

SMALL-SIZED TABLET HAVING EXCELLENT PRODUCIBILITY AND
ELUTION PROPERTIES

TECHNICAL FIELD

5 [0001]

The present invention relates to a pharmaceutical composition comprising imeglimin or a pharmaceutically acceptable salt thereof, and in detail, a small-sized tablet having excellent producibility and dissolubility.

10

BACKGROUND OF THE INVENTION

[0002]

There are many diabetic patients in the world, and the IDF (the International Diabetes Federation) published in 2017 that one in eleven adults worldwide were now diabetic patients, and the total number of diabetic patients in the world increased by 10 million people since 2015 to reach 425 million people, and the number was predicted to increase to about 700 million people by 2045. Particularly in Japan, most of diabetic patients suffer from type 2 diabetes, whose number is estimated to be 3,166,000 people.

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[0003]

Imeglimin is widely known as antidiabetic agent, which is used in the treatment of type 2 diabetes. For the treatment, however, imeglimin has to be administered in large

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doses, *i.e.*, 200 - 4000 mg a day (Patent literature 1), which has brought on a problem of oral administration method.

[0004]

Patent literature 1 discloses a film-coated tablet
5 comprising imeglimin in 83.4 % as an oral imeglimin
preparation, but does not disclose any practical preparing
processes thereof. And, Patent literature 2 discloses a
tablet comprising imeglimin in 87.0 % as an oral imeglimin
preparation, which was prepared in 1 kg scale by direct
10 compression, *i.e.*, blending composition ingredients followed
by compression. The direct compression is easy for small-
scale manufacturing, but the compressing time of powder is
shortened in case that the manufacturing scale is put up,
and thereby when the compression-moldability of the
15 medicament is bad, the tableting trouble may happen and the
tableting may become difficult. Thus, there had been no
practical process for preparing an oral tablet comprising
imeglimin stably in a large scale.

20 PRIOR ART

[0005]

(Patent Reference)

[Patent Literature 1] WO 2011/154497

[Patent Literature 2] WO 2010/066326

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SUMMARY OF INVENTION

[0006]

(Technical Problem)

As for the administration of imeglimin whose daily dose
5 is extremely large, the purpose of the present invention may
be to provide a small-sized tablet which contains a high
amount of imeglimin in one tablet and has excellent
dissolubility, and a stable process which makes it possible
to prepare such tablet.

10 [0007]

(Solution to Problem)

The present inventors have extensively studied to reach
the above purpose, and then have found that it is possible
to stably prepare a very small-sized tablet comprising
15 imeglimin which has excellent dissolubility, by using a
disintegrant, and further using a high percentage of
hydroxypropyl cellulose, polyvinyl alcohol or/and
hydroxypropylmethylcellulose as a water-soluble binder. In
addition, they have also found that the fluid-bed granulation
20 is useful for the process.

[0008]

Accordingly, the present invention is described as
follows:

[0009]

25 (Item 1)

A tablet comprising

(1) imeglimin or a pharmaceutically acceptable salt thereof in 84 - 95 wt % content,

(2) one or more binders selected from the group
5 consisting of hydroxypropyl cellulose, polyvinyl alcohol, and hydroxypropylmethylcellulose, and

(3) a disintegrant.

[0010]

(Item 2)

10 The tablet of Item 1, which comprises (1) imeglimin or a pharmaceutically acceptable salt thereof in 88 - 95 wt % content.

or

(Item 2')

15 A tablet comprising

(1) imeglimin or a pharmaceutically acceptable salt thereof in 88 - 95 wt % content,

(2) one or more binders selected from the group
20 consisting of hydroxypropyl cellulose, polyvinyl alcohol, and hydroxypropylmethylcellulose, and

(3) a disintegrant.

[0011]

(Item 3)

25 The tablet of Item 1, which comprises (1) imeglimin or a pharmaceutically acceptable salt thereof in 90 - 95 wt %

content.

[0012]

(Item 4)

5 The tablet of Item 1 or 2, which comprises (1) imeglimin
or a pharmaceutically acceptable salt thereof in 90 - 92
wt % content.

[0013]

(Item 5)

10 The tablet of Item 1 or 2, which comprises (3) a
disintegrant in 0.2 - 7.5 wt % content.

[0014]

(Item 6)

 The tablet of any one of Items 1 to 5, which comprises
(3) a disintegrant in 0.2 - 5.0 wt % content.

15 [0015]

(Item 7)

 The tablet of any one of Items 1 to 6, which comprises
(3) a disintegrant in 0.2 - 4.0 wt % content.

[0016]

20 (Item 8)

 The tablet of any one of Items 1 to 7, which comprises
(3) a disintegrant in 0.2 - 3.0 wt % content.

[0017]

(Item 9)

25 The tablet of any one of Items 1 to 8, which comprises

(3) a disintegrant in 0.2 - 2.0 wt % content.

[0018]

(Item 10)

5 The tablet of Item 1 or 2, which comprises (3) a
disintegrant in 0.5 - 7.5 wt % content.

[0019]

(Item 11)

The tablet of any one of Items 1 to 4 and 10, which
comprises (3) a disintegrant in 0.5 - 5.0 wt % content.

10 [0020]

(Item 12)

The tablet of any one of Items 1 to 4, 10, and 11, which
comprises (3) a disintegrant in 0.5 - 4.0 wt % content.

[0021]

15 (Item 13)

The tablet of any one of Items 1 to 4, and 10 to 12,
which comprises (3) a disintegrant in 0.5 - 3.0 wt % content.

[0022]

(Item 14)

20 The tablet of any one of Items 1 to 4, and 10 to 13,
which comprises (3) a disintegrant in 0.5 - 2.0 wt % content.

[0023]

(Item 15)

25 The tablet of any one of Items 1 to 14, which comprises
(2) one or more binders selected from the group consisting

of hydroxypropyl cellulose, polyvinyl alcohol, and hydroxypropylmethylcellulose in 4.5 - 7.0 wt % content.

[0024]

(Item 16)

5 The tablet of any one of Items 1 to 15, which comprises
(2) one or more binders selected from the group consisting
of hydroxypropyl cellulose, polyvinyl alcohol, and
hydroxypropylmethylcellulose in 4.5 - 6.0 wt % content.

[0025]

10 (Item 17)

 The tablet of any one of Items 1 to 16, which comprises
(2) one or more binders selected from the group consisting
of hydroxypropyl cellulose, polyvinyl alcohol, and
hydroxypropylmethylcellulose in 4.5 - 5.5 wt % content.

15 [0026]

(Item 18)

 The tablet of any one of Items 1 to 17, which comprises
(2) one or more binders selected from the group consisting
of hydroxypropyl cellulose, polyvinyl alcohol, and
20 hydroxypropylmethylcellulose in 4.8 - 5.5 wt % content.

[0027]

(Item 19)

 The tablet of any one of Items 1 to 18, wherein the
viscosity of hydroxypropyl cellulose is 2.0 - 400 mPa·s.

25 [0028]

(Item 20)

The tablet of any one of Items 1 to 19, wherein the viscosity of hydroxypropyl cellulose is 6.0 - 400 mPa·s.

[0029]

5 (Item 21)

The tablet of any one of Items 1 to 20, wherein the viscosity of polyvinyl alcohol is 3.4 - 9.2 mPa·s.

[0030]

(Item 22)

10 The tablet of any one of Items 1 to 21, wherein the viscosity of polyvinyl alcohol is 4.3 - 5.8 mPa·s.

[0031]

(Item 23)

15 The tablet of any one of Items 1 to 22, wherein the viscosity of hydroxypropylmethylcellulose is 4.0 - 12.0 mPa·s.

[0032]

(Item 24)

20 The tablet of any one of Items 1 to 23, wherein the viscosity of hydroxypropylmethylcellulose is 4.0 - 6.0 mPa·s.

[0033]

(Item 25)

The tablet of any one of Items 1 to 24, wherein the viscosity of hydroxypropylmethylcellulose is 4.5 - 6.0 mPa·s.

25 [0034]

(Item 26)

The tablet of any one of Items 1 to 19 and 21 to 25,
which comprises hydroxypropyl cellulose having a viscosity
of 2.0 - 2.9 mPa·s in not more than 3.5 wt % content, and
5 hydroxypropyl cellulose having a viscosity of 150 - 400 mPa·s
in not more than 1.5 wt % content.

[0035]

(Item 27)

The tablet of any one of Items 1 to 22 and 26, wherein
10 the (2) binder is one or two selected from the group
consisting of hydroxypropyl cellulose and polyvinyl alcohol.

[0036]

(Item 28)

The tablet of any one of Items 1 to 20 and 23 to 26,
15 wherein the (2) binder is one or two selected from the group
consisting of hydroxypropyl cellulose and
hydroxypropylmethylcellulose.

[0037]

(Item 29)

20 The tablet of any one of Items 1 to 20 and 26 to 28,
wherein the (2) binder is hydroxypropyl cellulose.

[0038]

(Item 30)

The tablet of any one of Items 1 to 29, wherein the (3)
25 disintegrant is one or more selected from the group

consisting of croscarmellose sodium, sodium starch glycolate, and crospovidone.

[0039]

(Item 31)

5 The tablet of any one of Items 1 to 30, wherein the (3) disintegrant is croscarmellose sodium.

[0040]

(Item 32)

10 The tablet of any one of Items 1 to 31, which is prepared by fluid-bed granulation.

[0041]

(Item 33)

A method for preparing the tablet of any one of Items 1 to 31, which is done by fluid-bed granulation.

15 [0042]

(Item 34)

The tablet of any one of Items 1 to 18, which is prepared by fluid-bed granulation.

[0043]

20 (Item 35)

A method for preparing the tablet of any one of Items 1 to 18, which is done by fluid-bed granulation.

[0044]

(Item 36)

25 The method of Item 35, comprising a step of preparing

a granulated particle comprising (1) imeglimin or a pharmaceutically acceptable salt thereof, (2) one or more binders selected from the group consisting of hydroxypropyl cellulose, polyvinyl alcohol, and hydroxypropylmethylcellulose, and (3) a disintegrant by fluid-bed granulation.

[0045]

(Item 37)

The method of Item 36, comprising a step of preparing the granulated particle by adding (2) one or more binders selected from the group consisting of hydroxypropyl cellulose, polyvinyl alcohol, and hydroxypropylmethylcellulose to a powder comprising (1) imeglimin or a pharmaceutically acceptable salt thereof and (3) a disintegrant, followed by the granulation by fluid-bed granulation.

[0046]

(Item 38)

The method of Item 36 or 37, further comprising tableting process or film coating process.

[0047]

(Item 39)

The method of Item 38, wherein the fluid-bed granulation process, the tableting process, or the film coating process is carried out in 10 kg or more production scale.

[0048]

(Item 40)

The method of Item 38, wherein the fluid-bed granulation process, the tableting process, or the film coating process
5 is carried out in 30 kg or more production scale.

[0049]

(Item 41)

The method of Item 38, wherein the fluid-bed granulation process, the tableting process, or the film coating process
10 is carried out in 50 kg or more production scale.

[0050]

(Effect of the Invention)

The present composition comprising imeglimin is prepared by fluid-bed granulation with a disintegrant, and
15 further with a high percentage of hydroxypropyl cellulose, polyvinyl alcohol or/and hydroxypropylmethylcellulose as a binder, which has a good producibility, i.e., which can be suitably prepared in a manufacturing scale though the composition comprises a high amount of imeglimin whose
20 compression-moldability is bad. And, the present composition comprising imeglimin has a good dissolubility, thus the present invention can provide an oral formulation comprising imeglimin having a good bioavailability. In addition, the present composition comprises an extremely
25 high percentage of imeglimin, thereby the present invention

can provide a small-sized tablet which can facilitate the continuation of taking the medicine.

DESCRIPTION OF EMBODIMENTS

5 [0051]

Hereinafter, the present invention is explained in more detail.

[0052]

(a) Tablet

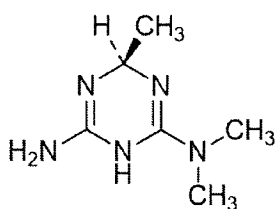
10 The tablet of the present invention includes uncoated tablets, film-coated tablets which are prepared by film-coating the surface of uncoated tablets (herein which may be also referred to as FC tablet), and sugar-coated tablets which are prepared by sugarcoating the surface of uncoated
15 tablets; and preferably uncoated tablets and film-coated tablets. The uncoated tablet contains a composition comprising imeglimin, and further may optionally comprise other additives to the extent that they do not lose the function of the present invention. The composition
20 comprising imeglimin comprises (1) imeglimin or a pharmaceutically acceptable salt thereof, (2) one or more water-soluble polymeric binders selected from the group consisting of hydroxypropyl cellulose, polyvinyl alcohol, and hydroxypropylmethylcellulose, and (3) a disintegrant,
25 and may optionally comprise an excipient and a lubricant,

and further may optionally comprise other additives to the extent that they do not lose the function of the present invention. The film-coating comprises a film-coating agent, and further may optionally comprise other additives to the extent that they do not lose the function of the present invention.

[0053]

(b) Imeglimin

"Imeglimin" in the present invention is a compound known as antidiabetic drug, said chemical name is (6R)-N²,N²,6-trimethyl-3,6-dihydro-1,3,5-triazine-2,4-diamine (CAS registry No.: 775351-65-0), and said chemical structure is shown below. And, "imeglimin" also includes (6S)-N²,N²,6-trimethyl-3,6-dihydro-1,3,5-triazine-2,4-diamine (CAS registry No.: 1251468-04-8).



[0054]

Imeglimin in the present invention includes all forms such as tautomer, amorphous form, crystalline form, and various polymorphism, and also includes optical isomers and a blend thereof. The blend comprises the R form preferably in 90 wt % or more content, 95 wt % or more content, 97 wt %

or more content, or 99 wt % or more content.

Imeglimin in the present invention may be milled to a desired particle size as appropriate. The mean particle size derived based on volume percentage (50 % particle size, D50) includes, for example, 11 - 274 μm , preferably 11 μm - 169 μm .

[0055]

The composition ratio of imeglimin in the present tablet is 84 wt % or more, preferably 88 wt % or more, 90 wt % or more. The composition ratio of imeglimin in the present tablet is preferably 90 wt % or less, 92 wt % or less, 95 wt % or less. As for the tablet of the present invention, the content of imeglimin or a pharmaceutically acceptable salt thereof in one tablet is preferably 500 mg.

