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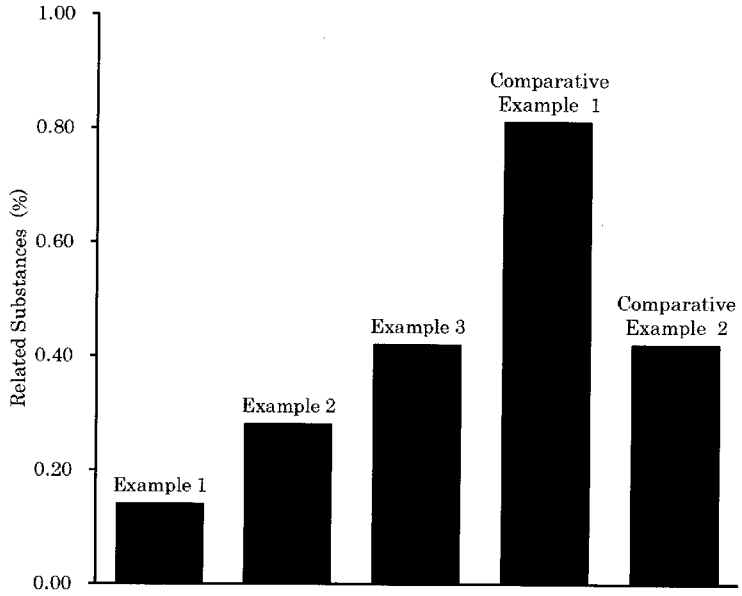
[Continued on next page]

(54) Title: CANDESARTAN CILEXETIL-CONTAINING PREPARATION

[Fig.1]



(57) Abstract: A candesartan cilexetil-containing preparation contains candesartan cilexetil and lauromacrogol. The lauromacrogol may be contained at a ratio of 2.4 parts by weight or less with respect to 100 parts by weight of the candesartan cilexetil-containing preparation. The candesartan cilexetil-containing preparation may further contain at least one kind of pharmacologically acceptable additives among a diluent, a disintegrant and a binder.

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Description

Title of Invention: CANDESARTAN CILEXETIL-CONTAINING PREPARATION

Technical Field

[0001]

The present invention relates to a candesartan cilexetil-containing preparation, and specifically to a stable candesartan cilexetil-containing preparation in which generation of related substances is inhibited during a production process or storage thereof.

Background Art

[0002]

Candesartan cilexetil, which is an angiotensin II receptor antagonist, is widely used as a therapeutic drug for hypertension. Regarding candesartan cilexetil, it is known that the crystals thereof are distorted by pressure, friction, heat or the like during granulation, tableting or the like in formulation process thereof, and as a result, the purity is decreased and over-time generation of related substances occurs. So far, various methods have been proposed for stabilizing candesartan cilexetil preparations. For example, Patent Literature 1 describes that in order to stabilize a candesartan cilexetil preparation, a low-melting fatty oil-like substance is incorporated to inhibit the generation of related substances. Patent Literature 2 describes that a hydrophilic substance with hydrocolloidal properties is incorporated to adequately stabilize the

candesartan cilexetil, against its degradation during the tableting process.

[0003]

Patent Literature 3 describes incorporating a pH adjuster to stabilize a candesartan cilexetil compound in the preparation. Patent Literature 4 describes incorporating at least one kind of nonionic surfactants at a ratio of about 0.01 to 10% by weight with respect to the pharmaceutical composition. Patent Literature 5 describes incorporating sodium stearyl fumarate. Patent Literature 6 describes incorporating triethyl citrate. Patent Literature 7 describes incorporating stearic acid. Patent Literature 8 describes incorporating D-mannitol to perform fluidized-bed granulation.

Citation List

Patent Literature

[0004]

PTL 1: Japanese Laid-Open Patent Publication No. Hei 5-194218

PTL 2: Japanese PCT National Phase Laid-Open Patent Publication No. 2008-528456

PTL 3: Japanese PCT National Phase Laid-Open Patent Publication No. 2010-522692

PTL 4: Japanese PCT National Phase Laid-Open Patent Publication No. 2010-535212

PTL 5: Japanese Laid-Open Patent Publication No. 2012-51829

PTL 6: Japanese Laid-Open Patent Publication No. 2012-149056

PTL 7: Japanese Laid-Open Patent Publication No. 2012-153629

PTL 8: Japanese Laid-Open Patent Publication No. 2012-162467

Summary of Invention

Technical Problem

[0005]

As described above, a method for improving the stability of the candesartan cilexetil in a preparation is desired.

