids and citric acids may be preferred.

The content of these organic acids may be usually 0.5-20 wt%, preferably 1-10 wt%, and more preferably 2-5 wt%, of the weight of the tablet.

[0019]

The tablet of the present invention may comprise additives that are commonly used in tablets as long as they do not specifically affect the bitterness-masking property, the enteric dissolution property, or the disintegrating property. Such additives may include, for example, excipients, binders, lubricants and flavors.

[0020]

As an intraorally disintegrating tablet of the present invention, one prepared by compression molding a particle in which an active ingredient-containing core particle is coated with a layer containing a water insoluble polymer and/or an enteric polymer and a granule in which a disintegrant-containing particle is coated with a disintegrant together with an organic acid, may be particularly preferred.

[0021]

The active ingredient in the tablet of the present invention include, but not particularly limited to, for example 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid (hereinafter referred to as "Compound I").

[0022]

The intraorally disintegrating tablet of the present invention can be produced without difficulty using a common production equipment or slighly modified production equipment. For example, it can be produced by preparing a granule in which an active ingredient is coated with a coating layer containing a water insoluble polymer and/or an enteric polymer and then by compression molding it together with particles of ascorbic acids or citric acids and one or more pharmaceutically acceptable additives.

EXAMPLES

[0023]

[Example 1]

(Ascorbic acid is present outside the granule)

After 15.1 g of polysorbate 80 (Nikko Chemicals Co., Ltd.) was added to 522.8 g of purified water, and mixed, 35.3 g of talc (Nikko Pharmaceutical Co., Ltd.) and 12.6 g

of croscarmellose sodium (FMC) were added thereto, and then sufficiently stirred (a first solution). Separately from this, a solution prepared by dissolving 1.4 g of sodium hydroxide (Wako Pure Chemical Industries, Ltd.) in 427 g of purified water was added to 380.3 g of methacrylic acid copolymer LD (trade name: EUDRAGIT L30D55, Evonik), and stirred (a second solution). The second solution was added to the first solution and suspended, and sieved to prepare a coating dispersion.

Drug-containing particles were obtained by charging a microparticle coating/granulating apparatus (POWREX CORPORATION, MP-01SFP) with 300 g of Compound I and 15 g of light anhydrous silicic acid (Freund Corporation), and the resulting mixture was sprayed with the above coating dispersion.

Granules were obtained by charging a fluidized bed granulator (POWREX CORPORATION, MP-01) with 870 g of D-mannitol (TOWAKASEI KOGYO, trade name: Mannit P), 40 g of light anhydrous silicic acid (Freund Corporation), and 45 g of crospovidone (ISP, trade name: Polyplasdone XL-10), and the resulting mixture was sprayed with 144 g of purified water. Disintegrant-coated granules were prepared by charging 45 g of crospovidone to powder-coat the above granules.

After 36.2 g of the drug-containing particles, 3.0 g of ascorbic acid (Takeda Pharmaceutical Company Limited), and 2.3 g of calcium stearate (NOF CORPORATION) were added to 108.5 g of the disintegrant-coated granules and mixed together, the resulting mixture was subjected to compression molding with a rotary tableting machine (HATA IRON WORKDS Co., Ltd., HT-AP6SS-U) to form tablets. The molding condition was a tablet weight of 250 mg, and the tableting

was performed using a ϕ8 mm flat punch with a cleavage line to give a hardness of about 78.5 N.

[0024]

[Example 2]

(Citric acid is present outside the granule)

Tablets were formed in the same manner as in Example 1, except that ascorbic acid was replaced with citric acid.

[0025]

[Example 3]

(Sodium ascorbate is present outside the granule)

Tablets were formed in the same manner as in Example 1, except that ascorbic acid was replaced with sodium ascorbate.

[0026]

[Example 4]

(Ascorbic acid 2-glucoside is present outside the granule)

Tablets were formed in the same manner as in Example 1, except that ascorbic acid was replaced with ascorbic acid 2-glucoside.

[0027]

[Comparative Example]

(Ascorbic acid, citric acid, sodium ascorbate, or ascorbic acid 2-glucoside are not present outside the granule)

After 15.1 g of polysorbate 80 (Nikko Chemicals Co., Ltd.) was added to 522.8 g of purified water and mixed, 35.3 g of talc (Nikko Pharmaceutical Co., Ltd.) and 12.6 g of croscarmellose sodium (FMC) were added thereto, and then sufficiently stirred (a first solution). Separately from this, a solution prepared by dissolving 1.4 g of sodium hydroxide (Wako Pure Chemical Industries, Ltd.) in 427 g of purified water was added to 380.3 g of methacrylic acid copolymer LD (trade name: EUDRAGIT L30D55, Evonik), and

stirred (a second solution). The second solution was added to the first solution and suspended, and sieved to prepare a coating dispersion.

Compound 1-containing particles were obtained by spraying the above coating dispersion to Compound I and light anhydrous silicic acid in the same manner as in the Examples. Also, disintegrant-coated granules were prepared in the same manner as in the Examples.

After 35.3 g of the drug-containing particles and 2.3 g of calcium stearate (NOF CORPORATION) were added to 112.4 g of the disintegrant-coated granules and mixed together, the mixture was subjected to compression molding in the same molding manner as in the Examples with a rotary tableting machine (HATA IRON WORKDS Co., Ltd., HT-AP6SS-U) to form tablets.

[0028]

[Test Example]

Oral disintegration time and masking properties were assessed for the tablets of Examples 1 to 4 and Comparative Example, immediately after preparation. The assessment was performed by two healthy males. That is, the tablets were placed on their tongues and allowed to disintegrate, and the properties of masking the irritation of a base component were rated on the following criteria.

0: Having a clear masking effect and causing no irritation.

1: Having a masking effect and causing little irritation

2: Having a masking effect but causing irritation

3: Having a weak masking effect and causing strong irritation (tolerable)

4: Having no masking effect and causing strong

irritation (intolerable)

The results are shown in Table 1.

[0029]

[Table 1]

	Oral disintegration time (sec)	Masking property
Example 1	18	1
Example 2	27	1
Example 3	35	1
Example 4	26	1
Comparative Example	43	2

[0030]

Although Comparative Example is a formulation in which a disintegrant was added, the disintegrating property slowed markedly and the masking property also decreased. It can be seen, however, that in Examples 1 to 4, the addition of an organic acid resulted in improvement of the disintegrating property and the masking property.

[INDUSTRIAL APPLICABILITY]

[0031]

The present invention is used in the preparation of intraorally disintegrating tablets.

CLAIMS:

1. An intraorally disintegrating tablet, in which

(i) an active ingredient-containing core particle coated with a layer comprising a water insoluble polymer and/or an enteric polymer, and a disintegrant; and

(ii) a granule obtained by coating a disintegrant-containing particle with a disintegrant,

have been compression molded together with an organic acid.

2. The tablet of claim 1, wherein the content of the organic acid is 1 to 10 wt%.

3. The tablet of claim 1 or 2, wherein the organic acid is ascorbic acids and/or citric acids.

4. The tablet of any one of claims 1 to 3, wherein the water insoluble polymer and/or the enteric polymer is a methacrylic acid copolymer.

5. The tablet of any one of claims 1 to 3, wherein the water insoluble polymer and/or the enteric polymer is ethyl cellulose.