[0056]

The pharmaceutically acceptable salt of imeglimin includes an acid addition salt thereof, but not limited thereto. The acid addition salt includes, for example, an inorganic acid salt such as hydrochloride, hydrobromide, sulfate, hydroiodide, nitrate, and phosphate, and an organic acid salt such as citrate, oxalate, phthalate, fumarate, maleate, succinate, malate, acetate, formate, propionate, benzoate, trifluoroacetate, methanesulfonate, benzenesulfonate, para-toluenesulfonate, and camphorsulfonate, as well as amino acid salt with an acidic

amino acid. The pharmaceutically acceptable salt of imeglimin is preferably hydrochloride.

[0057]

(c) Hydroxypropylcellulose

5 The viscosity of hydroxypropyl cellulose in the present invention is 2.0 - 400 mPa·s and preferably 6.0 - 400 mPa·s, but not limited thereto.

The composition ratio of hydroxypropyl cellulose in the present tablet is not limited, but preferably the tablet
10 comprises 3.5 wt % or less hydroxypropyl cellulose whose viscosity is 2.0 - 2.9 mPa·s and 1.5 wt % or less hydroxypropyl cellulose whose viscosity is 150 - 400 mPa·s.

The content of hydroxypropyl cellulose is preferably 4.5 wt % or more, 4.6 wt % or more, 4.7 wt % or more, 4.8
15 wt % or more, 4.9 wt % or more, 5.0 wt % or more. The content of hydroxypropyl cellulose is preferably 5.0 wt % or less, 5.1 wt % or less, 5.2 wt % or less, 5.3 wt % or less, 5.4 wt % or less, 5.5 wt % or less, 5.6 wt % or less, 5.7 wt % or less, 5.8 wt % or less, 5.9 wt % or less, 6.0 wt %
20 or less, 6.1 wt % or less, 6.2 wt % or less, 6.3 wt % or less, 6.4 wt % or less, 6.5 wt % or less, 6.6 wt % or less, 6.7 wt % or less, 6.8 wt % or less, 6.9 wt % or less, 7.0 wt % or less.

Further preferably, the content of hydroxypropyl
25 cellulose is 4.6 wt % or more, 4.7 wt % or more, 4.8 wt % or

more, 4.9 wt % or more, 5.0 wt % or more. Further preferably, the content of hydroxypropyl cellulose is 5.0 wt % or less, 5.1 wt % or less, 5.2 wt % or less, 5.3 wt % or less, 5.4 wt % or less, 5.5 wt % or less, 5.6 wt % or less, 5.7 wt % or less, 5.8 wt % or less, 5.9 wt % or less, 6.0 wt % or less.

The most preferably, the content of hydroxypropyl cellulose is 4.8 wt % or more, 4.9 wt % or more, 5.0 wt % or more. The most preferably, the content of hydroxypropyl cellulose is 5.0 wt % or less, 5.1 wt % or less, 5.2 wt % or less, 5.3 wt % or less, 5.4 wt % or less, 5.5 wt % or less.

[0058]

(d) Polyvinyl alcohol (polyvinyl alcohol-based resin)

The polyvinyl alcohol used herein is polyvinyl alcohol-based resin, which includes polyvinyl alcohol derivatives. Preferably, it is polyvinyl alcohol (PVA). The polyvinyl alcohol (PVA) used herein is preferably partially-saponified one, but not limited thereto. As for saponification, a product having a saponification degree of 97 mol % or more is called a completely-saponified one, and a product having a saponification degree of 79 to 96 mol % is called a partially-saponified one.

The viscosity of polyvinyl alcohol in the present invention is 3.4 - 9.2 mPa·s, preferably 4.3 - 5.8 mPa·s, and more preferably 4.8 - 5.8 mPa·s, but not limited thereto.

The content of polyvinyl alcohol in the present tablet is, for example, preferably 4.5 wt % or more, 4.6 wt % or more, 4.7 wt % or more, 4.8 wt % or more, 4.9 wt % or more, 5.0 wt % or more. The content of polyvinyl alcohol is
5 preferably 5.0 wt % or less, 5.1 wt % or less, 5.2 wt % or less, 5.3 wt % or less, 5.4 wt % or less, 5.5 wt % or less, 5.6 wt % or less, 5.7 wt % or less, 5.8 wt % or less, 5.9 wt % or less, 6.0 wt % or less, 6.1 wt % or less, 6.2 wt % or less, 6.3 wt % or less, 6.4 wt % or less, 6.5 wt % or
10 less, 6.6 wt % or less, 6.7 wt % or less, 6.8 wt % or less, 6.9 wt % or less, 7.0 wt % or less.

Further preferably, the content of polyvinyl alcohol is 4.6 wt % or more, 4.7 wt % or more, 4.8 wt % or more, 4.9 wt % or more, 5.0 wt % or more. Further preferably, the
15 content of polyvinyl alcohol 5.0 wt % or less, 5.1 wt % or less, 5.2 wt % or less, 5.3 wt % or less, 5.4 wt % or less, 5.5 wt % or less, 5.6 wt % or less, 5.7 wt % or less, 5.8 wt % or less, 5.9 wt % or less, 6.0 wt % or less.

The content of polyvinyl alcohol is the most preferably
20 4.8 wt % or more, 4.9 wt % or more, 5.0 wt % or more. The content of polyvinyl alcohol is the most preferably 5.0 wt % or less, 5.1 wt % or less, 5.2 wt % or less, 5.3 wt % or less, 5.4 wt % or less, 5.5 wt % or less.

The polyvinyl alcohol-based resin in the present
25 invention includes, for example, polyvinyl alcohol-acrylic

acid-methyl methacrylate copolymer, and polyvinyl alcohol-polyethylene glycol-graft-co-polymer.

[0059]

(e) Hydroxypropylmethylcellulose

5 The viscosity of hydroxypropylmethylcellulose in the present invention is 4.0 - 12.0 mPa·s, preferably 4.0 - 6.0 mPa·s, and more preferably 4.5 - 6.0 mPa·s, but not limited thereto.

10 The content of hydroxypropylmethylcellulose in the present tablet is preferably 4.5 wt % or more, 4.6 wt % or more, 4.7 wt % or more, 4.8 wt % or more, 4.9 wt % or more, 5.0 wt % or more. The content of hydroxypropylmethylcellulose is preferably 5.0 wt % or less, 5.1 wt % or less, 5.2 wt % or less, 5.3 wt % or less, 5.4
15 wt % or less, 5.5 wt % or less, 5.6 wt % or less, 5.7 wt % or less, 5.8 wt % or less, 5.9 wt % or less, 6.0 wt % or less, 6.1 wt % or less, 6.2 wt % or less, 6.3 wt % or less, 6.4 wt % or less, 6.5 wt % or less, 6.6 wt % or less, 6.7 wt % or less, 6.8 wt % or less, 6.9 wt % or less, 7.0 wt %
20 or less.

 Further preferably, the content of hydroxypropylmethylcellulose is 4.6 wt % or more, 4.7 wt % or more, 4.8 wt % or more, 4.9 wt % or more, 5.0 wt % or more. Further preferably, the content of
25 hydroxypropylmethylcellulose is 5.0 wt % or less, 5.1 wt %

or less, 5.2 wt % or less, 5.3 wt % or less, 5.4 wt % or less, 5.5 wt % or less, 5.6 wt % or less, 5.7 wt % or less, 5.8 wt % or less, 5.9 wt % or less, 6.0 wt % or less.

5 The most preferably, the content of hydroxypropylmethylcellulose is 4.8 wt % or more, 4.9 wt % or more, 5.0 wt % or more. The most preferably, the content of hydroxypropylmethylcellulose is 5.0 wt % or less, 5.1 wt % or less, 5.2 wt % or less, 5.3 wt % or less, 5.4 wt % or less, 5.5 wt % or less.

10 [0060]

(f) Disintegrant

15 A disintegrant is used herein for preventing the drug from absorbing moisture in wet-granulation to dissolve in the moisture, or from caking in wet-granulation, which is necessary for obtaining a good fluidity in a manufacturing equipment in granulation process. In order to miniaturizing the size of a table, the tablet preferably shows a good moisture-absorption property, and a good disintegrability of the prepared tablet, even when the content of a disintegrant is low.

20

The disintegrant used herein should not be limited, but may include a conventional disintegrant that is generally used in formulation process. It includes, for example, starches, low substituted hydroxypropyl cellulose, 25 carmellose, carmellose calcium, carmellose sodium,

crospovidone, croscarmellose sodium, and sodium carboxymethyl starch (also referred to as sodium starch glycolate). It may be a combination of two or more disintegrants.

5 Preferably, it is crospovidone, croscarmellose sodium, or sodium carboxymethyl starch, and more preferably it is croscarmellose sodium. The content of a disintegrant in the present tablet is preferably 0.1 wt % or more, 0.2 wt % or more, 0.5 wt % or more, 1.0 wt % or more, 1.5 wt % or more.

10 The content of a disintegrant in the present tablet is preferably 7.5 wt % or less, 7.4 wt % or less, 7.3 wt % or less, 7.2 wt % or less, 7.1 wt % or less, 7.0 wt % or less, 6.9 wt % or less, 6.8 wt % or less, 6.7 wt % or less, 6.6 wt % or less, 6.5 wt % or less, 6.4 wt % or less, 6.3 wt % or less, 6.2 wt % or less, 6.1 wt % or less, 6.0 wt % or less, 5.9 wt % or less, 5.8 wt % or less, 5.7 wt % or less, 5.6 wt % or less, 5.5 wt % or less, 5.0 wt % or less, 4.5 wt % or less, 4.0 wt % or less, 3.5 wt % or less, 3.0 wt % or less, 2.5 wt % or less, 2.0 wt % or less.

20 [0061]

(g) Filler

The filler used herein should not be limited, but may include a conventional filler that is generally used in formulation process. It includes, for example, crystalline
25 cellulose, a sugar, and a sugar alcohol. The sugar and the

sugar alcohol include, for example, mannitol, erythritol, xylitol, maltitol, sorbitol, lactose, white soft sugar, and trehalose. It may be a combination of two or more fillers.

The content of a filler in the present tablet is preferably 0.1 wt % or more, 0.5 wt % or more, 1.0 wt % or more, 2.0 wt % or more. The content of a filler in the present tablet is preferably 7.5 wt % or less, 7.4 wt % or less, 7.3 wt % or less, 7.2 wt % or less, 7.1 wt % or less, 7.0 wt % or less, 6.9 wt % or less, 6.8 wt % or less, 6.7 wt % or less, 6.6 wt % or less, 6.5 wt % or less, 6.4 wt % or less, 6.3 wt % or less, 6.2 wt % or less, 6.1 wt % or less, 6.0 wt % or less, 5.9 wt % or less, 5.8 wt % or less, 5.7 wt % or less, 5.6 wt % or less, 5.5 wt % or less, 5.0 wt % or less, 4.5 wt % or less, 4.0 wt % or less, 3.5 wt % or less, 3.0 wt % or less, 2.5 wt % or less, 2.0 wt % or less.

[0062]

(h) Lubricant

A tablet in the present invention may comprise a lubricant. A lubricant can prevent a drug substance or a drug granule from adhering to punches and dies at the time of tableting, and thereby can be expected to bring in an efficient manufacturing of tablets, and said adhesion may arise depending on the type of a drug substance or a drug granule. A lubricant may be mixed with other ingredients

before tableting, or sprayed to punches and dies on tableting. The lubricant used herein should not be limited, but may include, for example, stearic acid, magnesium stearate, calcium stearate, sodium stearyl fumarate, talc, carnauba wax, and fatty acid sucrose ester. It may be a combination of two or more lubricants. A preferred lubricant used herein is magnesium stearate.

The content of a lubricant in the present tablet is preferably 0.1 wt % or more, 0.2 wt % or more, 0.4 wt % or more, 0.6 wt % or more, 0.8 wt % or more, 1.0 wt % or more. The content of a lubricant in the present tablet is preferably 4.0 wt % or less, 3.5 wt % or less, 3.0 wt % or less, 2.5 wt % or less, 2.0 wt % or less, 1.8 wt % or less, 1.6 wt % or less, 1.4 wt % or less, 1.2 wt % or less, 1.0 wt % or less.

The content of a lubricant in the present tablet is more preferably 0.4 wt % or more, 0.6 wt % or more, 0.8 wt % or more, 1.0 wt % or more. The content of a lubricant in the present tablet is more preferably 2.0 wt % or less, 1.8 wt % or less, 1.6 wt % or less, 1.4 wt % or less, 1.2 wt % or less, 1.0 wt % or less.

[0063]

(i) Other additives

The tablet of the present invention may comprise other additives as long as they cannot lose the function of the

present invention. The other additives herein include, for example, sweetener, flavoring substance, deodorant, flavor, fluidizer (e.g., AEROSIL), antistatic agent, colorant, plasticizer, antiagglutination agent, and polish (e.g.,
5 carnauba wax, talc), but should not be limited thereto.

[0064]

(j) Film-coating agent

The film-coating agent used for film-coat in the present invention includes, for example, a combination of a base
10 material such as hypromellose, hydroxypropyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl alcohol·polyethylene glycol·graft polymer, methacrylic acid copolymer L, methacrylic acid copolymer LD, methacrylic acid copolymer S, aminoalkyl methacrylate copolymer RS, and ethyl
15 acrylate·methyl methacrylate copolymer; and a plasticizing agent such as polyethylene glycol, propylene glycol, triacetin, triethyl citrate, glycerin, and glycerin fatty acid ester, but should not be limited thereto. Further, it is possible to add another additive such as titanium oxide,
20 iron oxide, talc, and colorant to the above combination. Preferably, the base material includes hypromellose, hydroxypropyl cellulose, and polyvinyl alcohol; and the plasticizing agent includes polyethylene glycol, propylene glycol, and triethyl citrate.

25 [0065]

"Good dissolubility"

The "good dissolubility" used herein means that the dissolution rate is preferably 80 % or higher, 85 % or higher, 90 % or higher, or 95 % or higher at 30 minutes, and
5 preferably 97 % or higher, 98 % or higher, or 99 % or higher at 60 minutes, when the dissolution test of the test drug formulation is carried out according to the *Japanese Pharmacopoeia, Dissolution Test, Method 2*, under the condition mentioned below. And, the dissolution rate at 60
10 minutes is preferably 103 % or lower, 102 % or lower, or 100 % or lower.

Test medium: *the Japanese Pharmacopoeia, Dissolution Test*, 2nd fluid

Paddle rotating speed: 50 rpm

15 Medium volume: 900 mL

[0066]

"Preparation in a large scale"

The large scale in the present invention means that the production weight in granulating process, tableting process,
20 or film coating process is preferably 10 kg or more, 15 kg or more, 20 kg or more, 25 kg or more, 30 kg or more, 35 kg or more, 40 kg or more, 45 kg or more, or 50 kg or more.

[0067]

"Viscosity"

25 The viscosity of high polymer compounds in the present

invention is a viscosity derived by testing 2 wt % aqueous polymer solution at 20°C with a B-type viscometer.

The composition comprising imeglimin in the present table is prepared preferably by a granulation method which
5 can prepare a granule good for compression moldability, in order to prevent tableting trouble and give a suitable hardness to a tablet. For example, the granulation method includes fluid-bed granulation, preferably a fluid-bed granulation in which a binder is sprayed as binder solution,
10 and optionally part of the binder may be dispersed as powdered binder.

For example, a process for preparing a film-coated tablet by fluid-bed granulation is exemplified below, but the present invention should not be limited thereto.

15 [0068]

(1) Preparation of aqueous solution of hydroxypropyl cellulose

Hydroxypropyl cellulose is dissolved in purified water. The amount of hydroxypropyl cellulose may be selected from
20 the range of, for example, 1 - 20 wt %, preferably 2 - 6.5 wt %, for the weight of purified water.

[0069]

(2) Preparation of composition comprising imeglimin (fluid-bed granulation process)

25 Imeglimin, AEROSIL, and disintegrant are thrown into a

fluid-bed granulation machine, and the blend is granulated while spraying the aqueous solution of water-soluble polymer prepared in the above process (1)

[0070]

5 (3) Drying of composition comprising imeglimin

The granulated product prepared above is dried under reduced or ambient pressure. The drying is carried out so that the loss in weight on drying which is measured with a machine such as an infrared moisture analyzer and a halogen
10 moisture analyzer at 80°C may reach, for example, 3 wt % or lower, preferably 2 wt % or lower.

[0071]

(4) Addition of lubricant (blending process)

To the composition comprising imeglimin dried in the
15 above (3), a fluidizer and a lubricant are added, and the blend is mixed. The blending is carried out, for example, with a blender classified as stirring/blending machine. For example, the machine includes a tumbler blender, a V blender, a double cone blender, and a bin blender, but should not be
20 limited thereto.

[0072]

(5) Tableting (tableting process)

An uncoated tablet is prepared by tableting the above-prepared blend. The tableting machine includes, for example,
25 a tableting machine classified as rotary type.

[0073]

(6) film-coating (film coating process)

The above-prepared uncoated tablet is film-coated. The coating machine includes, for example, a machine classified as coating pan. It includes, preferably, a machine classified as vented coating system.

[0074]

(7) Drying of film-coated tablet

The film-coated tablet prepared above is dried. The drying is carried out under reduced or ambient pressure so that the loss in weight on drying which is measured with a machine such as an infrared moisture analyzer and a halogen moisture analyzer at 80°C may reach, for example, 3 wt % or lower, preferably 2 wt % or lower.

EXAMPLES

[0075]

The present invention is explained in more detail in the following by referring to Examples and Tests, but the present invention should not be limited thereto.

[0076]

The reagents and additives used in the present examples and tests were the following ones, unless otherwise indicated.

imeglimin hydrochloride: Sumitomo Dainippon Pharma Co., Ltd.

crystalline cellulose (CEOLUSTTM PH-101): Asahi Kasei

Corporation

light anhydrous silicic acid (AEROSIL™ 200): NIPPON AEROSIL CO., LTD.

croscarmellose sodium (Ac-Di-Sol™ SD-711): FMC Health and
5 Nutrition

hydroxypropyl cellulose (HPC-SSL/2.0 - 2.9 mPa·s¹⁾): NIPPON SODA CO., LTD.

hydroxypropyl cellulose (HPC-L/6.0 - 10.0 mPa·s¹⁾): NIPPON SODA CO., LTD.

10 hydroxypropyl cellulose (HPC-M/150 - 400 mPa·s¹⁾): NIPPON SODA CO., LTD.

hypromellose (hydroxypropylmethylcellulose) (TC-5R™/6 mPa·s²⁾): Shin-Etsu Chemical Co., Ltd.

povidone (Kollidon™ K30/5.5 - 8.5 mPa·s³⁾): BASF

15 polyvinyl alcohol (Gohsenol™ EG-05P/4.8 - 5.8 mPa·s⁴⁾): Mitsubishi Chemical Corporation

magnesium stearate (magnesium stearate (plant-based)): Taihei Chemical Industrial Co., Ltd.

OPADRY™tm 07F28588 WHITE: Colorcon

20 talc (high grade talc MSP): Nippon Talc Co., Ltd.

crospovidone (Kollidon™CL): BASF

sodium starch glycolate (Primojel™): DFE Pharma

¹⁾ vendor's catalog value of 2 % solution at 20°C

²⁾ vendor's catalog value of 2 % solution at 20°C

25 ³⁾ vendor's catalog value of 10 % solution at 20°C

⁴⁾ vendor's catalog value of 4 % solution at 20°C

[0077]

Example 1: Tablet comprising 500 mg of imeglimin hydrochloride (1)

5 A. Formulation composition of uncoated tablet comprising 500 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 1-1 were prepared.

Table 1-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granulated particle	imeglimin hydrochloride	500	90.7
	light anhydrous silicic acid	5.15	0.9
	croscarmellose sodium	10.5	1.9
	hydroxypropyl cellulose* ¹	24.8	4.5
	Total amount of granulated particle	540.45	98.0
Ingredients used in blending	light anhydrous silicic acid	5.5	1.0
	magnesium stearate	5.5	1.0
	Total amount of blended powder and uncoated tablet	551.45	100
*1: HPC-L was used.			

10 [0078]

B. Production process

(1) Preparation of 5 wt % hydroxypropyl cellulose solution

(1)

15 To 1900 g of purified water in a SUS beaker was gradually added 100 g of HPC-L while stirring to make HPC-L dissolved. The solution was let stand overnight, and then stirred again to prepare 5 wt % hydroxypropyl cellulose

solution (1).

[0079]

(2) Preparation of granule comprising imeglimin hydrochloride

5 According to the charging amount defined in Table 1-2 and the preparation condition defined Table 1-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are
10 defined in Table 1-2 were thrown into a fluidized bed granulator/dryer machine (POWREX CORPORATION, Multiplex MP-01), and the blend was blended while fluxing until the exhaust temperature became 35°C. Subsequently, 5 wt % hydroxypropyl cellulose solution (1) whose charging amount
15 is defined in Table 1-2 was sprayed to the blend while fluxing. Then, the product was dried while fluxing until the exhaust temperature became 45°C, and the product was got out of the container. The obtained granule was screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein
20 the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 1-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	700
	light anhydrous silicic acid	7.21
	croscarmellose sodium	14.7
	5 wt % hydroxypropyl cellulose solution (1)	694.4

Table 1-3. Preparation condition (granulation)	
Item	Preparation condition
Container used	standard container
Gun bore	1.0 mm
Gun height	middle
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	80°C
Charge air volume	55 - 70 m ³ /hr
Spray speed	about 12 g/min

[0080]

(3) Preparation of blended powder comprising imeglimin hydrochloride

5 According to the charging amount defined in Table 1-4,
a blended powder comprising imeglimin hydrochloride was
prepared. To V10-type container, the granule comprising
imeglimin hydrochloride whose charging amount is defined in
Table 1-4 was thrown, then light anhydrous silicic acid whose
10 charging amount is defined in Table 1-4 was thrown. The
blend in the V10-type container was blended with a blender
(TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-5) at 40 rpm
for 10 minutes. Subsequently, magnesium stearate was thrown
into the V10-type container, and the blend was blended with
15 the blender (TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-5)
at 40 rpm for 5 minutes.

Table 1-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	658.62
	light anhydrous silicic acid	6.7
	magnesium stearate	6.7

[0081]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press
 5 (KIKUSUI SEISAKUSHO LTD., AQUARIUS3) in the condition defined in Table 1-5 to prepare uncoated tablet containing 500 mg of imeglimin hydrochloride in each tablet.

Table 1-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 17.5 mm, short diameter: 7.0 mm, R: 5.8 mm
rotation speed of turn table	20 rpm
main pressure	14 kN
R means curvature radius. The same applies hereinafter.	

[0082]

Example 2: Tablet comprising 500 mg of imeglimin
 10 hydrochloride (2)

A. Formulation composition of uncoated tablet comprising 500 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 2-
 15 1 were prepared.

Table 2-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	91.6
	light anhydrous silicic acid	5.1	0.9
	croscarmellose sodium	2.72	0.5
	hydroxypropyl cellulose* ¹	27.3	5.0
	Total amount of granule	535.12	98.0
Ingredients used in blending	light anhydrous silicic acid	5.44	1.0
	magnesium stearate	5.44	1.0
	Total amount of blended powder and uncoated tablet	546	100
*1: HPC-L was used.			

[0083]

B. Production process

(1) Preparation of 5 wt % hydroxypropyl cellulose solution

(2)

5 To 1900 g of purified water in a SUS beaker was gradually added 100 g of HPC-L while stirring to make HPC-L dissolved. The solution was let stand overnight, and then stirred again to prepare 5 wt % hydroxypropyl cellulose solution (2).

10 [0084]

(2) Preparation of granule comprising imeglimin hydrochloride

According to the charging amount defined in Table 2-2 and the preparation condition defined Table 2-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are

15

defined in Table 2-2 were thrown into a fluidized bed granulator/dryer machine (POWREX CORPORATION, Multiplex MP-01), and the blend was blended while fluxing until the exhaust temperature became 35°C. Subsequently, 5 wt % hydroxypropyl cellulose solution (2) whose charging amount is defined in Table 2-2 was sprayed to the blend while fluxing. Then, the product was dried while fluxing until the exhaust temperature became 45°C, and the product was got out of the container. The obtained granule was screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.9 mm, and the rotating speed is 900 rpm to give a granule comprising imeglimin hydrochloride.

Table 2-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	700
	light anhydrous silicic acid	7.15
	croscarmellose sodium	3.81
	5 wt % hydroxypropyl cellulose solution (2)	764.4

Table 2-3. Preparation condition (granulation)	
Item	Preparation condition
Container used	standard container
Gun bore	1.0 mm
Gun height	middle
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	80°C
Charge air volume	55 - 70 m ³ /hr
Spray speed	about 12 g/min

[0085]

(3) Preparation of blended powder comprising imeglimin

hydrochloride

According to the charging amount defined in Table 2-4, a blended powder comprising imeglimin hydrochloride was prepared. To V2-type container, the granule comprising
 5 imeglimin hydrochloride whose charging amount is defined in Table 2-4 was thrown, then light anhydrous silicic acid whose charging amount is defined in Table 2-4 was thrown. The blend in the V2-type container was blended with a blender (TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-3) at 40 rpm
 10 for 10 minutes. Subsequently, magnesium stearate was thrown into the V2-type container, and the blend was blended with the blender (TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-3) at 40 rpm for 5 minutes.

Table 2-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	300.01
	light anhydrous silicic acid	3.04
	magnesium stearate	3.05

[0086]

15 (4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., AQUARIUS3) in the condition defined in Table 2-5 to prepare uncoated tablet containing
 20 500 mg of imeglimin hydrochloride in each tablet.

Table 2-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 17.5 mm, short diameter: 7.0 mm, R: 5.8 mm
rotation speed of rotating turret	20 rpm
main pressure	14 kN

[0087]

Example 3: Tablet comprising 500 mg of imeglimin hydrochloride (3)

A. Formulation composition of uncoated tablet comprising 500
5 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 3-1 were prepared.

Table 3-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	90.2
	light anhydrous silicic acid	5.26	0.95
	croscarmellose sodium	10.53	1.9
	hydroxypropyl cellulose* ¹	27.72	5.0
	Total amount of granule	543.51	98.05
Ingredients used in blending	light anhydrous silicic acid	5.54	1.0
	magnesium stearate	5.26	0.95
	Total amount of blended powder and uncoated tablet	554.31	100
*1 hydroxypropyl cellulose of HPC-SSL:HPC-M = 3.5:1.5 was used.			

[0088]

10 B. Production process

(1) Preparation of 4 wt % hydroxypropyl cellulose solution
(1)

To 1920 g of purified water in a SUS beaker were gradually added 56 g of HPC-SSL, then 24 g of HPC-M while

stirring to make them dissolved. The solution was let stand overnight, and then stirred again to prepare 4 wt % hydroxypropyl cellulose solution (1).

[0089]

5 (2) Preparation of granule comprising imeglimin hydrochloride

According to the charging amount defined in Table 3-2 and the preparation condition defined Table 3-3, a granule comprising imeglimin hydrochloride was prepared. First of
10 all, imeglimin hydrochloride, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are defined in Table 3-2 were thrown into a fluidized bed granulator/dryer machine (POWREX CORPORATION, Multiplex MP-01), and the blend was blended while fluxing until the
15 exhaust temperature became 35°C. Subsequently, 4 wt % hydroxypropyl cellulose solution (1) whose charging amount is defined in Table 3-2 was sprayed to the blend while fluxing. Then, the product was dried while fluxing until the exhaust temperature became 45°C, and the product was got
20 out of the container. The obtained granule was screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 3-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	700
	light anhydrous silicic acid	7.38
	croscarmellose sodium	14.76
	4 wt % hydroxypropyl cellulose solution (1)	776.2

Table 3-3. Preparation condition (granulation)	
Item	Preparation condition
Container used	standard container
Gun bore	1.0 mm
Gun height	middle
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	80°C
Charge air volume	55 - 80 m ³ /hr
Spray speed	about 12 g/min

[0090]

(3) Preparation of blended powder comprising imeglimin hydrochloride

5 According to the charging amount defined in Table 3-4,
a blended powder comprising imeglimin hydrochloride was
prepared. To V10-type container, the granule comprising
imeglimin hydrochloride whose charging amount is defined in
Table 3-4 was thrown, then light anhydrous silicic acid whose
10 charging amount is defined in Table 3-4 was thrown. The
blend in the V10-type container was blended with a blender
(TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-5) at 40 rpm
for 10 minutes. Subsequently, magnesium stearate was thrown
into the V10-type container, and the blend was blended with
15 the blender (TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-5)

at 40 rpm for 5 minutes.

Table 3-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	663.1
	light anhydrous silicic acid	6.77
	magnesium stearate	6.42

[0091]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

5 The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., AQUARIUS3) in the condition defined in Table 3-5 to prepare uncoated tablet containing 500 mg of imeglimin hydrochloride in each tablet.