[0006]

The present invention solves the above-described problems by means of a different method from methods reported so far. An object of the present invention is to provide a stable candesartan cilexetil-containing preparation in which generation of related substances is inhibited during a production process or storage thereof.

Solution to Problem

[0007]

According to an embodiment of the present invention, a candesartan cilexetil-containing preparation containing candesartan cilexetil and lauromacrogol is provided.

[0008]

The lauromacrogol may be contained at a ratio of 2.4 parts by weight or less with respect to 100 parts by weight of the candesartan cilexetil-containing preparation.

[0009]

The lauromacrogol may be selected from polyoxyethylene(2) lauryl ether, polyoxyethylene(4.2) lauryl ether, polyoxyethylene(9) lauryl ether, polyoxyethylene(21) lauryl ether, and polyoxyethylene(25) lauryl ether.

[0010]

The lauromacrogol may be polyoxyethylene(25) lauryl ether.

[0011]

The candesartan cilexetil-containing preparation may further contain at least one kind of pharmacologically acceptable additives among a diluent, a disintegrant and a binder.

[0012]

The additive may be contained in the range of 500 parts by weight or greater and 10000 parts by weight or less with respect to 100 parts by weight of candesartan cilexetil.

Advantageous Effects of Invention

[0013]

The present invention provides a stable candesartan cilexetil-containing preparation in which generation of related substances is inhibited during a production process or storage thereof.

Brief Description of Drawings

[0014]

[Fig. 1] FIG. 1 shows results of purity measurement on candesartan cilexetil-containing compositions in examples and comparative examples of the present

invention.

[Fig. 2] FIG. 2 shows results of purity measurement on candesartan cilexetil-containing compositions in examples and comparative examples of the present invention.

[Fig. 3] FIG. 3 shows results of hardness measurement on candesartan cilexetil-containing compositions in examples of the present invention.

[Fig. 4] FIG. 4 shows results of dissolution measurement on candesartan cilexetil from the candesartan cilexetil-containing compositions in examples of the present invention.

Description of Embodiments

[0015]

The present inventors made a research on an additive capable of inhibiting generation of related substances in a candesartan cilexetil-containing preparation. As a result of the research, the present inventors found that generation of related substances in a candesartan cilexetil-containing preparation could be inhibited during the preparation process or storage thereof by incorporating lauromacrogol thereto, and thus completed the present invention. The present invention reports that lauromacrogol contributes to stabilization of candesartan cilexetil in a tablet for the first time in history.

[0016]

Hereinafter, a candesartan cilexetil-containing preparation according to the present invention will be described with reference to the drawings. The candesartan cilexetil-containing preparation according to the present invention is not limited to any

of the following embodiments and examples.

[0017]

A candesartan cilexetil-containing preparation according to the present invention contains lauromacrogol. Specifically, lauromacrogol is contained at a ratio of 0.01 parts by weight or greater and 2.4 parts by weight or less with respect to 100 parts by weight of the candesartan cilexetil-containing preparation.

[0018]

In an embodiment according to the present invention, it is not preferable that lauromacrogol is contained at a ratio greater than 2.4 parts by weight with respect to 100 parts by weight of the candesartan cilexetil-containing preparation. When lauromacrogol is contained at a ratio greater than 2.4 parts by weight, the hardness of the tablet is decreased and the dissolution of candesartan cilexetil is decreased.

[0019]

Candesartan cilexetil is an active ingredient of a candesartan cilexetil-containing preparation according to the present invention, and has a chemical name of (RS)-1-[(cyclohexyloxy)carbonyloxy]ethyl 2-ethoxy-1-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate.

[0020]

Lauromacrogol, which is contained in a candesartan cilexetil-containing preparation according to the present invention is polyoxyethylene lauryl ether. Usable examples of the polyoxyethylene lauryl ether are polyoxyethylene(2) lauryl ether, polyoxyethylene(4.2) lauryl ether, polyoxyethylene(9) lauryl ether,

polyoxyethylene(21) lauryl ether, and polyoxyethylene(25) lauryl ether. