DESCRIPTION

Title of Invention: TABLET HAVING HIGH CONTENT OF ACOTIAMIDE OR SALT THEREOF

Technical Field

[0001]

The present invention relates to a tablet having a high content of acotiamide or a salt thereof.

Background Art

[0002]

Acotiamide is chemically named N-[2-[Bis(1-methylethyl)amino]ethyl]-2-[(2-hydroxy-4,5-dimethoxybenzoyl)amino]thiazole-4-carboxamide, and has the molecular formula $C_{21}H_{30}N_4O_5S$. Acotiamide is known to ameliorate a gastrointestinal motility disorder by markedly enhancing the gastrointestinal motility (Patent Literature 1), and a hydrochloride hydrate thereof has been commercially available as a therapeutic agent for functional dyspepsia.

[0003]

Acofide (registered trademark) Tablets 100 mg containing acotiamide hydrochloride hydrate are tablets having a total weight of 257 mg that contain, in addition to 100 mg of acotiamide hydrochloride hydrate, lactose hydrate, crystalline cellulose, low substituted

hydroxypropylcellulose, hydroxypropylcellulose, light anhydrous silicic acid, magnesium stearate, hypromellose, titanium oxide, and carnauba wax. In a treatment of the functional dyspepsia described above, 100 mg of acotiamide is administered three times per day before meals (Non Patent Literature 1).

[0004]

As a technique for reducing a size of a tablet containing acotiamide or a salt thereof, a technique has been reported in which a water-insoluble first filler such as calcium sulfate is added to acotiamide hydrochloride hydrate and the mixture is wet-granulated, followed by drying, then a second filler such as pregelatinized starch and a disintegrant such as crosslinked carboxymethylcellulose or low substituted hydroxypropylcellulose are added to the thus obtained granulated material, and then the mixture is tableted, thereby producing a tablet having a high content of acotiamide hydrochloride (Patent Literature 2).

[0005]

In general, a tablet having a high content of an active ingredient has a limitation in terms of a blending amount of an additive which can be incorporated during formulation, and thus such a tablet is difficult to mold, and is likely to undergo tableting failure such as sticking and capping. As a remedial measure against the tableting failure in a preparation having a high content

of taurine, a technique has been reported in which a finely pulverized taurine powder is coated with a water-soluble polymer on the powder surface thereof and then compression-molded (Patent Literature 3).

Citation List

Patent Literature

[0006]

Patent Literature 1: WO 1996/36619

Patent Literature 2: CN-A-105769784

Patent Literature 3: JP-A-H11-060476

Non Patent Literature

[0007]

Non Patent Literature 1: Acofide Tablets 100 mg Interview Form

Non Patent Literature 2: Res. Rep. Urol. 2015; 7: 81-83

Non Patent Literature 3: Res. Rep. Urol. 2017; 9: 141-143

Non Patent Literature 4: Int. J. Urol. 2019; 26(8): 848-849

Non Patent Literature 5: The Journal of Japanese Continence Society. 2022; 33(1): 224

Summary of Invention

Technical Problem

[0008]

The tablet containing acotiamide or a salt thereof described in Patent Literature 2 has a reduced total weight, which means achievement of the size reduction of the tablet. However, since the size of the tablet is reduced, a content of the active ingredient per tablet increases, and as a result, a problem such as a decrease in storage stability of the tablet has been caused.

Accordingly, an object of the present invention is to provide a tablet containing acotiamide or a salt thereof at a high concentration, having not only a good dissolution property but also good storage stability, and being suitable for continuous tableting.

Solution to Problem

[0009]

Thus, the present inventors have made extensive studies in order to solve the problem described above, and as a result, found that, by obtaining a granulated material containing (A) acotiamide or a salt thereof, (B) pregelatinized starch, and (C) a disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate, and compression molding the granulated material, it is possible to obtain a tablet containing the component (A) acotiamide or a salt thereof at a high concentration of 65% by mass or more and 91% by mass or less in an uncoated tablet. The present inventors also found that

such a tablet does not only have a good dissolution property but also can maintain the dissolution property and further maintain a tablet hardness even after it is stored under a high humidity condition, and completed the present invention. The present inventors further found that, by adjusting the moisture content of the granulated material and the tablet within an appropriate range, uniformity of distribution of the active ingredient in the resulting tablet is enhanced, the resulting tablet has a good dissolution property, and reduction in hardness after storage under a high humidity condition is suppressed.

[0010]

In other words, the present invention provides the following [1] to [18].

[1] A tablet, comprising a granulated material which contains (A) acotiamide or a salt thereof, (B) pregelatinized starch, and (C) a disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate, wherein the component (A) is contained in an amount of 65% by mass or more and 91% by mass or less in an uncoated tablet.

[2] The tablet according to [1], wherein the granulated material is a wet-granulated material.

[3] The tablet according to [1] or [2], wherein a content of the component (B) is 2% by mass or more and 10% by mass or less in the uncoated tablet.

[4] The tablet according to any one of [1] to [3], wherein a content of the component (C) is 5% by mass or more and 20% by mass or less in the uncoated tablet.

[5] The tablet according to any one of [1] to [4], wherein a total content of the component (B) and the component (C) is 8% by mass or more in the uncoated tablet.

[6] The tablet according to any one of [1] to [5], wherein the content of the component (B) is 2% by mass or more and 8% by mass or less in the uncoated tablet.

[7] The tablet according to any one of [1] to [6], wherein the content of the component (C) is 5% by mass or more and 15% by mass or less in the uncoated tablet.

[8] The tablet according to any one of [1] to [7], wherein the total content of the component (B) and the component (C) is 8% by mass or more and 25% by mass or less in the uncoated tablet.

[9] The tablet according to any one of [1] to [8], wherein the content of the component (B) is 3% by mass or more and 8% by mass or less in the uncoated tablet.

[10] The tablet according to any one of [1] to [9], wherein the total content of the component (B) and the component (C) is 8% by mass or more and 22% by mass or less in the uncoated tablet.

[11] A method for producing a tablet, comprising compression molding a wet-granulated material containing (A) acotiamide or a salt thereof, (B) pregelatinized starch, and (C) a disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate, wherein the tablet contains the component (A) in an amount of 65% by mass or more and 91% by mass or less in an uncoated tablet.

[12] A tablet, comprising a wet-granulated material which contains (D) an active ingredient, (B) pregelatinized starch, and (C) a disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate, wherein a moisture content of a dried powder of the wet-granulated material is 4.0% or more and 11.0% or less.

[13] The tablet according to [12], wherein the moisture content of the dried powder of the wet-granulated material is 4.0% or more and 9.0% or less.

[14] The tablet according to [12] or [13], wherein a moisture content of the tablet is 4.0% or more and 13.0% or less.

[15] The tablet according to [12] or [13], wherein the moisture content of the tablet is 4.0% or more and 11.0% or less.

[16] The tablet according to any one of [12] to [15], wherein (D) the active ingredient is acotiamide or a salt thereof.

[17] The tablet according to any one of [12] to [16], wherein a ratio of a water-holding capacity of the component (B) to that of the component (A) in the tablet is 0.07 or more and 2.4 or less.
[18] The tablet according to any one of [12] to [17], wherein the ratio of a water-holding capacity of the component (B) to that of the component (A) in the tablet is 0.15 or more and 2.0 or less.

Advantageous Effects of Invention

[0011]

The tablet containing acotiamide or a salt thereof according to the present invention is a table containing acotiamide or a salt thereof at a high concentration of 65% by mass or more and 91% by mass or less in the uncoated tablet, and nevertheless does not only have a good dissolution property of the acotiamide or a salt thereof but also maintains the dissolution property and further maintains a tablet hardness even after it is stored under a high humidity condition. Therefore, the tablet of the present invention is useful as a tablet which can reduce the total weight per tablet and which has excellent ease of use even when a dose per administration is increased.

Furthermore, by adjusting the moisture content of the granulated material and the tablet within an appropriate range, the uniformity of distribution of the

active ingredient in the resulting tablet is enhanced, the resulting tablet has a good dissolution property, and reduction in hardness after storage under a high humidity condition is suppressed. It should be noted that, although the tablet according to the present invention has a high drug content, it does not undergo tableting failure such as lamination and capping during the compression molding of the tablet, and the tablet remains stable even in a process of high-speed continuous tableting, and therefore the industrial production efficiency is improved.

Brief Description of Drawings

[0012]

Figure 1 is a diagram illustrating a relationship between a composition ratio of sulfur element (acotiamide hydrochloride) and a color.

Figure 2 is a diagram illustrating uniformity of distribution of acotiamide hydrochloride in tablets of Example 2, Example 4, Comparative Example 2, and Comparative Example 8.

Figure 3 is a diagram illustrating uniformity of distribution of acotiamide hydrochloride in tablets of Comparative Example 10 and Comparative Example 11.

Description of Embodiments

[0013]

The tablet containing acotiamide or a salt thereof according to the present invention is a tablet in which a content of the acotiamide or the salt thereof in an uncoated tablet is as high as 65% by mass or more and 91% by mass or less.

One aspect of the present invention is a tablet containing a granulated material which contains (A) acotiamide or a salt thereof, (B) pregelatinized starch, and (C) a disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate, wherein the component (A) is contained in an amount of 65% by mass or more and 91% by mass or less in an uncoated tablet.

[0014]

Acotiamide is chemically named N-[2-[Bis(1-methylethyl)amino]ethyl]-2-[(2-hydroxy-4,5-dimethoxybenzoyl)amino]thiazole-4-carboxamide, and has the molecular formula $C_{21}H_{30}N_4O_5S$. Acotiamide is known to ameliorate a gastrointestinal motility disorder by markedly enhancing the gastrointestinal motility (Patent Literature 1), and a hydrochloride hydrate thereof has been commercially available as a therapeutic agent for functional dyspepsia. More specifically, the indications and the effects of the therapeutic agent for functional dyspepsia containing acotiamide are postprandial fullness, upper abdominal bloating, and early satiety in functional dyspepsia, and regarding the dosage and

administration thereof, 100 mg of acotiamide hydrochloride hydrate per administration is orally administered to an adult three times per day before meals.

[0015]

It has been reported that acotiamide or a salt thereof is effective for urination disorders in a test using underactive bladder model rats and in a pilot study in underactive bladder patients when used in combination with an α1 receptor blocking agent (Non Patent Literatures 2 to 5). Furthermore, when acotiamide or a salt thereof was administered at a high dose far exceeding the dose exhibiting an effect to improve the gastrointestinal motility and a detrusor muscle contraction pressure, a urine flow rate, and an urethral pressure were examined, it was found that, unlike existing cholinergic agonists, acotiamide or a salt thereof increases a bladder contraction pressure during urination and a maximum contraction pressure during urination at a dose higher than the dose for treating functional dyspepsia, and does not affect the urethral pressure at that dose, and is therefore useful as a urination disorder-alleviating agent. When acotiamide or a salt thereof is used as a urination disorder-alleviating agent, it is preferably used so that from 200 mg to 300 mg per administration and from 600 mg to 900 mg per day of acotiamide or a salt thereof are orally

administered to an adult (Japanese Patent Application No. 2023-040926).

[0016]

Examples of the salt of acotiamide include acid addition salts, specifically including, for example, acid addition salts with inorganic acids such as a hydrochloride, a sulfate, a nitrate, a phosphate, a hydrobromide, and a hydroiodide, and acid addition salts with organic acids such as an acetate, an oxalate, a malonate, a succinate, a maleate, a fumarate, a lactate, a malate, a citrate, a tartrate, a methanesulfonate, and an ethanesulfonate. Among these, acotiamide hydrochloride is more preferred. Various solvates such as hydrates of acotiamide or a salt thereof are also included. Acotiamide hydrochloride hydrate is still more preferred. These acotiamide or salts thereof can be produced, for example, by the method described in Patent Literature 1.

[0017]

From the viewpoint of improving the ease of use by reducing the size of the tablet, and from the viewpoint of improving the ease of use of a high-dose tablet such that from 200 mg to 300 mg per administration and from 600 mg to 900 mg per day are orally administered as described above, acotiamide or a salt thereof is preferably contained in the uncoated tablet of the present invention in an amount of 65% by mass or more and

91% by mass or less, more preferably 65% by mass or more and 88% by mass or less, and further more preferably 65% by mass or more and 75% by mass or less. When acotiamide or a salt thereof is used as a urination disorder-alleviating agent, this content is particularly preferred, because the single dose is large.

[0018]

The tablet according to the present invention contains a granulated material containing (A) acotiamide or a salt thereof, (B) pregelatinized starch, and (C) a disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate. In other words, in the tablet according to the present invention, it is preferable that the granulated material contains (A) acotiamide or a salt thereof, (B) pregelatinized starch, and (C) a disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate, from the viewpoint of not only having a good dissolution property but also maintaining the dissolution property and further maintaining the tablet hardness even after storage under a high humidity condition.

[0019]

(B) The pregelatinized starch is obtained by heating starch derived from wheat, corn, potato, rice, tapioca, or the like with water under normal pressure or high

pressure to pregelatinize (gelatinize) the starch granules, and then drying the resulting product.

(B) The Pregelatinized starch in the present invention includes any of "pregelatinized starch" and "partly pregelatinized starch" listed in the Japanese Pharmaceutical Excipients 2018, and pregelatinized starch which can generally be added to a pharmaceutical product and a food.

Examples of a commercially available product of pregelatinized starch include PCS PC-10 (Asahi Kasei Corporation), SWELSTAR (trademark) WB-1 (Asahi Kasei Corporation), SWELSTAR (trademark) PD-1 (Asahi Kasei Corporation), SWELSTAR (trademark) MX-1 (Asahi Kasei Corporation), Corn Alpha W (Sanwa Starch Co., Ltd.), Waxy Alpha Y (Sanwa Starch Co., Ltd.), Tapioca Alpha NTP (Sanwa Starch Co., Ltd.), Lycatab (trademark) C (Roquette Frères), Lycatab (trademark) CLM (Roquette Frères), Lycatab (trademark) CT (Roquette Frères), Lycatab (trademark) PGS (Roquette Frères), Starch 1500 (trademark) (Colorcon, Inc.), Starch 1500 (trademark) LM (Colorcon, Inc.), Starch 1500 (trademark) G (Colorcon, Inc.), Prejel PA5 PH (DFE Pharma), Nutrofeli (trademark) ST200 (DFE Pharma), Nutrofeli (trademark) ST300 (DFE Pharma), and the like.

From the viewpoints of the dissolution property and the stability of the tablet, a content of the pregelatinized starch is preferably 2% by mass or more

and 10% by mass or less, more preferably 2% by mass or more and 8% by mass or less, and further more preferably 3% by mass or more and 8% by mass or less in the uncoated tablet.

[0020]

As (B) the pregelatinized starch, pregelatinized starch having a cold-water-soluble content of 1.0% or more is preferred. Here, the cold-water-soluble content is defined as a value obtained by the following method for measurement.

<Method for Measuring Cold-Water-Soluble Content (%)>

To about 1 g of a sample (W_{A0}), 99 g of purified water at 20±5°C was added, and the mixture was stirred for two hours to disperse the sample. Then, 40 mL of the resulting dispersion was transferred to a 50 mL centrifuge tube and separated by centrifugation (at about 5000 G, for 15 minutes). Twenty mL of the supernatant was dried at 110°C to a constant mass, and then a dry mass W_A (g) of the cold-water-soluble content was determined. Separately, about 1 g of the sample (W_{B0}) was dried at 110°C to a constant mass, and then a dry mass W_B (g) of the sample was determined. A value calculated from these values and the following formula was defined as the cold-water-soluble content (%).

[0021]

Cold-water-soluble content (%) =

(WA/WA0×100/20)/(WB/WB0)×100

[0022]

The component (C) is a disintegrant. In detail, it is preferably one or two selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate.

The disintegrant used in the present invention preferably has a water-holding capacity of 500% or more from the viewpoint of the dissolution property. Here, the water-holding capacity is defined as a value obtained by the following method for measurement.

<Method for Measuring Water-Holding Capacity>

To about 1 g of a sample (W_0) placed in a 50 mL centrifuge tube, 15 mL of purified water at 20±5°C was added, and the sample was dispersed, followed by shaking at 200 rpm for ten minutes. Further, 15 mL of purified water at 20±5°C was added, and the mixture was allowed to stand still for 20 minutes and then separated by centrifugation (at about 2000 G, for ten minutes). A value calculated from a mass W (g) of the residue after removal of the supernatant and the initial sample mass W_0 (g) in accordance with the following formula was defined as the water-holding capacity (%).

[0023]

Water-Holding Capacity (%) = (W-W0)/W×100

[0024]

Low substituted hydroxypropylcellulose is a cellulose derivative in which a small amount of

hydroxypropoxy groups has been introduced into a glucose ring of cellulose, and preferably has a molar substitution of the hydroxypropoxy groups of from 0.2 to 0.4, whereas ordinary hydroxypropylcellulose has a molar substitution of hydroxypropoxy groups of 3. Here, the molar substitution is the average number of hydroxyl groups substituted with hydroxypropoxy groups per glucose unit.

Examples of a commercially available product of low substituted hydroxypropylcellulose include L-HPC (trademark) (Shin-Etsu Chemical Co., Ltd.). A plurality of grades are commercially available, and examples of the grades of L-HPC (trademark) include LH-11, LH-21, LH-22, LH-B1, LH-31, LH-32, NBD-020, NBD-021, and NBD-022.

[0025]

Sodium starch glycolate is a sodium salt of a carboxymethyl ether of starch or a crosslinked product thereof. There are neutralization degree types of A and B, which contain from 2.8% to 4.2% and from 2.0% to 3.4% of sodium (Na: 22.99), respectively, when those insoluble in ethanol (99.5)/water mixture (8:2) are dried and subjected for quantification.

Examples of a commercially available product of sodium starch glycolate include GLYCOLYS (trademark) (Roquette Frères), Primojel (trademark) (DFE Pharma), EXPLOTAB (trademark) (JRS Pharma), EXPLOTAB (trademark)

CLV (JRS Pharma), EXPLOTAB (trademark) PCF (JRS Pharma), EXPLOTAB (trademark) Low pH (JRS Pharma), and the like.

[0026]

From the viewpoints of the dissolution property and the stability of the tablet, a content of the disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate is preferably 5% by mass or more and 20% by mass or less, and more preferably 5% by mass or more and 15% by mass or less in the uncoated tablet.

[0027]

From the viewpoints of the dissolution property and the stability of the tablet, a content in parts by mass of (B) the pregelatinized starch with respect to 100 parts by mass of the component (A) (acotiamide or a salt thereof) is preferably 2 parts by mass or more and 15 parts by mass or less, more preferably 2 parts by mass or more and 11 parts by mass or less, and further more preferably 3 parts by mass or more and 11 parts by mass or less.

From the viewpoints of the dissolution property and the stability of the tablet, a content in parts by mass of (C) the disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate with respect to 100 parts by mass of the component (A) (acotiamide or a salt thereof) is preferably 5 parts by mass or more and 30 parts by mass

or less, and more preferably 5 parts by mass or more and 20 parts by mass or less.

From the viewpoints of the dissolution property and the stability of the tablet, a total content of the component (B) pregelatinized starch and the component (C) disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate in the uncoated tablet is preferably 8% by mass or more, more preferably 8% by mass or more and 25% by mass or less, and further more preferably 8% by mass or more and 22% by mass or less.

From the viewpoints of the dissolution property and the stability of the tablet, a content mass ratio of (C) the disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate with respect to (B) the pregelatinized starch (C/B) is preferably 1 or more and 6 or less, and more preferably 1 or more and 3 or less.

[0028]

From the viewpoints of the dissolution property and the stability of the tablet, an average particle size D50 of the granulated material containing the components (A), (B), and (C) is preferably 90 μm or more and 700 μm or less, and preferably 120 μm or more and 500 μm or less.

[0029]

The granulated material described above may contain, in addition to the components (A), (B), and (C), an

excipient normally used for producing a tablet. Examples of such an excipient include crystalline cellulose, lactose, powdered cellulose, mannitol, sucrose, corn starch, potato starch, and the like. Among these excipients, crystalline cellulose, lactose, and powdered cellulose are more preferred.

From the viewpoints of the dissolution property and the stability of the tablet, a content of such an excipient in the granulated material is preferably 25% by mass or less, and from the viewpoint of reducing the size of the tablet, it is more preferably 11% by mass or less, and further more preferably 8% by mass or less.

[0030]

Another aspect of the present invention is a method for producing a tablet, including compression molding a granulated material containing (A) acotiamide or a salt thereof, (B) pregelatinized starch, and (C) a disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate, wherein the tablet contains the component (A) in an amount of 65% by mass or more and 91% by mass or less in an uncoated tablet.

Here, the granulated material is preferably a wet-granulated material, from the viewpoint of the dissolution property and the stability and the ease of manufacture of the tablet.

[0031]

The granulated material can be produced by mixing the components (A), (B), and (C), and, if necessary, an excipient, and then using an ordinary granulation method, preferably a wet granulation method.

Examples of the wet granulation method include an agitation granulation method, a fluidized bed granulation method, and a tumbling fluidized bed granulation method.

In detail, the components (A), (B), and (C), and, if necessary, an excipient, may be mixed together, water or a water/ethanol mixed liquid may be added to the mixture, and then the resulting mixture may be granulated using the granulation apparatus, followed by drying and adjustment of the particle size. Alternatively, the components (A) and (C), and, if necessary, an excipient, may be mixed together, water or a water/ethanol mixed liquid in which (B) is dispersed may be added, and then the resulting mixture may be granulated using the granulation apparatus, followed by drying and adjustment of the particle size. It should be noted that the amount of the liquid to be added during the granulation is preferably from 25% by mass to 60% by mass with respect to the charged amount for granulation in the case of agitation granulation, and is preferably from 25% by mass to 100% by mass with respect to the charged amount for the granulation in the case of fluidized bed granulation and tumbling fluidized bed granulation.

[0032]

The tablet according to the present invention can be obtained by adding, if necessary, a lubricating agent, a fluidizing agent, an excipient, and the like to the obtained granulated material, and then compression molding the mixture.

As the excipient, those described above can be used. As the lubricating agent, magnesium stearate, sodium stearyl fumarate, sodium lauryl sulfate, carnauba wax, macrogols, and the like can be used. Among these, magnesium stearate and sodium stearyl fumarate are more preferred.

As the fluidizing agent, light anhydrous silicic acid, heavy anhydrous silicic acid, magnesium aluminometasilicate, synthetic aluminum silicate, talc, and the like can be used. Among these, light anhydrous silicic acid is more preferred.

Amounts of these ingredients such as the lubricating agents, the fluidizing agents, and the excipients, to be added are desirably small, since the component (A) is contained in an amount of 65% by mass or more and 91% by mass or less in the uncoated tablet.

Further, although the tablet according to the present invention may be the uncoated tablet thus obtained, the uncoated tablet may be coated with a film.

[0033]

The present inventors also found that, by adjusting the moisture content of the granulated material and the

tablet to 4.0% or more and 11.0% or less, the uniformity of distribution of the active ingredient in the resulting tablet is enhanced, the resulting tablet has a good dissolution property, and reduction in hardness after storage under a high humidity condition is suppressed.

In other words, another aspect of the present invention is a tablet containing a wet-granulated material which contains (D) an active ingredient, (B) pregelatinized starch, and (C) a disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate, wherein a moisture content of a dried powder of the wet-granulated material is 4.0% or more and 11.0% or less.

[0034]

Here, (A) acotiamide or a salt thereof is preferred as (D) the active ingredient, but it is not limited thereto.

From the viewpoints of the dissolution property and the stability of the tablet, the moisture content of the dried powder of the wet-granulated material is preferably 4.0% or more and 11.0% or less, and more preferably 4.0% or more and 9.0% or less. Examples of a method for measuring the moisture content include a loss-on-drying method, a Karl Fischer titration method, and a near-infrared analysis method.

[0035]

From the viewpoints of the dissolution property and the stability of the tablet, the moisture content of the obtained tablet according to the present invention is preferably 4.0% or more and 13.0% or less, and more preferably 4.0% or more and 11.0% or less. Examples of a method for measuring the moisture content include the loss-on-drying method, the Karl Fischer titration method, and the near-infrared analysis method.

Further, from the viewpoints of the dissolution property and the stability of the tablet, a ratio of the water-holding capacity of the component (B) to that of the component (A) in the tablet is preferably 0.07 or more and 2.4 or less, and more preferably 0.15 or more and 2.0 or less.

[0036]

Regarding the distribution of (D) the active ingredient in the obtained tablet according to the present invention, from the viewpoints of the dissolution property and the stability of the tablet, it is preferable that the component (D) is not localized, that is, the component (D), the component (B) pregelatinized starch, and the component (C) the disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate are uniformly distributed in the tablet. Examples of a method for evaluating the distribution of the components in the tablet include an elemental analysis of the tablet

surface and/or the tablet cross section by energy dispersive X-ray spectroscopy (EDS), Auger electron spectroscopy (AES), laser-induced breakdown spectroscopy (LIBS), X-ray photoelectron spectroscopy (XPS), or X-ray fluorescence analysis, and a component mapping analysis of the tablet surface and/or the tablet cross section by time-of-flight secondary ion mass spectrometry (TOF-SIMS) or microscopic Raman spectrophotometry.

Preferred examples and contents of the component (B) and the component (C), the content of the component (D), and the like in the tablet of this aspect are the same as those for the tablet described above.

[0037]

Although the tablet according to the present invention has a high content of the component (A) acotiamide or a salt thereof, it does not only have a good dissolution property of the component (A) but also has good storage stability. In particular, the tablet of the present invention maintains the dissolution property and further maintains the tablet hardness even after it is stored under a high humidity condition. Therefore, it is possible to further reduce the size of the tablet containing 100 mg of the component (A), and to reduce the size of the tablet and improve the ease of use even in a case where the content of the component (A) in a single tablet is high.

Examples

[0038]

Next, the present invention will be described below in detail with reference to Examples, but the present invention is not limited to these Examples.

[0039]

(Raw Ingredients Used)

The acotiamide hydrochloride hydrate used in Examples of the present invention was pulverized using a pulverizer at Zeria Pharmaceutical Co., Ltd., and had a water-holding capacity (%) of 59.

(B) The Pregelatinized starch used in Examples is as shown in Table 1.

[0040]

[Table 1]

	Cold-water-soluble content (%)	Water-holding capacity (%)
Pregelatinized starch A	60.6	1499
Pregelatinized starch B	14.4	318
Pregelatinized starch C	7.3	538
Pregelatinized starch D	1.1	517
Pregelatinized starch E	45.7	1150

[0041]

The low substituted hydroxypropylcellulose used in Examples is as shown in Table 2.

[0042]

[Table 2]

	Water-holding capacity (%)
Low substituted hydroxypropylcellulose A	854
Low substituted hydroxypropylcellulose B	812

Low substituted hydroxypropylcellulose C	789
Low substituted hydroxypropylcellulose D	729
Low substituted hydroxypropylcellulose E	614

[0043]

The sodium starch glycolate used in Examples is as shown in Table 3.

[0044]

[Table 3]

	Water-holding capacity (%)
Sodium starch glycolate A	1625
Sodium starch glycolate B	1499

[0045]

(Granulation Equipment)

The agitation granulation apparatus, the fluidized-bed granulation apparatus, or the tumbling fluidized-bed granulation apparatus described in the tables were used.

(Tableting Conditions)

The tableting pressure shown in Examples were used.

[0046]

(Measurement of Moisture Content)

The moisture content was measured under the conditions of 80°C for 20 minutes in accordance with the loss-on-drying test method described in the Japanese Pharmacopoeia.

[0047]

(Measurement of Tablet Hardness)

The hardness was measured using a hardness tester, PTB-502, manufactured by PHARMA TEST Apparatebau AG.

[0048]

(Measurement of Dissolution Rate)

A dissolution test was carried out using the paddle method prescribed in the Japanese Pharmacopoeia (test solution: water or Dissolution Test Solution No. 2; paddle rotation speed: 50 rpm), and a dissolution rate (%) at 15 minutes after the start of the test was calculated.

[0049]

(Storage Conditions for Tablets)

The tablets were stored under open conditions for one week or two weeks in a test chamber with a constant temperature and a constant humidity set at 40°C/75% RH.

[0050]

(Evaluation of Uniformity of Acotiamide Hydrochloride Hydrate in Tablets)

An elemental analysis of the tablet surface was carried out by laser-induced breakdown spectroscopy using a microscope equipped with a laser elemental analysis head. The measurement area was the central portion of the tablet face measuring 720 μm × 450 μm, and a total of 400 measurement points were set at 30 μm intervals. Oxygen, carbon, hydrogen, sulfur, and silicon were selected as the elements to be detected, and the elemental analysis was carried out to calculate the composition ratios of these elements. Based on the obtained measurement results, mapping corresponding to

the composition ratio of the sulfur element was prepared using the colors shown in Figure 1.

[0051]

(Evaluation)

For the initial hardness of the tablet, a hardness of 120 N or more was rated as "very good," and a hardness of less than 120 N was rated as "poor."

For the dissolution rate of the active ingredient, a dissolution rate of 85% or more at 15 minutes after the start of the dissolution test was rated as "very good," and a dissolution rate of less than 85% at 15 minutes after the start of the dissolution test was rated as "poor."

For a rate of reduction in hardness after the storage, a value of 30% or less was rated as "very good," a value of more than 30% and less than 50% was rated as "good," and a value of more than 50% was rated as "poor."

For the dissolution rate after the storage, a value of 85% or more was rated as "very good," and a value of less than 85% was rated as "poor."

For the uniformity of acotiamide hydrochloride hydrate in the tablet, among the 400 measurement points, when a composition ratio of sulfur element was 60% or more at less than five points, it was rated as "very good," when the composition ratio of sulfur element was 60% or more at five points or more and less than ten points, it was rated as "good," and when the composition

ratio of sulfur element was 60% or more at ten points or more, it was rated as "poor."

[0052]

Example 1

Acotiamide hydrochloride hydrate (75.0% by mass), pregelatinized starch A (5.0% by mass), lactose hydrate (6.0% by mass), crystalline cellulose (2.0% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and water in an amount of 33.5% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then subjected to adjustment of the particle size using a sizing machine having a screen diameter of 1.905 mm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 10.7 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0053]

Example 2

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and a binder liquid prepared by dispersing

pregelatinized starch B (5.0% by mass) in water in an amount of 57.4% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.1 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0054]

Example 3

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and the mixture was granulated in a fluidized-bed granulation apparatus while adding a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 31.3% by mass with respect to the granulation components. The granulated material was dried and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure

of 11.2 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0055]

Example 4

Acotiamide hydrochloride hydrate (75.4% by mass), crystalline cellulose (8.0% by mass), and low substituted hydroxypropylcellulose A (10.1% by mass) were mixed together, and the mixture was granulated in a tumbling fluidized-bed granulation apparatus while adding a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 45.9% by mass with respect to the granulation components. The granulated material was dried and then passed through a sieve having an opening of 850 μm. Magnesium stearate (1.5% by mass) was added to and mixed with the resulting granulated material, followed by compression molding at tableting pressures of 11.0 kN and 15.0 kN into a diameter of 10.5 mm, thereby producing 398 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0056]

Example 5

Acotiamide hydrochloride hydrate (66.7% by mass), pregelatinized starch A (5.0% by mass), lactose hydrate (4.3% by mass), crystalline cellulose (2.0% by mass), and low substituted hydroxypropylcellulose A (20.0% by mass)

were mixed together, and water in an amount of 49.0% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then subjected to adjustment of the particle size using a sizing machine having a screen diameter of 1.905 mm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 10.9 kN into a diameter of 11 mm, thereby producing 450 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0057]

Example 6

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (11.0% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and a binder liquid prepared by dispersing pregelatinized starch B (2.0% by mass) in water in an amount of 44.6% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting

granulated material, followed by compression molding at a tableting pressure of 11.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0058]

Example 7

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (2.0% by mass), powdered cellulose (3.5% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and the mixture was granulated in a tumbling fluidized-bed granulation apparatus while adding a binder liquid prepared by dispersing pregelatinized starch B (7.5% by mass) in water in an amount of 45.8% by mass with respect to the granulation components. The granulated material was dried and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 10.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0059]

Example 8

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (3.0% by mass), and low substituted

hydroxypropylcellulose A (10.0% by mass) were mixed together, and a binder liquid prepared by dispersing pregelatinized starch B (10.0% by mass) in water in an amount of 44.6% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 11.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0060]

Example 9

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and a binder liquid prepared by dispersing pregelatinized starch C (5.0% by mass) in water in an amount of 44.6% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5%

by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 11.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0061]

Example 10

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and a binder liquid prepared by dispersing pregelatinized starch D (5.0% by mass) in water in an amount of 44.6% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0062]

Example 11

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and low substituted

hydroxypropylcellulose C (10.0% by mass) were mixed together, and a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 44.6% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.1 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0063]

Example 12

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and low substituted hydroxypropylcellulose D (10.0% by mass) were mixed together, and a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 44.6% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5%

by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.1 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0064]

Example 13

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and low substituted hydroxypropylcellulose E (10.0% by mass) were mixed together, and a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 44.6% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0065]

Example 14

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and sodium starch

glycolate having a water-holding capacity of 1625% (10.0% by mass) were mixed together, and a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 57.4% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.1 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0066]

Example 15

Acotiamide hydrochloride hydrate (85.7% by mass), crystalline cellulose (4.1% by mass), and low substituted hydroxypropylcellulose A (5.1% by mass) were mixed together, and a binder liquid prepared by dispersing pregelatinized starch B (3.0% by mass) in water in an amount of 36.4% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous

silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.0 kN into a diameter of 10.5 mm, thereby producing 350 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0067]

Example 16

Acotiamide hydrochloride hydrate (90.9% by mass) and low substituted hydroxypropylcellulose A (5.2% by mass) were mixed together, and a binder liquid prepared by dispersing pregelatinized starch B (2.9% by mass) in water in an amount of 38.3% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Magnesium stearate (1.0% by mass) was added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.0 kN into a diameter of 10.5 mm, thereby producing 330 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0068]

Example 17

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (13.0% by mass), and sodium starch glycolate B (5.0% by mass) were mixed together, and the

mixture was subjected to agitation granulation while adding a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 44.6% by mass with respect to the granulation components. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0069]

Example 18

Acotiamide hydrochloride hydrate (66.7% by mass), crystalline cellulose (6.3% by mass), and sodium starch glycolate A (20.0% by mass) were mixed together, and the mixture was subjected to agitation granulation while adding a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 61.2% by mass with respect to the granulation components. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material,

followed by compression molding at a tableting pressure of 7.2 kN into a diameter of 10.5 mm, thereby producing 450 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0070]

Example 19

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and the mixture was granulated in a fluidized-bed granulation apparatus while adding a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 96.9% by mass with respect to the granulation components. The granulated material was dried and then subjected to adjustment of the particle size using a sizing machine having a screen diameter of 1.4 mm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding using a high-speed rotary tableting machine at a tableting pressure of 9.4 kN into tablets having a major axis of 13.0 mm and a minor axis of 6.9 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0071]

Example 20

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and the mixture was granulated in a tumbling fluidized-bed granulation apparatus while adding a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 45.9% by mass with respect to the granulation components. The granulated material was dried and then passed through a sieve having an opening of 850 μm. The granulated material had a particle size D50 of 278.7 μm and a moisture content at the end of drying of 6.91%. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 9.6 kN into tablets having a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate. A coating liquid containing hypromellose, titanium oxide, and purified water was sprayed onto the tablets to give film-coated tablets. The initial hardness and dissolution rate (%) of the tablets were 241.8 N and 88.2%, respectively. The rate of reduction in hardness and the dissolution rate of the tablets after the storage for six months were 12.7% and 88.7%, respectively.

[0072]

Example 21

Acotiamide hydrochloride hydrate (66.7% by mass), crystalline cellulose (6.3% by mass), low substituted hydroxypropylcellulose A (15.0% by mass), and sodium starch glycolate A (5.0% by mass) were mixed together, and the mixture was subjected to agitation granulation while adding a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 51.0% by mass with respect to the granulation components. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 6.6 kN into a diameter of 10.5 mm, thereby producing 450 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0073]

Example 22

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (12.0% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and the mixture was subjected to agitation granulation while adding a binder liquid prepared by dispersing pregelatinized starch B (1.0% by mass) in water in an amount of 44.6% by mass with respect

to the granulation components. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 6.7 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0074]

Example 23

Acotiamide hydrochloride hydrate (66.7% by mass), crystalline cellulose (6.3% by mass), low substituted hydroxypropylcellulose A (17.0% by mass), and pregelatinized starch E (8.0% by mass) were mixed together, and the mixture was subjected to agitation granulation while adding water in an amount of 34.0% by mass with respect to the granulation components. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 6.7 kN into a diameter of 10.5 mm, thereby producing 450 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0075]

Example 24

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and the mixture was subjected to tumbling fluidized-bed granulation while adding a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 96.9% by mass with respect to the granulation components. Subsequently, the granulated material was dried at 80°C and then subjected to adjustment of the particle size using a sizing machine having a screen diameter of 1.905 mm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 10.9 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0076]

Comparative Example 1

Acotiamide hydrochloride hydrate (75.0% by mass) and crystalline cellulose (23.0% by mass) were mixed together, and water in an amount of 28.7% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C

and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0077]

Comparative Example 2

Acotiamide hydrochloride hydrate (75.0% by mass) and crystalline cellulose (18.0% by mass) were mixed together, and a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 28.7% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 11.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0078]

Comparative Example 3

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and crospovidone having a water-holding capacity of 670% (10.0% by mass) were mixed together, and the mixture was granulated in a tumbling fluidized-bed granulation apparatus while adding a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 45.9% by mass with respect to the granulation components. The granulated material was dried and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 10.6 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0079]

Comparative Example 4

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (8.0% by mass), and carmellose having a water-holding capacity of 215% (10.0% by mass) were mixed together, and a binder liquid prepared by dispersing pregelatinized starch B (5.0% by mass) in water in an amount of 31.9% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a

sieve having an opening of 850 μm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0080]

Comparative Example 5

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (13.0% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and water in an amount of 47.8% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 11.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0081]

Comparative Example 6

Acotiamide hydrochloride hydrate (66.7% by mass), hypromellose (5.0% by mass), lactose hydrate (4.3% by mass), crystalline cellulose (2.0% by mass), and low substituted hydroxypropylcellulose A (20.0% by mass) were mixed together, and water in an amount of 34.0% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 11.8 kN into a diameter of 11.5 mm, thereby producing 450 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0082]

Comparative Example 7

Acotiamide hydrochloride hydrate (66.7% by mass), hydroxypropylcellulose (5.0% by mass), lactose hydrate (4.3% by mass), crystalline cellulose (2.0% by mass), and low substituted hydroxypropylcellulose A (20.0% by mass) were mixed together, and water in an amount of 34.0% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850

μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 10.6 kN into a diameter of 11.5 mm, thereby producing 450 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0083]

Comparative Example 8

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (13.0% by mass), and low substituted hydroxypropylcellulose A (10.0% by mass) were mixed together, and water in an amount of 47.8% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (1.0% by mass) and magnesium stearate (1.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 11.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0084]

Comparative Example 9

A binder liquid prepared by dispersing pregelatinized starch B (10.0% by mass) in 25% ethanol in an amount of 29.4% by mass with respect to the granulation components was added to acotiamide hydrochloride hydrate (75.0% by mass), followed by agitation granulation. Subsequently, the granulated material was dried at 50°C and then passed through a sieve having an opening of 850 μm. Crystalline cellulose (8.5% by mass), crospovidone having a water-holding capacity of 312% (5.0% by mass), and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 14.8 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0085]

Comparative Example 10

A binder liquid prepared by dispersing pregelatinized starch B (4.3% by mass) in water in an amount of 20.3% by mass with respect to the granulation components was added to acotiamide hydrochloride hydrate (84.9% by mass), followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Low substituted hydroxypropylcellulose A (8.7% by mass) and magnesium stearate (2.0% by mass) were added to and mixed with the resulting granulated material,

followed by compression molding at a tableting pressure of 15.0 kN into a diameter of 10.5 mm, thereby producing 345 mg tablets each containing 293 mg of acotiamide hydrochloride hydrate.

[0086]

Comparative Example 11

Acotiamide hydrochloride hydrate (75.6% by mass) and hydroxypropylcellulose (2.7% by mass) were mixed together, and water in an amount of 6.8% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Pregelatinized starch D (8.0% by mass), crystalline cellulose (9.3% by mass), corn starch (2.7% by mass), light anhydrous silicic acid (1.3% by mass), and magnesium stearate (0.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 11.0 kN into a diameter of 10.5 mm, thereby producing 377 mg tablets each containing 285 mg of acotiamide hydrochloride hydrate.

[0087]

Comparative Example 12

An attempt was made to mix acotiamide hydrochloride hydrate (76.4% by mass), pregelatinized starch B (13.4% by mass), methylcellulose (2.3% by mass), low substituted

hydroxypropylcellulose B (6.9% by mass), and magnesium stearate (0.9% by mass) and produce 432 mg tablets with a diameter of 10.5 mm each containing 330 mg of acotiamide hydrochloride hydrate, but the tablets could not be produced because the powder for tableting had poor fluidity.

[0088]

Comparative Example 13

Acotiamide hydrochloride hydrate (58.0% by mass) and calcium sulfate (18.0% by mass) were mixed together, and 40% ethanol in an amount of 20.6% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 45°C and then passed through a sieve having an opening of 850 μm. Pregelatinized starch B (15.0% by mass), low substituted hydroxypropylcellulose A (8.8% by mass), and magnesium stearate (0.2% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.0 kN into a diameter of 10.5 mm, thereby producing 344.7 mg tablets each containing 200 mg of acotiamide hydrochloride hydrate.

[0089]

Comparative Example 14

Acotiamide hydrochloride hydrate (75.0% by mass) and calcium sulfate (10.0% by mass) were mixed together, and

40% ethanol in an amount of 19.6% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 45°C and then passed through a sieve having an opening of 850 μm. Pregelatinized starch B (5.7% by mass), low substituted hydroxypropylcellulose A (8.8% by mass), and magnesium stearate (0.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 15.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0090]

Comparative Example 15

Acotiamide hydrochloride hydrate (75.6% by mass) and hydroxypropylcellulose (2.7% by mass) were mixed together, and water in an amount of 16.9% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Pregelatinized starch D (8.0% by mass), crystalline cellulose (9.3% by mass), corn starch (2.7% by mass), light anhydrous silicic acid (1.3% by mass), and magnesium stearate (0.5% by mass) were added to and mixed with the resulting granulated material, followed by

compression molding at a tableting pressure of 11.0 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 302 mg of acotiamide hydrochloride hydrate.

[0091]

Comparative Example 16

A binder liquid prepared by dispersing pregelatinized starch B (4.3% by mass) in water in an amount of 28.4% by mass with respect to the granulation components was added to acotiamide hydrochloride hydrate (84.9% by mass), followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Low substituted hydroxypropylcellulose A (8.7% by mass) and magnesium stearate (2.0% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 14.6 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 340 mg of acotiamide hydrochloride hydrate.

[0092]

Comparative Example 17

Acotiamide hydrochloride hydrate (75.0% by mass), crystalline cellulose (13.0% by mass), and sodium starch glycolate A (10.0% by mass) were mixed together, and water in an amount of 44.6% by mass with respect to the granulation components was added to the mixture, followed

by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 10.4 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0093]

Comparative Example 18

Acotiamide hydrochloride hydrate (75.0% by mass), hypromellose (5.0% by mass), crystalline cellulose (8.0% by mass), and sodium starch glycolate A (10.0% by mass) were mixed together, and water in an amount of 44.6% by mass with respect to the granulation components was added to the mixture, followed by agitation granulation. Subsequently, the granulated material was dried at 80°C and then passed through a sieve having an opening of 850 μm. Light anhydrous silicic acid (0.5% by mass) and magnesium stearate (1.5% by mass) were added to and mixed with the resulting granulated material, followed by compression molding at a tableting pressure of 14.6 kN into a diameter of 10.5 mm, thereby producing 400 mg tablets each containing 300 mg of acotiamide hydrochloride hydrate.

[0094]

The results for the obtained granulated material are shown in Tables 4 to 7.

The results for tablets stored for two weeks under open conditions in the test chamber with a constant temperature and a constant humidity set at 40°C/75% RH are shown in Tables 4 and 5.

The evaluation results for the tablets stored for one week under the same conditions are shown in Tables 6 and 7.

The ratios of the water-holding capacity of pregelatinized starch to that of acotiamide hydrochloride hydrate in the tablets obtained in Examples 1 to 24 are shown in Table 8.

Table 9 shows the appearance inspection results, tableting pressure deviation (%), and mass variation coefficient (%) for tablets obtained by granulation on a 130 kg scale and tableting with a high-speed rotary tableting machine under conditions in which the rotational speed of the rotary table was 30 rpm, 40 rpm, and 50 rpm.

[0095]

[Table 4]

	Granulated material		Tablet (Initial)				Tablet (after storage for two weeks)			
	Particle size D50	Moisture content at the end of drying	Hardness	Evaluation	Dissolution rate	Evaluation	Rate of reduction in hardness	Evaluation	Dissolution rate	Evaluation
	(μm)	(%)	(N)		(%)		(%)		(%)	
Example 1	216.5	6.54	206.4	Very good	99.4	Very good	18	Very good	87.4	Very good
Example 2	435.1	6.87	178.3	Very good	91.8	Very good	7	Very good	91.3	Very good
Example 3	143.7*	6.87*	228.8	Very good	98.7	Very good	27	Very good	94.8	Very good
Example 4	278.8	5.83	208.0	Very good	88.3	Very good	30	Very good	89.4	Very good
Example 5	158.5	5.57	209.9	Very good	102.9	Very good	39	Good	94.1	Very good
Example 6	165.7	6.38	181.2	Very good	96.3	Very good	44	Good	97.6	Very good
Example 7	199.9	6.65	207.9	Very good	95.9	Very good	24	Very good	95.5	Very good
Example 8	274.8	5.82	192.9	Very good	97.7	Very good	44	Good	98.1	Very good
Example 17	118.2	8.28	181.3	Very good	87.2	Very good	26	Very good	87.7	Very good
Comparative Example 1	233.4	5.56	200.3	Very good	38.0	Poor	47	Good	37.7	Poor
Comparative Example 2	208.8	4.39	184.3	Very good	61.8	Poor	73	Poor	53.2	Poor
Comparative Example 3	107.9	6.77	204.9	Very good	93.7	Very good	56	Poor	94.2	Very good
Comparative Example 6	NT	3.86	208.8	Very good	46.8	Poor	57	Poor	52.1	Poor
Comparative Example 7	NT	6.08	175.5	Very good	36.7	Poor	NT		NT	
Comparative Example 8	109.7	1.26	165.6	Very good	97.2	Very good	72	Poor	94.2	Very good

*: Average values of the two lots are indicated.

[0096]

[Table 5]

	Granulated material		Tablet (Initial)				Tablet (after storage for two weeks)			
	Particle size D50	Moisture content at the end of drying	Hardness	Evaluation	Dissolution rate	Evaluation	Rate of reduction in hardness	Evaluation	Dissolution rate	Evaluation
	(μm)	(%)	(N)		(%)		(%)		(%)	
Comparative Example 9	150.2	3.43	184.6	Very good	101.6	Very good	89	Poor	100.7	Very good
Comparative Example 10	303.2	2.74	55.5	Poor	103.6	Very good	78	Poor	99.5	Very good
Comparative Example 11	89.3	1.76	173.6	Very good	90.8	Very good	79	Poor	90.1	Very good
Comparative Example 12			Impossible for tableting		NT		NT		NT	
Comparative Example 15	376.1	5.20	134.2	Very good	89.5	Very good	55	Poor	90.7	Very good
Comparative Example 16	417.4	4.35	155	Very good	99.2	Very good	75	Poor	96.9	Very good
Comparative Example 17	94.0	5.20	146.1	Very good	80.2	Poor	35	Good	81.2	Poor
Comparative Example 18	417.1	6.66	235.0	Very good	84.4	Poor	29	Very good	78.7	Poor

[0097]

[Table 6]

	Granulated material		Tablet (Initial)				Tablet (after storage for one week)			
	Particle size D50	Moisture content at the end of drying	Hardness	Evaluation	Dissolution rate	Evaluation	Rate of reduction in hardness	Evaluation	Dissolution rate	Evaluation
	(μm)	(%)	(N)		(%)		(%)		(%)	
Example 9	265.7	7.39	196.2	Very good	96.0	Very good	48	Good	94.2	Very good
Example 10	196.5	6.98	207.2	Very good	95.6	Very good	18	Very good	94.8	Very good
Example 11	319.9	7.58	184.0	Very good	92.3	Very good	14	Very good	91.8	Very good
Example 12	440.6	6.42	201.8	Very good	90.6	Very good	29	Very good	87.6	Very good
Example 13	279.9	6.49	206.1	Very good	96.1	Very good	32	Good	92.9	Very good
Example 14	410.9	7.59	172.6	Very good	89.6	Very good	6	Very good	87.5	Very good
Example 15	337.7	7.14	178.5	Very good	88.3	Very good	17	Very good	96.2	Very good
Example 16	438.3	6.96	169.4	Very good	86.0	Very good	18	Very good	91.7	Very good
Example 18	312.2	8.44	129.4	Very good	98.2*	Very good	45	Very good	94.5*	Very good
Example 19	181.2	6.36	209.7	Very good	NT		NT		NT	
Example 21	149.9	8.75	137.3	Very good	91.2	Very good	27	Very good	89.0	Very good

*: Results for the Dissolution Test Solution No. 2 are indicated.

[0098]

[Table 7]

	Granulated material		Tablet (Initial)				Tablet (after storage for one week)			
	Particle size D50	Moisture content at the end of drying	Hardness	Evaluation	Dissolution rate	Evaluation	Rate of reduction in hardness	Evaluation	Dissolution rate	Evaluation
	(μm)	(%)	(N)		(%)		(%)		(%)	
Example 22	141.2	5.59	125.3	Very good	90.6	Very good	46	Good	88.3	Very good
Example 23	325.4	6.41	129.0	Very good	89.0	Very good	46	Good	84.8	Very good
Example 24	651.5	6.85	180.1	Very good	87.6	Very good	36	Good	90.6	Very good
Comparative Example 4	306.1	6.87	166.3	Very good	62.8	Poor	29	Very good	71.6	Poor
Comparative Example 5	118.8	4.71	194.9	Very good	93.0	Very good	62	Poor	91.0	Very good
Comparative Example 13	325.7	5.73	90.0	Poor	69.0	Poor	41	Good	57.7	Poor
Comparative Example 14	255.2	6.05	162.2	Very good	85.9	Very good	41	Good	74.2	Poor

[0099]

The ratio of the water-holding capacity was determined by (water-holding capacity of pregelatinized starch/100 × mass (%) of pregelatinized starch in the formulation)/(water-holding capacity of acotiamide or a salt thereof/100 × mass (%) of acotiamide or a salt thereof in the formulation).

[0100]

[Table 8]

	Ratio of water-holding capacity		Ratio of water-holding capacity
Example 1	1.69	Example 16	0.17
Example 2	0.36	Example 17	0.36
Example 3	0.36	Example 18	0.40
Example 4	0.36	Example 19	0.36
Example 5	1.90	Example 20	0.36
Example 6	0.14	Example 21	0.40
Example 7	0.54	Example 22	0.07
Example 8	0.72	Example 23	2.34
Example 9	0.60	Example 24	0.36
Example 10	0.58		
Example 11	0.36		
Example 12	0.36		
Example 13	0.36		
Example 14	0.36		
Example 15	0.19		

[0101]

[Table 9]

Rotation speed of rotary table	Tableting pressure deviation (%)	Mass variation coefficient for tablets (%)
30 rpm	1.72	0.28
40 rpm	1.29	0.25
50 rpm	1.61	0.20

[0102]

From the results of Comparative Example 12, when a high content of acotiamide hydrochloride hydrate is contained, compression molding of tablets without carrying out a granulation step is difficult from the viewpoint of ease of manufacture.

[0103]

From the results of Comparative Examples 1 and 2, it can be seen that, when the granulated material does not contain (C) low substituted hydroxypropylcellulose or sodium starch glycolate, poor dissolution property becomes a problem.

From the results of Comparative Example 5, it can be seen that, when the granulated material does not contain the component (B), pregelatinized starch, a reduction in hardness after the storage under high humidity conditions is a problem.

From the results of Comparative Examples 9 and 10, it can be seen that, when the disintegrant is added to a granulated material containing the component (A), acotiamide hydrochloride, and the component (B), a reduction in hardness after the storage under the high humidity conditions is a problem.

In contrast, from the results of Examples 1 to 16, it can be seen that, when a granulated material containing the component (A), the component (B), and the component (C) is contained, the dissolution property is good, and a reduction in hardness after the storage under

the high humidity conditions is suppressed to a low level, whereby the effects of the present invention are obtained.

[0104]

From the results of Example 1 and Comparative Examples 6, 7, 13, and 14, it was confirmed that the component (B), pregelatinized starch, is suitable as a binder to be added to the granulated material from the viewpoint of the dissolution property of the tablet.

From the results of Examples 2, 9, and 10, it was confirmed that the effects of the present invention are exhibited even when the component (B) has different cold-water-soluble content values.

[0105]

From the results of Examples 2 and 14, and Comparative Examples 3 and 4, it was confirmed that the component (C), low substituted hydroxypropylcellulose or sodium starch glycolate, is suitable as a disintegrant to be added to the granulated material from the viewpoints of the dissolution property and the stability of the tablet.

From the results of Examples 2 and 11 to 14, it was confirmed that, when the water-holding capacity of the disintegrant is 500% or more, the effects of the present invention are exhibited.

[0106]

From the results of Example 16, it was confirmed that the effects of the present invention are obtained even at a content of acotiamide hydrochloride hydrate of 90.9%.

[0107]

From the results of Examples 2, 6, 7, 8, and 15, it was confirmed that, when the content of the component (B), pregelatinized starch, becomes lower or higher, the reduction in hardness after the storage under the high humidity conditions tends to become larger, and that there is an optimal range of the content of the component (B) for the stability of the tablet.

[0108]

From the results of Examples 2, 5, 14, and 15, it was confirmed that, when the content of the component (C), low substituted hydroxypropylcellulose or sodium starch glycolate, becomes lower or higher, the reduction in hardness after the storage under the high humidity conditions tends to become larger, and that there is an optimal range of the content of the component (C) for the stability of the tablet.

[0109]

From the results of Examples 2, 5, 6, 14, and 15, it was confirmed that, when the total content of the component (B), pregelatinized starch, and the component (C), low substituted hydroxypropylcellulose or sodium starch glycolate, becomes higher, the reduction in

hardness of the tablet after the storage under the high humidity conditions tends to become larger, and that there is an optimal range for the dissolution property and the stability of the tablet.

[0110]

The evaluation results for the uniformity of acotiamide hydrochloride hydrate in the tablets are shown in Figures 2 and 3.

From the results of Figures 2 and 3, in Comparative Examples 2, 8, 11, and 12, many points at which the composition ratio of sulfur element was 60% or more were distributed. This indicates that acotiamide hydrochloride hydrate having sulfur element was localized in the tablets. In contrast, in Examples 2 and 4, there were almost no points at which the composition ratio of sulfur element was 60% or more, indicating that acotiamide hydrochloride hydrate was present uniformly in the tablets.

Claims

[Claim 1]

A tablet, comprising a granulated material which contains (A) acotiamide or a salt thereof, (B) pregelatinized starch, and (C) a disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate, wherein the component (A) is contained in an amount of 65% by mass or more and 91% by mass or less in an uncoated tablet.

[Claim 2]

The tablet according to claim 1, wherein the granulated material is a wet-granulated material.

[Claim 3]

The tablet according to claim 1 or 2, wherein a content of the component (B) is 2% by mass or more and 10% by mass or less in the uncoated tablet.

[Claim 4]

The tablet according to any one of claims 1 to 3, wherein a content of the component (C) is 5% by mass or more and 20% by mass or less in the uncoated tablet.

[Claim 5]

The tablet according to any one of claims 1 to 4, wherein a total content of the component (B) and the component (C) is 8% by mass or more in the uncoated tablet.

[Claim 6]

The tablet according to any one of claims 1 to 5, wherein the content of the component (B) is 2% by mass or more and 8% by mass or less in the uncoated tablet.

[Claim 7]

The tablet according to any one of claims 1 to 6, wherein the content of the component (C) is 5% by mass or more and 15% by mass or less in the uncoated tablet.

[Claim 8]

The tablet according to any one of claims 1 to 7, wherein the total content of the component (B) and the component (C) is 8% by mass or more and 25% by mass or less in the uncoated tablet.

[Claim 9]

The tablet according to any one of claims 1 to 8, wherein the content of the component (B) is 3% by mass or more and 8% by mass or less in the uncoated tablet.

[Claim 10]

The tablet according to any one of claims 1 to 9, wherein the total content of the component (B) and the component (C) is 8% by mass or more and 22% by mass or less in the uncoated tablet.

[Claim 11]

A method for producing a tablet, comprising compression molding a wet-granulated material containing (A) acotiamide or a salt thereof, (B) pregelatinized starch, and (C) a disintegrant selected from the group

consisting of low substituted hydroxypropylcellulose and sodium starch glycolate, wherein the tablet contains the component (A) in an amount of 65% by mass or more and 91% by mass or less in an uncoated tablet.

[Claim 12]

A tablet, comprising a wet-granulated material which contains (D) an active ingredient, (B) pregelatinized starch, and (C) a disintegrant selected from the group consisting of low substituted hydroxypropylcellulose and sodium starch glycolate, wherein a moisture content of a dried powder of the wet-granulated material is 4.0% or more and 11.0% or less.

[Claim 13]

The tablet according to claim 12, wherein the moisture content of the dried powder of the wet-granulated material is 4.0% or more and 9.0% or less.

[Claim 14]

The tablet according to claim 12 or 13, wherein a moisture content of the tablet is 4.0% or more and 13.0% or less.

[Claim 15]

The tablet according to any one of claims 12 to 14, wherein the moisture content of the tablet is 4.0% or more and 11.0% or less.

[Claim 16]

The tablet according to any one of claims 12 to 15, wherein (D) the active ingredient is acotiamide or a salt thereof.

[Claim 17]

The tablet according to any one of claims 12 to 16, wherein a ratio of a water-holding capacity of the component (B) to that of the component (A) in the tablet is 0.07 or more and 2.4 or less.

[Claim 18]

The tablet according to any one of claims 12 to 17, wherein the ratio of a water-holding capacity of the component (B) to that of the component (A) in the tablet is 0.15 or more and 2.0 or less.