Table 3-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 17.5 mm, short diameter: 7.0 mm, R: 4.1 mm
rotation speed of rotating turret	20 rpm
main pressure	10 kN

[0092]

10 Example 4: Tablet comprising 500 mg of imeglimin hydrochloride (4)

A. Formulation composition of uncoated tablet comprising 500 mg of imeglimin hydrochloride

15 Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 4-1 were prepared.

Table 4-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	90.2
	light anhydrous silicic acid	5.16	0.9
	croscarmellose sodium	10.53	1.9
	hydroxypropyl cellulose* ¹	27.72	5.0
	Total amount of granule	543.41	98.0
Ingredients used in blending	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.51	100
*1: HPC-L was used.			

[0093]

B. Production process

(1) Preparation of 6.5 wt % hydroxypropyl cellulose solution

(1)

5 To 1870 g of purified water in a SUS beaker was gradually added 130 g of HPC-L while stirring to make HPC-L dissolved. The solution was let stand overnight, and then stirred again to prepare 6.5 wt % hydroxypropyl cellulose solution (1).

10 [0094]

(2) Preparation of granule comprising imeglimin hydrochloride

According to the charging amount defined in Table 4-2 and the preparation condition defined Table 4-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are

15

defined in Table 4-2 were thrown into a fluidized bed granulator/dryer machine (POWREX CORPORATION, Multiplex MP-01), and the blend was blended while fluxing until the exhaust temperature became 35°C. Subsequently, 6.5 wt % hydroxypropyl cellulose solution (1) whose charging amount is defined in Table 4-2 was sprayed to the blend while fluxing. Then, the product was dried while fluxing until the exhaust temperature became 45°C, and the product was got out of the container. The obtained granule was screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 4-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	700
	light anhydrous silicic acid	7.22
	croscarmellose sodium	14.74
	6.5 wt % hydroxypropyl cellulose solution (1)	597.08

Table 4-3. Preparation condition (granulation)	
Item	Preparation condition
Container used	standard container
Gun bore	1.0 mm
Gun height	middle
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	80°C
Charge air volume	55 - 70 m ³ /hr
Spray speed	about 12 g/min

[0095]

(3) Preparation of blended powder comprising imeglimin

hydrochloride

According to the charging amount defined in Table 4-4, a blended powder comprising imeglimin hydrochloride was prepared. To V10-type container, the granule comprising imeglimin hydrochloride whose charging amount is defined in Table 4-4 was thrown, then light anhydrous silicic acid whose charging amount is defined in Table 4-4 was thrown. The blend in the V10-type container was blended with a blender (TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-5) at 40 rpm for 10 minutes. Subsequently, magnesium stearate was thrown into the V10-type container, and the blend was blended with the blender (TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-5) at 40 rpm for 5 minutes.

Table 4-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	674.21
	light anhydrous silicic acid	6.89
	magnesium stearate	6.89

[0096]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., AQUARIUS3) in the condition defined in Table 4-5 to prepare uncoated tablet containing 500 mg of imeglimin hydrochloride in each tablet.

Table 4-5 Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 17.5 mm, short diameter: 7.0 mm, R: 5.8 mm
rotation speed of rotating turret	20 rpm
main pressure	14 kN

[0097]

Example 5: Tablet comprising 500 mg of imeglimin hydrochloride (5)

A. Formulation composition of uncoated tablet comprising 500
5 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 5-1 were prepared.

Table 5-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	90.2
	light anhydrous silicic acid	5.15	0.9
	croscarmellose sodium	10.55	1.9
	hydroxypropyl cellulose* ¹	27.7	5.0
	Total amount of granule	543.4	98.0
Ingredients used in blending	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.5	100
*1 hydroxypropyl cellulose of HPC-L:HPC-M = 4.5:0.5 was used.			

[0098]

10 B. Production process

- (1) Preparation of 4 wt % hydroxypropyl cellulose solution
- (2)

To 64.8 kg of purified water in a SUS beaker were gradually added 2.43 kg of HPC-L, then 0.27 kg of HPC-M while

stirring to make them dissolved. Another one of the same was prepared. The solutions were let stand overnight, and then stirred again to prepare 4 wt % hydroxypropyl cellulose solution (2) (totally 135 kg).

5 [0099]

(2) Preparation granule comprising imeglimin hydrochloride

According to the charging amount defined in Table 5-2 and the preparation condition defined Table 5-3, a granule comprising imeglimin hydrochloride was prepared. First of
10 all, imeglimin hydrochloride, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are defined in Table 5-2 were thrown into a fluidized bed granulator/dryer machine (Freund Corporation, NFLO-120SJC), and the blend was blended while fluxing until the exhaust
15 temperature became 60°C. Subsequently, 4 wt % hydroxypropyl cellulose solution (2) whose charging amount is defined in Table 5-2 was sprayed to the blend while fluxing. Then, the product was dried while fluxing until the exhaust temperature became 45°C, and the product was got out of the container.
20 The obtained granule was screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 5-2. Charging amount (granule)		
	Ingredients	Charging amount (kg)
Ingredients in granule	imeglimin hydrochloride	97.5
	light anhydrous silicic acid	1
	croscarmellose sodium	2.06
	4 wt % hydroxypropyl cellulose solution (2)	135

Table 5-3. Preparation condition (granulation)	
Item	Preparation condition
Gun bore	1.8 mm
Number of guns	3
Spray type	top-spray
Spray pressure	0.5 MPa
Charge air temperature	90°C
Charge air volume	30 - 35 m ³ /min
Spray speed	about 700 - 800 mL/min

[0100]

(3) Preparation blended powder comprising imeglimin hydrochloride

5 According to the charging amount defined in Table 5-4, a blended powder comprising imeglimin hydrochloride was prepared. To an 800 L container, the granule comprising imeglimin hydrochloride whose charging amount is defined in Table 5-4 was thrown, then light anhydrous silicic acid whose

10 charging amount is defined in Table 5-4 was thrown. The blend in the container was blended with a container blender (YAMAZAKI BULK SYSTEM, Tumbler blender) at 12 rpm for 5 minutes. Subsequently, magnesium stearate was thrown into the 800 L container, and the blend was blended with the

15 container blender (YAMAZAKI BULK SYSTEM, Tumbler blender) at 12 rpm for 5 minutes.

Table 5-4. Charging amount (blend)		
	Ingredients	Charging amount (kg)
Ingredients used in blending	granule comprising imeglimin hydrochloride	96.7
	light anhydrous silicic acid	0.99
	magnesium stearate	0.99

[0101]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., AQUARIUS3) in the condition defined in Table 5-5 to prepare uncoated tablet containing 500 mg of imeglimin hydrochloride in each tablet.

Table 5-5 Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 17.5 mm, short diameter: 7.0 mm, R: 5.8 mm
rotation speed of rotating turret	30 rpm
main pressure	20 kN

[0102]

Example 6: Tablet comprising 500 mg of imeglimin hydrochloride (6)

A. Formulation composition of uncoated tablet comprising 500 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 6-1 were prepared.

Table 6-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	90.2
	light anhydrous silicic acid	5.15	0.9
	croscarmellose sodium	10.55	1.9
	hydroxypropyl cellulose* ¹	27.7	5.0
	Total amount of granule	543.4	98.0
Ingredients used in blending	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.5	100
*1 hydroxypropyl cellulose of HPC-L:HPC-M = 4:1 was used.			

[0103]

B. Production process

- (1) Preparation of 4 wt % hydroxypropyl cellulose solution
(3)

5 To 64.8 kg of purified water in a SUS beaker were gradually added 2.16 kg of HPC-L, then 0.54 kg of HPC-M while stirring to make them dissolved. Another one of the same was prepared. The solutions were let stand overnight, and then stirred again to prepare 4 wt % hydroxypropyl cellulose solution (3) (totally 135 kg).

[0104]

- (2) Preparation of granule comprising imeglimin hydrochloride

15 According to the charging amount defined in Table 6-2 and the preparation condition defined Table 6-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid,

and croscarmellose sodium whose amounts of preparation are defined in Table 6-2 were thrown into a fluidized bed granulator/dryer machine (Freund Corporation, NFLO-120SJC), and the blend was blended while fluxing until the exhaust
 5 temperature became 55°C. Subsequently, 4 wt % hydroxypropyl cellulose solution (3) whose charging amount is defined in Table 6-2 was sprayed to the blend while fluxing. Then, the product was dried while fluxing until the exhaust temperature became 45°C, and the product was got out of the container.
 10 The obtained granule was screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 6-2. Charging amount (granule)

	Ingredients	Charging amount (kg)
Ingredients in granule	imeglimin hydrochloride	97.5
	light anhydrous silicic acid	1
	croscarmellose sodium	2.06
	4 wt % hydroxypropyl cellulose solution (3)	135

Table 6-3. Preparation condition (granulation)

Item	Preparation condition
Gun bore	1.8 mm
Number of guns	3
Spray type	top-spray
Spray pressure	0.5 MPa
Charge air temperature	90°C
Charge air volume	30 - 35 m ³ /min
Spray speed	about 720 mL/min

15 [0105]

(3) Preparation of blended powder comprising imeglimin

hydrochloride

According to the charging amount defined in Table 6-4, a blended powder comprising imeglimin hydrochloride was prepared. To an 800 L container, the granule comprising
 5 imeglimin hydrochloride whose charging amount is defined in Table 6-4 was thrown. And, light anhydrous silicic acid and magnesium stearate whose amounts of preparation are defined in Table 6-4 were roughly blended and added to the container. The blend in the container was blended with a container
 10 blender (YAMAZAKI BULK SYSTEM, Tumbler blender) at 12 rpm for 5 minutes.

Table 6-4. Charging amount (blend)		
	Ingredients	Charging amount (kg)
Ingredients used in blending	granule comprising imeglimin hydrochloride	99.6
	light anhydrous silicic acid	1.015
	magnesium stearate	1.015

[0106]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

15 The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., AQUARIUS3) in the condition defined in Table 6-5 to prepare uncoated tablet containing 500 mg of imeglimin hydrochloride in each tablet.

Table 6-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 17.5 mm, short diameter: 7.0 mm, R: 5.8 mm
rotation speed of rotating turret	30 rpm
main pressure	20 kN

[0107]

(5) Preparation of solution for film-coating (1)

To 55.2 kg of purified water in a SUS tank was added gradually 4.8 kg of OPADRY™ tm 07F28588 WHITE while stirring
5 to make the OPADRY dispersed/dissolved. The obtained solution was passed through a screen having opening size of 106 µm to give Solution (1) for film-coating.

[0108]

(6) Preparation of film-coated tablet comprising 500 mg of
10 imeglimin hydrochloride

A film-coated tablet comprising 500 mg of imeglimin hydrochloride was prepared according to Table 6-6. First, 82.5 kg of the uncoated tablet was thrown into a coating machine (Freund Corporation, AQC-170FS), which was heated
15 while rotating the coating pan with inching operation, according to Table 6-6 until the exhaust temperature reach 50°C. Subsequently, Solution (1) for film-coating was sprayed into the coating pan rotating at 4 rpm according to Table 6-6, until the weight of the coating runs up about 14
20 mg. Then, the coated tablet was dried while the coating pan was being rotated at 2 rpm until the exhaust temperature reached 55°C, and 21.38 g of talc was sprayed.

Table 6-6. Preparation condition (film-coating)	
Item	Preparation condition
Number of guns	5
Pressure of sprayed air	0.5 MPa
Flow of atomized air	130 NL/min
Flow of pattern air	60 NL/min
Distance between tablet and gun's tip	about 33 cm
Interval of guns	12 cm
Charge air temperature	69°C
Charge air volume	35 m ³ /min
Spray speed	about 270 mL/min

[0109]

Example 7: Tablet comprising 500 mg of imeglimin hydrochloride (7)

A. Formulation composition of uncoated tablet comprising 500 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 7-1 were prepared.

Table 7-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	90.2
	light anhydrous silicic acid	5.1	0.9
	croscarmellose sodium	10.53	1.9
	hydroxypropyl cellulose* ¹	27.72	5.0
	Total amount of granule	543.35	98.0
Ingredients used in blending	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.45	100

*1 hydroxypropyl cellulose of HPC-L:HPC-M = 3.5: 1.5 was used.

[0110]

10 B. Production process

(1) Preparation of 4 wt % hydroxypropyl cellulose solution

(4)

To 23284.9 g of purified water in a SUS beaker were gradually added 679.0 g of HPC-L, then 291.2 g of HPC-M while stirring to make them dissolved. The solution was let stand
5 overnight, and then stirred again to prepare 4 wt % hydroxypropyl cellulose solution (4).

[0111]

(2) Preparation of granule comprising imeglimin hydrochloride

10 According to the charging amount defined in Table 7-2 and the preparation condition defined Table 7-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are
15 defined in Table 7-2 were thrown into a fluidized bed granulator/dryer machine (Freund Corporation, NFLF-30), and the blend was blended while fluxing until the exhaust temperature became 35°C. Subsequently, 4 wt % hydroxypropyl cellulose solution (4) whose charging amount is defined in
20 Table 7-2 was sprayed to the blend while fluxing. Then, the product was dried while fluxing until the exhaust temperature became 45°C, and the product was got out of the container. The obtained granule was screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm,
25 and the rotating speed is 1400 rpm to give a granule

comprising imeglimin hydrochloride.

Table 7-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	17500
	light anhydrous silicic acid	178.51
	croscarmellose sodium	368.56
	4 wt % hydroxypropyl cellulose solution (4)	24255

Table 7-3. Preparation condition (granulation)	
Item	Preparation condition
Gun bore	1.8 mm
Number of guns	1
Spray type	top-spray
Spray pressure	0.5 MPa
Charge air temperature	80 - 89°C
Charge air volume	8 - 9 m ³ /min
Spray speed	131 - 180 mL/min

[0112]

(3) Preparation of blended powder comprising imeglimin
5 hydrochloride

According to the charging amount defined in Table 7-4,
a blended powder comprising imeglimin hydrochloride was
prepared. To a 110 L container, the granule comprising
imeglimin hydrochloride whose charging amount is defined in
10 Table 7-4 was thrown, then light anhydrous silicic acid whose
charging amount is defined in Table 7-4 was thrown. The
blend in the container was blended with a container blender
(Pickstechnica, Picks blender) at 20 rpm for 10 minutes.
Subsequently, magnesium stearate was thrown into the 110 L
15 container, and the blend was blended with the container
blender (Pickstechnica, Picks blender) at 20 rpm for 5

minutes.

Table 7-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	16978
	light anhydrous silicic acid	173.4
	magnesium stearate	173.4

[0113]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

5 The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., AQUARIUS3) in the condition defined in Table 7-5 to prepare uncoated tablet containing 500 mg of imeglimin hydrochloride in each tablet.

Table 7-5 Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 17.5 mm, short diameter: 7.0 mm, R: 4.1 mm
rotation speed of rotating turret	30 rpm
main pressure	12 kN

[0114]

10 Example 8: Tablet comprising 500 mg of imeglimin hydrochloride (8)

A. Formulation composition of uncoated tablet comprising 500 mg of imeglimin hydrochloride

15 Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 8-1 were prepared.

Table 8-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	89.7
	light anhydrous silicic acid	5.16	0.9
	croscarmellose sodium	10.57	1.9
	hydroxypropyl cellulose* ¹	30.65	5.5
	Total amount of granule	546.38	98.0
Ingredients used in blending	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	557.48	100
*1: HPC-L was used.			

[0115]

B. Production process

(1) Preparation of 6.5 wt % hydroxypropyl cellulose solution

(2)

5 To 1870 g of purified water in a SUS beaker was gradually added 130 g of HPC-L while stirring to make HPC-L dissolved. The solution was let stand overnight, and then stirred again to prepare 6.5 wt % hydroxypropyl cellulose solution (2).

10 [0116]

(2) Preparation of granule comprising imeglimin hydrochloride

According to the charging amount defined in Table 8-2 and the preparation condition defined Table 8-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are

15

defined in Table 8-2 were thrown into a fluidized bed granulator/dryer machine (POWREX CORPORATION, Multiplex MP-01), and the blend was blended while fluxing until the exhaust temperature became 36°C. Subsequently, 6.5 wt % hydroxypropyl cellulose solution (2) whose charging amount is defined in Table 8-2 was sprayed to the blend while fluxing. Then, the product was dried while fluxing until the exhaust temperature became 45°C, and the product was got out of the container. The obtained granule was screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 8-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	700
	light anhydrous silicic acid	7.22
	croscarmellose sodium	14.79
	6.5 wt % hydroxypropyl cellulose solution (2)	660.15

Table 8-3. Preparation condition (granulation)	
Item	Preparation condition
Container used	standard container
Gun bore	1.0 mm
Gun height	middle
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	80°C
Charge air volume	55 - 70 m ³ /hr
Spray speed	about 12 g/min

[0117]

(3) Preparation of blended powder comprising imeglimin

hydrochloride

According to the charging amount defined in Table 8-4, a blended powder comprising imeglimin hydrochloride was prepared. To V10-type container, the granule comprising
 5 imeglimin hydrochloride whose charging amount is defined in Table 8-4 was thrown, then light anhydrous silicic acid whose charging amount is defined in Table 8-4 was thrown. The blend in the V10-type container was blended with a blender (TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-5) at 40 rpm
 10 for 10 minutes. Subsequently, magnesium stearate was thrown into the V10-type container, and the blend was blended with the blender (TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-5) at 40 rpm for 5 minutes.

Table 8-4 charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	671.07
	light anhydrous silicic acid	6.82
	magnesium stearate	6.82

[0118]

15 (4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., AQUARIUS3) in the condition defined in Table 8-5 to prepare uncoated tablet containing
 20 500 mg of imeglimin hydrochloride in each tablet.

Table 8-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 17.5 mm, short diameter: 7.0 mm, R: 5.8 mm
rotation speed of rotating turret	20 rpm
main pressure	14 kN

[0119]

Example 9: Tablet comprising 500 mg of imeglimin hydrochloride (9)

A. Formulation composition of uncoated tablet comprising 500
5 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 9-1 were prepared.

Table 9-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	90.2
	light anhydrous silicic acid	5.15	0.9
	croscarmellose sodium	10.55	1.9
	hypromellose* ¹	27.7	5.0
	Total amount of granule	543.4	98.0
Ingredients used in blending	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.5	100
*1: TC-5R TM was used.			

[0120]

10 B. Production process

(1) Preparation of 4 wt % hypromellose solution (1)

To 1920 g of purified water in a SUS beaker was gradually added 80 g of TC-5RTM while stirring to make TC-

5R™ dissolved. The solution was let stand overnight, and then stirred again to prepare 4 wt % hypromellose solution (2).

[0121]

5 (2) Preparation of granule comprising imeglimin hydrochloride

According to the charging amount defined in Table 9-2 and the preparation condition defined Table 9-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are defined in Table 9-2 were thrown into a fluidized bed granulator/dryer machine (Multiplex MP-01), and the blend was blended while fluxing for 2 minutes. Subsequently, 4 wt % hypromellose solution (1) whose charging amount is defined in Table 9-2 was sprayed to the blend while fluxing. The obtained granule was dried and then screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 9-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	300
	light anhydrous silicic acid	3.08
	croscarmellose sodium	6.34
	4 wt % hypromellose solution (1)	415.5

Table 9-3. Preparation condition (granulation)	
Item	Preparation condition
Container used	small container
Gun bore	1.0 mm
Gun height	middle
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	80°C
Charge air volume	50 - 55 m ³ /hr
Spray speed	about 10 g/min

[0122]

(3) Preparation of blended powder comprising imeglimin hydrochloride

According to the charging amount defined in Table 9-4, a blended powder comprising imeglimin hydrochloride was prepared. To a plastic bag containing granule comprising imeglimin hydrochloride whose charging amount is defined in Table 9-4, light anhydrous silicic acid whose charging amount is defined in Table 9-4 was thrown, and the blend was blended while shaking for 2 minutes. Subsequently, magnesium stearate whose charging amount is defined in Table 9-4 was thrown into the plastic bag, and the blend was blended while shaking for a minute.

Table 9-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	257.45
	light anhydrous silicic acid	2.62
	magnesium stearate	2.63

[0123]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., VELA2) in the condition defined in Table 9-5 to prepare uncoated tablets containing 500 mg of imeglimin hydrochloride in each tablet.

Table 9-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 16.0 mm, short diameter: 6.5 mm, R: 4.1 mm
rotation speed of rotating turret	20 rpm
main pressure	14 kN

5 [0124]

Example 10: Tablet comprising 500 mg of imeglimin hydrochloride (10)

A. Formulation composition of uncoated tablet comprising 500 mg of imeglimin hydrochloride

10 Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 10-1 were prepared.

Table 10-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	90.2
	light anhydrous silicic acid	5.15	0.9
	croscarmellose sodium	10.55	1.9
	polyvinyl alcohol*1	27.7	5.0
	Total amount of granule	543.4	98.0
Ingredients used in blending	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.5	100
*1 Gohsenol™ EG-05P was used.			

[0125]

B. Production process

(1) Preparation of 4 wt % polyvinyl alcohol solution (1)

1920 g of purified water in a SUS beaker was heated to boiling. To the heated purified water was gradually added 80 g of Gohsenol™ EG-05P while stirring to make Gohsenol™ dissolved. The solution was let stand overnight, and then stirred again. Purified water was added to the solution to adjust the total weight to 2000 g, and thus 4 wt % polyvinyl alcohol solution (1) was prepared.

[0126]

10 (2) Preparation of granule comprising imeglimin hydrochloride

According to the charging amount defined in Table 10-2 and the preparation condition defined Table 10-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are defined in Table 10-2 were thrown into a fluidized bed granulator/dryer machine (Multiplex MP-01), and the blend was blended while fluxing for 3 minutes. Subsequently, 4 wt % polyvinyl alcohol solution (1) whose charging amount is defined in Table 10-2 was sprayed to the blend while fluxing. The obtained granule was dried, and then screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 10-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	300
	light anhydrous silicic acid	3.08
	croscarmellose sodium	6.34
	4 wt % polyvinyl alcohol solution (1)	415.5

Table 10-3 Preparation condition (granulation)	
Item	Preparation condition
Container used	small container
Gun bore	1.0 mm
Gun height	middle
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	80°C
Charge air volume	50 - 90 m ³ /hr
Spray speed	about 10 g/min

[0127]

(3) Preparation of blended powder comprising imeglimin hydrochloride

5 According to the charging amount defined in Table 10-4, a blended powder comprising imeglimin hydrochloride was prepared. To a plastic bag containing granule comprising imeglimin hydrochloride whose charging amount is defined in Table 10-4, light anhydrous silicic acid whose charging amount is defined in Table 10-4 was thrown, and the blend was blended while shaking for 2 minutes. Subsequently, magnesium stearate whose charging amount is defined in Table 10-4 was thrown into the plastic bag, and the blend was blended while shaking for a minute.

Table 10-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	262.56
	light anhydrous silicic acid	2.68
	magnesium stearate	2.68

[0128]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., VELA2) in the condition defined in Table 10-5 to prepare uncoated tablet containing 500 mg of imeglimin hydrochloride in each tablet.

Table 10-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 16.0 mm, short diameter: 6.5 mm, R: 4.1 mm
rotation speed of rotating turret	20 rpm
main pressure	14 kN

[0129]

Example 11: Tablet comprising 500 mg of imeglimin hydrochloride (11)

A. Formulation composition of uncoated tablet comprising 500 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 11-1 were prepared.

Table 11-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	90.17
	light anhydrous silicic acid	5.15	0.93
	crospovidone	10.55	1.9
	hydroxypropyl cellulose* ¹	27.7	5.0
	Total amount of granule	543.4	98.0
Ingredients used in blending	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.5	100
*1 hydroxypropyl cellulose of HPC-L:HPC-M = 4:1 was used.			

[0130]

B. Production process

(1) Preparation of 4 wt % hydroxypropyl cellulose solution
(5)

5 To 2880 g of purified water in a SUS beaker were gradually added 95.99 g of HPC-L, then 24 g of HPC-M while stirring to make them dissolved. The solution was let stand overnight, and then stirred again to prepare 4 wt % hydroxypropyl cellulose solution (5).

10 [0131]

(2) Preparation of granule comprising imeglimin hydrochloride

According to the charging amount defined in Table 11-2 and the preparation condition defined Table 11-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid, and crospovidone whose amounts of preparation are defined in

Table 11-2 were thrown into a fluidized bed granulator/dryer machine (POWREX CORPORATION, Multiplex MP-01), and the blend was blended while fluxing until the exhaust temperature became 38°C. Subsequently, 4 wt % hydroxypropyl cellulose solution (5) whose charging amount is defined in Table 11-2 was sprayed to the blend while fluxing. Then, the product was dried while fluxing until the exhaust temperature became 45°C, and the product was got out of the container. The obtained granule was screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 11-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	300
	light anhydrous silicic acid	3.08
	crospovidone	6.33
	4 wt % hydroxypropyl cellulose solution (5)	415.5

Table 11-3. Preparation condition (granulation)	
Item	Preparation condition
Container used	standard container
Gun bore	1.0 mm
Gun height	low
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	78 - 80°C
Charge air volume	55 m ³ /hr
Spray speed	about 10 g/min

[0132]

(3) Preparation of blended powder comprising imeglimin

hydrochloride

According to the charging amount defined in Table 11-4, a blended powder comprising imeglimin hydrochloride was prepared. To a polyethylene bag were added the granule comprising imeglimin hydrochloride whose charging amount is defined in Table 11-4, and then light anhydrous silicic acid whose charging amount is defined in Table 11-4, and the blend was blended by hand for 2 minutes. Subsequently, magnesium stearate was thrown into the bag, and the blend was blended by hand for a minute.

Table 11-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	254.4
	light anhydrous silicic acid	2.61
	magnesium stearate	2.61

[0133]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., VELA2) in the condition defined in Table 11-5 to prepare uncoated tablet containing 500 mg of imeglimin hydrochloride in each tablet.

Table 11-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 16.0 mm, short diameter: 6.5 mm, R: 4.1 mm
rotation speed of rotating turret	20 rpm
main pressure	17 kN

[0134]

Example 12: Tablet comprising 500 mg of imeglimin hydrochloride (12)

A. Formulation composition of uncoated tablet comprising 500 mg of imeglimin hydrochloride

5 Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 12-1 were prepared.

Table 12-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	90.17
	light anhydrous silicic acid	5.15	0.93
	sodium starch glycolate	10.55	1.9
	hydroxypropyl cellulose* ¹	27.7	5.0
	Total amount of granule	543.4	98.0
Ingredients used in blending	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.5	100
*1 hydroxypropyl cellulose of HPC-L:HPC-M = 4:1 was used.			

[0135]

B. Production process

10 (1) Preparation of 4 wt % hydroxypropyl cellulose solution
(6)

To 2880 g of purified water in a SUS beaker were gradually added 95.99 g of HPC-L, then 24 g of HPC-M while stirring to make them dissolved. The solution was let stand
15 overnight, and then stirred again to prepare 4 wt % hydroxypropyl cellulose solution (6).

[0136]

(2) Preparation of granule comprising imeglimin hydrochloride

According to the charging amount defined in Table 12-2 and the preparation condition defined Table 12-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid, and sodium starch glycolate whose amounts of preparation are defined in Table 12-2 were thrown into a fluidized bed granulator/dryer machine (POWREX CORPORATION, Multiplex MP-01), and the blend was blended while fluxing until the exhaust temperature became 39°C. Subsequently, 4 wt % hydroxypropyl cellulose solution (6) whose charging amount is defined in Table 12-2 was sprayed to the blend while fluxing. Then, the product was dried while fluxing until the exhaust temperature became 45°C, and the product was got out of the container. The obtained granule was screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 12-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	300
	light anhydrous silicic acid	3.09
	sodium starch glycolate	6.32
	4 wt % hydroxypropyl cellulose solution (6)	415.5

Table 12-3. Preparation condition (granulation)	
Item	Preparation condition
Container used	standard container
Gun bore	1.0 mm
Gun height	low
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	80°C
Charge air volume	55 m ³ /hr
Spray speed	about 10 g/min

[0137]

(3) Preparation of blended powder comprising imeglimin hydrochloride

According to the charging amount defined in Table 12-4, a blended powder comprising imeglimin hydrochloride was prepared. To a polyethylene bag were added the granule comprising imeglimin hydrochloride whose charging amount is defined in Table 12-4, and then light anhydrous silicic acid whose charging amount is defined in Table 12-4, and the blend was blended by hand for 2 minutes. Subsequently, magnesium stearate was thrown into the bag, and the blend was blended by hand for a minute.

Table 12-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	257.29
	light anhydrous silicic acid	2.64
	magnesium stearate	2.63

[0138]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press

(KIKUSUI SEISAKUSHO LTD., VELA2) in the condition defined in Table 12-5 to prepare uncoated tablet containing 500 mg of imeglimin hydrochloride in each tablet.

Table 12-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 16.0 mm, short diameter: 6.5 mm, R: 4.1 mm
rotation speed of rotating turret	20 rpm
main pressure	17 kN

[0139]

5 Example 13: Tablet comprising 500 mg of imeglimin hydrochloride (13)

A. Formulation composition of uncoated tablet comprising 500 mg of imeglimin hydrochloride

10 Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 13-1 were prepared.

Table 13-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	84.57
	light anhydrous silicic acid	5.52	0.93
	croscarmellose sodium	44.33	7.5
	hydroxypropyl cellulose* ¹	29.55	5.0
	Total amount of granule	579.4	98.0
Ingredients used in blending	light anhydrous silicic acid	5.9	1.0
	magnesium stearate	5.9	1.0
	Total amount of blended powder and uncoated tablet	591.2	100
*1 hydroxypropyl cellulose of HPC-L:HPC-M = 4:1 was used.			

[0140]

B. Production process

(1) Preparation of 4 wt % hydroxypropyl cellulose solution

(7)

To 2880 g of purified water in a SUS beaker were gradually added 95.99 g of HPC-L, then 24 g of HPC-M while stirring to make them dissolved. The solution was let stand
5 overnight, and then stirred again to prepare 4 wt % hydroxypropyl cellulose solution (7).

[0141]

(2) Preparation of granule comprising imeglimin hydrochloride

10 According to the charging amount defined in Table 13-2 and the preparation condition defined Table 13-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are
15 defined in Table 13-2 were thrown into a fluidized bed granulator/dryer machine (POWREX CORPORATION, Multiplex MP-01), and the blend was blended while fluxing until the exhaust temperature became 35°C. Subsequently, 4 wt % hydroxypropyl cellulose solution (7) whose charging amount
20 is defined in Table 13-2 was sprayed to the blend while fluxing. Then, the product was dried while fluxing until the exhaust temperature became 45°C, and the product was got out of the container. The obtained granule was screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein
25 the opening size is 1.4 mm, and the rotating speed is 1400

rpm to give a granule comprising imeglimin hydrochloride.

Table 13-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	300
	light anhydrous silicic acid	3.31
	croscarmellose sodium	26.61
	4 wt % hydroxypropyl cellulose solution (7)	443.25

Table 13-3. Preparation condition (granulation)	
Item	Preparation condition
Container used	standard container
Gun bore	1.0 mm
Gun height	low
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	80°C
Charge air volume	50-55 m ³ /hr
Spray speed	about 10 g/min

[0142]

(3) Preparation of blended powder comprising imeglimin
5 hydrochloride

According to the charging amount defined in Table 13-4, a blended powder comprising imeglimin hydrochloride was prepared. To a polyethylene bag were added the granule comprising imeglimin hydrochloride whose charging amount is
10 defined in Table 13-4, and then light anhydrous silicic acid whose charging amount is defined in Table 13-4, and the blend was blended by hand for 2 minutes. Subsequently, magnesium stearate was thrown into the bag, and the blend was blended by hand for a minute.

Table 13-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	264.95
	light anhydrous silicic acid	2.71
	magnesium stearate	2.71

[0143]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., VELA2) in the condition defined in Table 13-5 to prepare uncoated tablets containing 500 mg of imeglimin hydrochloride in each tablet.

Table 13-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 16.0 mm, short diameter: 6.5 mm, R: 4.1 mm
rotation speed of rotating turret	20 rpm
main pressure	17 kN

[0144]

Reference example 1: Tablet comprising 167 mg of imeglimin hydrochloride (14)

A. Formulation composition of uncoated tablet comprising 167 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 14-1 were prepared.

Table 14-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	167	30.1
	crystalline cellulose	333	60.1
	light anhydrous silicic acid	5.15	0.9
	croscarmellose sodium	10.55	1.9
	hydroxypropyl cellulose* ¹	27.7	5.0
	Total amount of granule	543.4	98.0
Ingredients used in blending	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.5	100
*1 hydroxypropyl cellulose of HPC-L:HPC-M = 4: 1 was used.			

[0145]

B. Production process

(1) Preparation of 4 wt % hydroxypropyl cellulose solution
(8)

5 To 1920 g of purified water in a SUS beaker were gradually added 64 g of HPC-L, then 16 g of HPC-M while stirring to make them dissolved. The solution was let stand overnight, and then stirred again to prepare 4 wt % hydroxypropyl cellulose solution (8).

10 [0146]

(2) Preparation of granule comprising imeglimin hydrochloride

According to the charging amount defined in Table 14-2 and the preparation condition defined Table 14-3, a granule
15 comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, crystalline cellulose, light anhydrous silicic acid, and croscarmellose sodium whose

amounts of preparation are defined in Table 14-2 were thrown into a fluidized bed granulator/dryer machine (Multiplex MP-01), and the blend was blended while fluxing for 3 minutes. Subsequently, 4 wt % hydroxypropyl cellulose solution (8) whose charging amount is defined in Table 14-2 was sprayed to the blend while fluxing. The obtained granule was dried and then screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 14-2. Charging amount (granule)

	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	100.2
	crystalline cellulose	199.8
	light anhydrous silicic acid	3.1
	croscarmellose sodium	6.33
	4 wt % hydroxypropyl cellulose solution (8)	415.5

Table 14-3. Preparation condition (granulation)

Item	Preparation condition
Container used	small container
Gun bore	1.0 mm
Gun height	middle
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	85°C
Charge air volume	40 - 50 m ³ /hr
Spray speed	about 10 g/min

[0147]

(3) Preparation of blended powder comprising imeglimin hydrochloride

According to the charging amount defined in Table 14-

4, a blended powder comprising imeglimin hydrochloride was prepared. To a plastic bag containing granule comprising imeglimin hydrochloride whose charging amount is defined in Table 14-4, light anhydrous silicic acid whose charging amount is defined in Table 14-4 was thrown, and the blend was blended while shaking for 2 minutes. Subsequently, magnesium stearate whose charging amount is defined in Table 14-4 was thrown into the plastic bag, and the blend was blended while shaking for a minute.

Table 14-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	253.46
	light anhydrous silicic acid	2.59
	magnesium stearate	2.6

10 [0148]

(4) Preparation of uncoated tablet comprising 167 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., VELA2) in the condition defined in Table 14-5 to prepare uncoated tablets containing 167 mg of imeglimin hydrochloride in each tablet.

Table 14-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 16.0 mm, short diameter: 6.5 mm, R: 4.1 mm
rotation speed of rotating turret	20 rpm
main pressure	12 kN

[0149]

Reference example 2: Tablet comprising 500 mg of imeglimin

hydrochloride (15)

A. Formulation composition of uncoated tablet comprising 500 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are
5 composed of the formulation composition defined in Table 15-1 were prepared.

Table 15-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	91.2
	light anhydrous silicic acid	5.1	0.9
	croscarmellose sodium	10.4	1.9
	hydroxypropyl cellulose* ¹	21.9	4.0
	Total amount of granule	537.4	98.0
Ingredients used in blending	light anhydrous silicic acid	5.5	1.0
	magnesium stearate	5.5	1.0
	Total amount of blended powder and uncoated tablet	548.4	100
*1 hydroxypropyl cellulose of HPC-L:HPC-M = 3:1 was used.			

[0150]

B. Production process

(1) Preparation of 4 wt % hydroxypropyl cellulose solution
10 (9)

To 1152 g of purified water in a SUS beaker were gradually added 36 g of HPC-L, then 12 g of HPC-M while stirring to make them dissolved. The solution was let stand overnight, and then stirred again to prepare 4 wt %
15 hydroxypropyl cellulose solution (9).

[0151]

(2) Preparation of Preparation of granule comprising

imeglimin hydrochloride

According to the charging amount defined in Table 15-2 and the preparation condition defined Table 15-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are defined in Table 15-2 were thrown into a fluidized bed granulator/dryer machine (Multiplex MP-01), and the blend was blended while fluxing for 3 minutes. Subsequently, 4 wt % hydroxypropyl cellulose solution (9) whose charging amount is defined in Table 15-2 was sprayed to the blend while fluxing. The obtained granule was dried and then screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 15-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	1000
	light anhydrous silicic acid	10.2
	croscarmellose sodium	20.8
	4 wt % hydroxypropyl cellulose solution (9)	1095

Table 15-3. Preparation condition (granulation)	
Item	Preparation condition
Container used	standard container
Gun bore	1.0 mm
Gun height	middle
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	80°C
Charge air volume	55 - 70 m ³ /hr
Spray speed	about 12 g/min

[0152]

(3) Preparation of blended powder comprising imeglimin hydrochloride

According to the charging amount defined in Table 15-4, a blended powder comprising imeglimin hydrochloride was prepared. To V10-type container, the granule comprising imeglimin hydrochloride whose charging amount is defined in Table 15-4 was thrown, then light anhydrous silicic acid whose charging amount is defined in Table 15-4 was thrown. The blend in the V10-type container was blended with a blender (TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-5) at 40 rpm for 10 minutes. Subsequently, magnesium stearate was thrown into the V10-type container, and the blend was blended with the blender (TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-5) at 40 rpm for 5 minutes.

Table 15-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	479.34
	light anhydrous silicic acid	4.91
	magnesium stearate	4.91

[0153]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., AQUARIUS3) in the condition defined in Table 15-5 to prepare uncoated tablet containing 500 mg of imeglimin hydrochloride in each tablet.

Table 15-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 17.5 mm, short diameter: 7.0 mm, R: 6.5 mm
rotation speed of rotating turret	20 rpm
main pressure	14 kN

[0154]

Reference example 3: Tablet comprising 500 mg of imeglimin hydrochloride (16)

10 A. Formulation composition of uncoated tablet comprising 500 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 16-1 were prepared.

Table 16-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	91.2
	light anhydrous silicic acid	5.1	0.9
	croscarmellose sodium	10.4	1.9
	hydroxypropyl cellulose* ¹	21.9	4.0
	Total amount of granule	537.4	98.0
Ingredients used in blending	light anhydrous silicic acid	5.5	1.0
	magnesium stearate	5.5	1.0
	Total amount of blended powder and uncoated tablet	548.4	100
*1 HPC-L was used.			

[0155]

B. Production process

(1) Preparation of 5 wt % hydroxypropyl cellulose solution

(3)

5 To 1900 g of purified water in a SUS beaker was gradually added 100 g of HPC-L while stirring to make HPC-L dissolved. The solution was let stand overnight, and then stirred again to prepare 5 wt % hydroxypropyl cellulose solution (3).

10 [0156]

(2) Preparation of granule comprising imeglimin hydrochloride

15 According to the charging amount defined in Table 16-2 and the preparation condition defined Table 16-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are

defined in Table 16-2 were thrown into a fluidized bed granulator/dryer machine (POWREX CORPORATION, Multiplex MP-01), and the blend was blended while fluxing until the exhaust temperature became 31°C. Subsequently, 5 wt % hydroxypropyl cellulose solution (3) whose charging amount is defined in Table 16-2 was sprayed to the blend while fluxing. The obtained granule was dried and then screened with a screen mill (POWREX CORPORATION, COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride. Another one of the same was prepared.

Table 16-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	700
	light anhydrous silicic acid	7.14
	croscarmellose sodium	14.56
	5 wt % hydroxypropyl cellulose solution (3)	613.2

Table 16-3. Preparation condition (granulation)	
Item	Preparation condition
Container used	standard container
Gun bore	1.0 mm
Gun height	middle
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	78°C
Charge air volume	55 - 65 m ³ /hr
Spray speed	about 10 - 12 g/min

[0157]

(3) Preparation of blended powder comprising imeglimin hydrochloride

According to the charging amount defined in Table 16-4, a blended powder comprising imeglimin hydrochloride was prepared. To V10-type container, the granule comprising imeglimin hydrochloride whose charging amount is defined in Table 16-4 was thrown, then light anhydrous silicic acid whose charging amount is defined in Table 16-4 was thrown. The blend in the V10-type container was blended with a blender (TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-5) at 40 rpm for 10 minutes. Subsequently, magnesium stearate was thrown into the V10-type container, and the blend was blended with the blender (TSUTSUI SCIENTIFIC INSTRUMENTS CO., LTD., S-5) at 40 rpm for 5 minutes.

Table 16-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	979.99
	light anhydrous silicic acid	10
	magnesium stearate	9.99

[0158]

(4) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., AQUARIUS3) in the condition defined in Table 16-5 to prepare uncoated tablet containing 500 mg of imeglimin hydrochloride in each tablet.

Table 16-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 17.5 mm, short diameter: 7.0 mm, R: 6.5 mm
rotation speed of rotating turret	20 rpm
main pressure	14 kN

[0159]

Reference example 4: Tablet comprising 500 mg of imeglimin hydrochloride (17)

A. Formulation composition of uncoated tablet comprising 500
5 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 17-1 were prepared.

Table 17-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	90.2
	light anhydrous silicic acid	5.15	0.9
	croscarmellose sodium	10.55	1.9
	povidone*1	27.7	5.0
	Total amount of granule	543.4	98.0
Ingredients used in blending	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.5	100
*1 Kollidon™ K30 was used.			

[0160]

10 B. Production process

(1) Preparation of 4 wt % povidone solution (1)

To 1920 g of purified water in a SUS beaker was gradually added 80 g of Kollidon™ K30 while stirring to make Kollidon™ K30 dissolved. The solution was let stand

overnight, and then stirred again to prepare 4 wt % povidone solution (1).

[0161]

(2) Preparation of granule comprising imeglimin
5 hydrochloride

According to the charging amount defined in Table 17-2 and the preparation condition defined Table 17-3, a granule comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, light anhydrous silicic acid,
10 and croscarmellose sodium whose amounts of preparation are defined in Table 17-2 were thrown into a fluidized bed granulator/dryer machine (Multiplex MP-01), and the blend was blended while fluxing for 3 minutes. Subsequently, 4 wt % povidone solution (1) whose charging amount is defined
15 in Table 17-2 was sprayed to the blend while fluxing. And, the sprayed granule was dried and then passed through a screen having opening size of 1000 μm . Then, the obtained granule was screened with a screen mill (POWREX CORPORATION, COMIL 194S), wherein the opening size is 1.4 mm and the
20 rotating speed is 1400 rpm, to give a granule comprising imeglimin hydrochloride.

Table 17-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	300
	light anhydrous silicic acid	3.09
	croscarmellose sodium	6.33
	4 wt % povidone solution (1)	415.5

Table 17-3. Preparation condition (granulation)	
Item	Preparation condition
Container used	small container
Gun bore	1.0 mm
Gun height	middle
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	85 - 90°C
Charge air volume	45 - 50 m ³ /hr
Spray speed	about 10 g/min

[0162]

(3) Preparation of blended powder comprising imeglimin hydrochloride

5 According to the charging amount defined in Table 17-4, a blended powder comprising imeglimin hydrochloride was prepared. To a plastic bag containing granule comprising imeglimin hydrochloride whose charging amount is defined in Table 17-4, light anhydrous silicic acid whose charging
10 amount is defined in Table 17-4 was thrown, and the blend was blended while shaking for 2 minutes. Subsequently, magnesium stearate whose charging amount is defined in Table 17-4 was thrown into the plastic bag, and the blend was blended while shaking for a minute.

Table 17-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	260.09
	light anhydrous silicic acid	2.67
	magnesium stearate	2.66

15 [0163]

(4) Preparation of uncoated tablet comprising 500 mg of

imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., VELA2) in the condition defined in Table 17-5 to prepare uncoated tablet containing 500 mg of
 5 imeglimin hydrochloride in each tablet.

Table 17-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 16.0 mm, short diameter: 6.5 mm, R: 4.1 mm
rotation speed of rotating turret	20 rpm
main pressure	12 kN

[0164]

Reference example 5: Tablet comprising 500 mg of imeglimin hydrochloride (18)

A. Formulation composition of uncoated tablet comprising 500
 10 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 18-1 were prepared.

Table 18-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	500	90.2
	light anhydrous silicic acid	5.15	0.9
	hydroxypropyl cellulose* ¹	27.7	5.0
	Total amount of granule	532.85	96.1
Ingredients used in blending	croscarmellose sodium	10.55	1.9
	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.5	100

*1 hydroxypropyl cellulose of HPC-L:HPC-M = 4:1 was used.

[0165]

B. Production process

(1) Preparation of granule comprising imeglimin hydrochloride

Imeglimin hydrochloride, light anhydrous silicic acid, and hydroxypropyl cellulose (3.32 g of HPC-M and 13.3 g of HPC-L) whose amounts of preparation are defined in Table 18-1 were thrown into a high shear granulating blender (POWREX CORPORATION, FM-VG-05), and the blend was blended for two minutes according to Table 18-3. Subsequently, purified water whose charging amount is defined in Table 18-2 was sprayed to the blend while stirring with a POWREX standard spray gun, and then the stirring was continued for two minutes. The product was taken out of the granulating blender (POWREX CORPORATION, FM-VG-05), passed through a screen having opening size of 1000 μm , and then thrown into a fluidized bed granulator/dryer machine (POWREX CORPORATION, Multiplex MP-01). The product was dried while fluxing according to Table 18-2, and passed through a screen having opening size of 710 μm to give a granule comprising imeglimin hydrochloride.

Table 18-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	300
	light anhydrous silicic acid	3.09
	hydroxypropyl cellulose* ¹	16.62
	purified water	16.83
*1 hydroxypropyl cellulose of HPC-L:HPC-M = 4:1 was used.		

Table 18-3. Preparation condition (granulation)		
	Item	Preparation condition
Vertical granulator	blade	straight
	blade rotating speed	400 rpm
	cross screw rotating speed	3000 rpm
	spray time	約1分
	spray sir pressure	0.05 MPa
Tumbling fluid bed granulator dryer	Charge air temperature	80°C
	Charge air volume	45 m ³ /hr

[0166]

(2) Preparation of blended powder comprising imeglimin hydrochloride

According to the charging amount defined in Table 18-4, a blended powder comprising imeglimin hydrochloride was prepared. To a plastic bag containing granule comprising imeglimin hydrochloride whose charging amount is defined in Table 18-4, light anhydrous silicic acid and croscarmellose sodium whose amounts of preparation are defined in Table 18-4 were thrown, and the blend was blended while shaking for 2 minutes. Subsequently, magnesium stearate whose charging amount is defined in Table 18-4 was thrown into the plastic bag, and the blend was blended while shaking for a minute.

Table 18-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	236.65
	croscarmellose sodium	4.7
	light anhydrous silicic acid	2.47
	magnesium stearate	2.46

[0167]

(3) Preparation of uncoated tablet comprising 500 mg of

imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., VELA2) in the condition defined in Table 18-5 to prepare uncoated tablet containing 500 mg of imeglumin hydrochloride in each tablet.

Table 18-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 16.0 mm, short diameter: 6.5 mm, R: 4.1 mm
rotation speed of rotating turret	20 rpm
main pressure	12 kN

[0168]

Reference example 6: Tablet comprising 500 mg of imeglumin hydrochloride (19)

A. Formulation composition of uncoated tablet comprising 500 mg of imeglumin hydrochloride

Blended powder and uncoated tablet which are composed of the formulation composition defined in Table 19-1 were prepared.

Table 19-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients used in blending	imeglimin hydrochloride	500	90.2
	light anhydrous silicic acid	10.7	1.9
	hydroxypropyl cellulose* ¹	27.7	5.0
	croscarmellose sodium	10.55	1.9
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.5	100
*1 hydroxypropyl cellulose of HPC-L:HPC-M = 4:1 was used.			

[0169]

15 B. Production process

(1) Preparation of blended powder comprising imeglimin hydrochloride

According to the charging amount defined in Table 19-2, a blended powder comprising imeglimin hydrochloride was prepared. Imeglimin hydrochloride, light anhydrous silicic acid, hydroxypropyl cellulose, and croscarmellose sodium whose amounts of preparation are defined in Table 19-2 were thrown to a plastic bag, and the blend was blended while shaking for 2 minutes. Subsequently, magnesium stearate whose charging amount is defined in Table 19-2 was thrown into the plastic bag, and the blend was blended while shaking for a minute.

Table 19-2. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	imeglimin hydrochloride	300
	light anhydrous silicic acid	6.42
	hydroxypropyl cellulose	16.62
	croscarmellose sodium	6.33
	magnesium stearate	3.33

[0170]

(2) Preparation of uncoated tablet comprising 500 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., VELA2) in the condition defined in Table 19-3 to prepare uncoated tablet containing 500 mg of imeglimin hydrochloride in each tablet.

Table 19-3. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 16.0 mm, short diameter: 6.5 mm, R: 4.1 mm
rotation speed of rotating turret	20 rpm
main pressure	12 kN

[0171]

Reference example 7: Tablet comprising 388 mg of imeglimin hydrochloride (20)

A. Formulation composition of uncoated tablet comprising 388
5 mg of imeglimin hydrochloride

Granule, blended powder, and uncoated tablet which are composed of the formulation composition defined in Table 20-1 were prepared.

Table 20-1. Formulation composition			
	Ingredients	Formulation composition	
		(mg)	(wt%)
Ingredients in granule	imeglimin hydrochloride	388.16	70.0
	crystalline cellulose	111.84	20.17
	light anhydrous silicic acid	5.15	0.93
	croscarmellose sodium	10.55	1.9
	hydroxypropyl cellulose* ¹	27.7	5.0
	Total amount of granule	543.4	98.0
Ingredients used in blending	light anhydrous silicic acid	5.55	1.0
	magnesium stearate	5.55	1.0
	Total amount of blended powder and uncoated tablet	554.5	100
*1 hydroxypropyl cellulose of HPC-L:HPC-M = 4:1 was used.			

[0172]

10 B. Production process

(1) Preparation of 4 wt % hydroxypropyl cellulose solution
(10)

To 1920 g of purified water in a SUS beaker were

gradually added 64 g of HPC-L, then 16 g of HPC-M while stirring to make them dissolved. The solution was let stand overnight, and then stirred again to prepare 4 wt % hydroxypropyl cellulose solution (10).

5 [0173]

(2) Preparation of granule comprising imeglimin hydrochloride

According to the charging amount defined in Table 20-2 and the preparation condition defined Table 20-3, a granule
10 comprising imeglimin hydrochloride was prepared. First of all, imeglimin hydrochloride, crystalline cellulose, light anhydrous silicic acid, and croscarmellose sodium whose amounts of preparation are defined in Table 20-2 were thrown into a fluidized bed granulator/dryer machine (Multiplex MP-
15 01), and the blend was blended while fluxing for 3 minutes. Subsequently, 4 wt % hydroxypropyl cellulose solution (10) whose charging amount is defined in Table 20-2 was sprayed to the blend while fluxing. The obtained granule was dried and then screened with a screen mill (POWREX CORPORATION,
20 COMIL 194S) wherein the opening size is 1.4 mm, and the rotating speed is 1400 rpm to give a granule comprising imeglimin hydrochloride.

Table 20-2. Charging amount (granule)		
	Ingredients	Charging amount (g)
Ingredients in granule	imeglimin hydrochloride	232.9
	crystalline cellulose	67.10
	light anhydrous silicic acid	3.09
	croscarmellose sodium	6.33
	4 wt % hydroxypropyl cellulose solution (10)	415.5

Table 20-3. Preparation condition (Granulation)	
Item	Preparation condition
Container used	small container
Gun bore	1.0 mm
Gun height	low
Spray type	top-spray
Spray pressure	0.1 MPa
Charge air temperature	80°C
Charge air volume	55 m ³ /hr
Spray speed	about 10 g/min

[0174]

(3) Preparation of blended powder comprising imeglimin hydrochloride

5 According to the charging amount defined in Table 20-4, blended powder comprising imeglimin hydrochloride were prepared. To a plastic bag containing granule comprising imeglimin hydrochloride whose charging amount is defined in Table 20-4, light anhydrous silicic acid whose charging amount is defined in Table 20-4 was thrown, and the blend was blended while shaking for 2 minutes. Subsequently, magnesium stearate whose charging amount is defined in Table 20-4 was thrown into the plastic bag, and the blend was blended while shaking for a minute.

10

Table 20-4. Charging amount (blend)		
	Ingredients	Charging amount (g)
Ingredients used in blending	granule comprising imeglimin hydrochloride	251.45
	light anhydrous silicic acid	2.57
	magnesium stearate	2.57

[0175]

(4) Preparation of uncoated tablet comprising 388 mg of imeglimin hydrochloride

The blend was compressed with a rotary tablet press (KIKUSUI SEISAKUSHO LTD., VELA2) in the condition defined in Table 20-5 to prepare uncoated tablet containing 388 mg of imeglimin hydrochloride in each tablet.

Table 20-5. Preparation condition (tableting)	
Item	Preparation condition
punch shape	long diameter: 16.0 mm, short diameter: 6.5 mm, R: 4.1 mm
rotation speed of rotating turret	20 rpm
main pressure	17 kN

[0176]

Test 1: Bulk density of blended powder

The blended powders of Examples 1 - 13 and Reference examples 1, 2, and 4 - 7 were evaluated about bulk density. The bulk density was obtained by putting about 10 g of each blended powder gently into a 25 mL measuring cylinder or a 50 mL measuring cylinder, reading the height of each powder volume, and calculating each bulk density with the following formula. The results are shown in Table 21.

<Calculating formula of bulk density>

Bulk density (g/mL) = Sample weight (g)/Height of powder

volume (mL)

Table 21. Measured results of bulk density	
	bulk density
Example 1	0.35 g/ mL
Example 2	0.36 g/ mL
Example 3	0.51 g/ mL
Example 4	0.37 g/ mL
Example 5	0.43 g/ mL
Example 6	0.38 g/ mL
Example 7	0.45 g/ mL
Example 8	0.37 g/ mL
Example 9	0.39 g/ mL
Example 10	0.36 g/ mL
Example 11	0.47 g/ mL
Example 12	0.47 g/ mL
Example 13	0.48 g/ mL
Reference example 1	0.29 g/ mL
Reference example 2	0.48 g/ mL
Reference example 3	
Reference example 4	0.45 g/ mL
Reference example 5	0.57 g/ mL
Reference example 6	0.45 g/ mL
Reference example 7	0.46 g/ mL

[0177]

Test 2: Evaluation of tabletability and measurement of shape, hardness, and friability of uncoated tablet

5 Each tabletability of Examples 1 - 13 and Reference examples 1 - 7 were evaluated, and the thickness, hardness, and friability of each uncoated tablet thereof were measured. The thickness and hardness of the uncoated tablets were measured with MultiCheck 5 (ERWEKA), and the results were
 10 obtained from the average of 5 or 10 tablets. And, the friability was measured with FRIABILATOR TFT-1200 (Toyama Sangyo Co., Ltd.) according to the Japanese

Pharmacopoeia. The results are shown in Table 22.

Table 22. Measured results of shape, hardness, and friability of uncoated tablet							
	tabletability	shape of uncoated tablet (mm)			hardness of uncoated tablet	measured result of friability	
		long diameter	short diameter	thickness		friability	the number of capping tablet
Example 1	-	17.5	7.0	5.20	131 N	0.08%	0/12 tablets
Example 2	-	17.5	7.0	5.07	133 N	0.17%	0/12 tablets
Example 3	-	17.5	7.0	5.72	62 N	0.10%	0/12 tablets
Example 4	-	17.5	7.0	5.22	124 N	0.06%	0/12 tablets
Example 5	-	17.5	7.0	5.11	85 N	0.17%	0/12 tablets
Example 6	-	17.5	7.0	5.13	110 N	0.10%	0/12 tablets
Example 7	-	17.5	7.0	5.70	60 N	0.00%	0/12 tablets
Example 8	-	17.5	7.0	5.19	124 N	0.09%	0/12 tablets
Example 9	-	16.0	6.5	6.22	106 N	0.12%	0/12 tablets
Example 10	-	16.0	6.5	6.28	152 N	0.06%	0/12 tablets
Example 11	-	16.0	6.5	6.29	125 N	0.40%	0/12 tablets
Example 12	-	16.0	6.5	6.27	121 N	0.34%	0/12 tablets
Example 13	-	16.0	6.5	6.80	127 N	0.23%	0/12 tablets
Reference example 1	-	16.0	6.5	5.52	274 N	0.0%	0/12 tablets
Reference example 2	+	17.5	7.0	5.62	34 N	1.46%	11/12 tablets
Reference example 3	+	17.5	7.0	5.59	64 N	0.56% (1.98%)* ¹	1/12 tablets (6/12 tablets)* ¹
Reference example 4	++						
Reference example 5	++						
Reference example 6	++						

Reference example 7	-	16.0	6.5	6.33	143 N	0.24%	0/12 tablets
*1 The original test time defined in the Japanese Pharmacopoeia is 4 minutes (100 rotations), but 6 minutes were further added to the original 4 minutes to make the total test time 10 minutes (250 rotations), whose result was shown. -: The tendency of capping did not happen. +: The tendency of capping happened, but it was possible to obtain the sample. ++: The tendency of capping strongly happened, and it was impossible to make a tablet stably.							

As shown in Table 22, it has been clarified that Examples 1 - 13 have good strength, i.e., they have enough strength to be distributed as pharmaceutical products. On the other hand, Reference example 2 and Reference example 3 resulted in capping tablets, and did not meet the physical strength index (1.0 % or lower) that is based on the friability test of tablets according to the Japanese Pharmacopoeia, which means that the tablets are difficult to be on the market as tablet product. And, Reference examples 4 - 6 were not able to be tableted due to capping. The results suggested that the compression moldability of imeglimin is poor, and the preparation of a tablet comprising imeglimin may easily result in tableting trouble (capping) when the content of imeglimin in a tablet is high. In addition, as for the preparation of a tablet comprising imeglimin, it has been clarified that capping easily happens when the granulation is carried out by stirring-granulation which is generally chosen in case of a high-drug-containing tablet. In general, fluid-bed granulation is not used for high-drug-containing tablet since high content of a drug may

cause poor fluidity and thereby the granulation becomes difficult. In case of imeglimin, however, it has been found that even high-drug-containing composition can be easily flowed in a fluid-bed granulator by adding a disintegrant to the composition. In addition, although it has been known that the high-volume use of water-soluble polymeric binder may cause coarse-large grain and thereby may degrade the tabletability and the dissolution of tablets, the present inventors tried using a relatively large amount of water-soluble polymeric binder such as hydroxypropyl cellulose, polyvinyl alcohol, and hydroxypropylmethylcellulose and then succeeded in preparing a small tablet comprising imeglimin which does not result in tableting trouble.

[0178]

Test 3: The assumed number of dosage form for daily dose

The assumed numbers of each dosage form for daily dose are shown in Table 23. The reference examples were not able to be stably tableted due to capping, instead the assumed numbers in the reference examples were determined by calculating according the following formula, assuming that a capsule is filled with each blended powder. Each calculated number was indicated as an integer by rounding up to the first decimal place.

<Calculating formula for the number of capsule for daily dose>

The number of dosage form = weight (g) of blended powder
comprising 2000 mg of imeglimin/bulk density (g/mL)/volume
of capsule body (mL)

<Size of capsule>

5 #1 capsule

Volume of body (mL): about 0.50

Overall length of capsule (mm): about 19.4

Outer diameter of body (mm): about 6.63

#2 capsule

10 Volume of body (mL): about 0.37

Overall length of capsule (mm): about 18.0

Outer diameter of body (mm): about 6.07

Table 23. The number of dosage form for daily dose			
	The number of dosage form comprising 2000 mg of imeglimin for daily dose		
	tablet	#1 capsule	#2 capsule
Example 1	4 tablets	13 capsules	18 capsules
Example 2	4 tablets	13 capsules	17 capsules
Example 3	4 tablets	9 capsules	12 capsules
Example 4	4 tablets	12 capsules	17 capsules
Example 5	4 tablets	11 capsules	14 capsules
Example 6	4 tablets	12 capsules	16 capsules
Example 7	4 tablets	11 capsules	14 capsules
Example 8	4 tablets	13 capsules	17 capsules
Example 9	4 tablets	12 capsules	16 capsules
Example 10	4 tablets	13 capsules	17 capsules
Example 11	4 tablets	10 capsules	13 capsules
Example 12	4 tablets	10 capsules	13 capsules
Example 13	4 tablets	10 capsules	14 capsules
Reference example 1	12 tablets	46 capsules	62 capsules
Reference example 2		10 capsules	13 capsules
Reference example 3			
Reference example 4		10 capsules	14 capsules
Reference example 5		8 capsules	11 capsules
Reference example 6		10 capsules	14 capsules
Reference example 7	6 tablets	13 capsules	17 capsules

As shown in Table 23, undoubtedly the present invention can make it possible to reduce the number of dosage form for daily dose, thereby it is expected that the productivity can be improved and the adherence to administration can be improved.

[0179]

Test 4: Dissolution test

The tablets prepared in Example 1 - Example 13 and Reference example 7 were evaluated by dissolution test according to the Japanese Pharmacopoeia, General Tests, Dissolution Test.

5 <Condition of dissolution test>

Method: the Japanese Pharmacopoeia, General Tests, Dissolution Test (Basket Method)

Rotating speed: 100 rpm

Volume of dissolution medium: 900 mL

10 Temperature of dissolution medium: $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$

Dissolution medium: 2nd fluid for dissolution test

Number tested: N = 3 or more

<Preparation of test solution>

15 The tablet was put into a vessel filled with 900 mL of the dissolution medium and the test was started. 30 minutes later, 5 mL of the test solution was collected with a 10 mL syringe, and filtrated slowly with a membrane filter (Millex LG 0.2 μm x 25 mm, Millipore). The early 1 mL of the filtrate was removed, and the rest of the filtrate was used as the
20 test sample.

<Preparation of standard solution>

25 27.78 mg of imeglimin hydrochloride was put into 50 mL measuring flask, which was filled with 2nd fluid for dissolution test to be dissolved. The solution was used as the standard solution.

<Analytical condition of high-performance liquid chromatography>

High-performance liquid chromatography machine: Shimadzu UFLC-XR

- 5 Detective wave length: 240 nm
- Column: Phenomenex, Luna PFP (2) 150 mm x 4.6 mm I.D.
particle size 3 μ m
- Mobile phase: a mixture of water/methanol/trifluoroacetic acid (1000/250/1)
- 10 Analytical time: 6 minutes
- Flow rate: 1.2 mL/min
- Column temperature: 40°C
- Injection volume: 2 μ L
- Temperature of sample cooler: 25°C
- 15 Washing solution for syringe: a mixture of methanol/water (1/4)
- [0180]

The results of the dissolution test are shown in Table 24.

Table 24. Results of dissolution test			
	tablet	Mean dissolution rate (%)	
		30 min. later	60 min. later
Example 1	uncoated tablet	100.8%	101.5%
Example 2	uncoated tablet	98.2%	99.5%
Example 3	uncoated tablet	94.8%	97.5%
Example 4	uncoated tablet	99.9%	101.3%
Example 5	uncoated tablet	97.1%	100.7%
Example 6	uncoated tablet	97.6%	103.1%

	film-coated tablet	99.5%	103.0%
Example 7	uncoated tablet	89.9%	101.4%
Example 8	uncoated tablet	100.0%	100.7%
Example 9	uncoated tablet	103.8%	103.7%
Example 10	uncoated tablet	103.9%	104.6%
Example 11	uncoated tablet	102.2%	102.7%
Example 12	uncoated tablet	101.8%	102.2%
Example 13	uncoated tablet	97.3%	102.4%
Reference example 7	uncoated tablet	73.6%	102.1%

As shown in Table 24, both of uncoated tablets and FC tablets of the present invention have quick dissolution, which is expected to be high absorption in bodies. And, the film-coating had little influence on the dissolution.

Although it has been known that the high-volume use of water-soluble polymeric binder may cause coarse-large grain and thereby may degrade the tabletability and the dissolution of tablets, the present inventors tried using a relatively large amount of water-soluble polymeric binder such as hydroxypropyl cellulose, polyvinyl alcohol, and hydroxypropylmethylcellulose and then succeeded in preparing a small tablet comprising imeglimin which does not result in tableting trouble.

INDUSTRIAL APPLICABILITY

[0181]

The present inventors have found that it is possible to stably prepare a small-sized tablet comprising imeglimin which has excellent dissolubility, by fluid-bed granulation

with a disintegrant, and a high percentage of one or more water-soluble binders selected from the group consisting of hydroxypropyl cellulose, polyvinyl alcohol and hydroxypropylmethylcellulose. Thereby, the finding has made
5 it possible to effectively and stably prepare a table that can facilitate the high continuation of taking the medicine, which is a more excellent therapy for diabetes.

CLAIMS

1. A tablet comprising

(1) imeglimin or a pharmaceutically acceptable salt
5 thereof in 84 - 95 wt % content,

(2) one or more binders selected from the group
consisting of hydroxypropyl cellulose, polyvinyl alcohol,
and hydroxypropylmethylcellulose, and

(3) a disintegrant.

10

2. The tablet of claim 1, which comprises (1) imeglimin or
a pharmaceutically acceptable salt thereof in 88 - 95 wt %
content.

15 3. The tablet of claim 1, which comprises (1) imeglimin or
a pharmaceutically acceptable salt thereof in 90 - 95 wt %
content.

4. The tablet of claim 1 or 2, which comprises (1)
20 imeglimin or a pharmaceutically acceptable salt thereof in
90 - 92 wt % content.

5. The tablet of claim 1 or 2, which comprises (3) a
disintegrant in 0.2 - 7.5 wt % content.

25

6. The tablet of any one of claims 1 to 5, which comprises
(3) a disintegrant in 0.2 - 5.0 wt % content.

7. The tablet of any one of claims 1 to 6, which comprises
5 (3) a disintegrant in 0.2 - 4.0 wt % content.

8. The tablet of any one of claims 1 to 7, which comprises
(3) a disintegrant in 0.2 - 3.0 wt % content.

10 9. The tablet of any one of claims 1 to 8, which comprises
(3) a disintegrant in 0.2 - 2.0 wt % content.

10. The tablet of claim 1 or 2, which comprises (3) a
disintegrant in 0.5 - 7.5 wt % content.

15

11. The tablet of any one of claims 1 to 4 and 10, which
comprises (3) a disintegrant in 0.5 - 5.0 wt % content.

12. The tablet of any one of claims 1 to 4, 10, and 11,
20 which comprises (3) a disintegrant in 0.5 - 4.0 wt % content.

13. The tablet of any one of claims 1 to 4, and 10 to 12,
which comprises (3) a disintegrant in 0.5 - 3.0 wt % content.

25 14. The tablet of any one of claims 1 to 4, and 10 to 13,

which comprises (3) a disintegrant in 0.5 - 2.0 wt % content.

15. The tablet of any one of claims 1 to 14, which comprises
(2) one or more binders selected from the group consisting
5 of hydroxypropyl cellulose, polyvinyl alcohol, and
hydroxypropylmethylcellulose in 4.5 - 7.0 wt % content.

16. The tablet of any one of claims 1 to 15, which comprises
(2) one or more binders selected from the group consisting
10 of hydroxypropyl cellulose, polyvinyl alcohol, and
hydroxypropylmethylcellulose in 4.5 - 6.0 wt % content.

17. The tablet of any one of claims 1 to 16, which comprises
(2) one or more binders selected from the group consisting
15 of hydroxypropyl cellulose, polyvinyl alcohol, and
hydroxypropylmethylcellulose in 4.5 - 5.5 wt % content.

18. The tablet of any one of claims 1 to 17, which comprises
(2) one or more binders selected from the group consisting
20 of hydroxypropyl cellulose, polyvinyl alcohol, and
hydroxypropylmethylcellulose in 4.8 - 5.5 wt % content.

19. The tablet of any one of claims 1 to 18, wherein the
viscosity of hydroxypropyl cellulose is 2.0 - 400 mPa·s.

20. The tablet of any one of claims 1 to 19, wherein the viscosity of hydroxypropyl cellulose is 6.0 - 400 mPa·s.

21. The tablet of any one of claims 1 to 20, wherein the
5 viscosity of polyvinyl alcohol is 3.4 - 9.2 mPa·s.

22. The tablet of any one of claims 1 to 21, wherein the viscosity of polyvinyl alcohol is 4.3 - 5.8 mPa·s.

10 23. The tablet of any one of claims 1 to 22, wherein the viscosity of hydroxypropylmethylcellulose is 4.0 - 12.0 mPa·s.

24. The tablet of any one of claims 1 to 23, wherein the
15 viscosity of hydroxypropylmethylcellulose is 4.0 - 6.0 mPa·s.

25. The tablet of any one of claims 1 to 24, wherein the viscosity of hydroxypropylmethylcellulose is 4.5 - 6.0 mPa·s.

20 26. The tablet of any one of claims 1 to 19 and 21 to 25, which comprises hydroxypropyl cellulose having a viscosity of 2.0 - 2.9 mPa·s in not more than 3.5 wt % content, and hydroxypropyl cellulose having a viscosity of 150 - 400 mPa·s in not more than 1.5 wt % content.

27. The tablet of any one of claims 1 to 22 and 26, wherein the (2) binder is one or two selected from the group consisting of hydroxypropyl cellulose and polyvinyl alcohol.

5 28. The tablet of any one of claims 1 to 20 and 23 to 26, wherein the (2) binder is one or two selected from the group consisting of hydroxypropyl cellulose and hydroxypropylmethylcellulose.

10 29. The tablet of any one of claims 1 to 20 and 26 to 28, wherein the (2) binder is hydroxypropyl cellulose.

15 30. The tablet of any one of claims 1 to 29, wherein the (3) disintegrant is one or more selected from the group consisting of croscarmellose sodium, sodium starch glycolate, and crospovidone.

31. The tablet of any one of claims 1 to 30, wherein the (3) disintegrant is croscarmellose sodium.

20

32. The tablet of any one of claims 1 to 31, which is prepared by fluid-bed granulation.

25 33. A method for preparing the tablet of any one of claims 1 to 31, which is done by fluid-bed granulation.

34. The tablet of any one of claims 1 to 18, which is prepared by fluid-bed granulation.

5 35. A method for preparing the tablet of any one of claims 1 to 18, which is done by fluid-bed granulation.

36. The method of claim 35, comprising a step of preparing a granule comprising (1) imeglimin or a pharmaceutically acceptable salt thereof, (2) one or more binders selected
10 from the group consisting of hydroxypropyl cellulose, polyvinyl alcohol, and hydroxypropylmethylcellulose, and (3) a disintegrant by fluid-bed granulation.

15 37. The method of claim 36, comprising a step of preparing the granule by adding (2) one or more binders selected from the group consisting of hydroxypropyl cellulose, polyvinyl alcohol, and hydroxypropylmethylcellulose to a powder comprising (1) imeglimin or a pharmaceutically acceptable
20 salt thereof and (3) a disintegrant, followed by the granulation by fluid-bed granulation.

38. The method of claim 36 or 37, further comprising tableting process or film coating process.

39. The method of claim 38, wherein the fluid-bed granulation process, the tableting process, or the film coating process is carried out in 10 kg or more production scale.

5

40. The method of claim 38, wherein the fluid-bed granulation process, the tableting process, or the film coating process is carried out in 30 kg or more production scale.

10

41. The method of claim 38, wherein the fluid-bed granulation process, the tableting process, or the film coating process is carried out in 50 kg or more production scale.

15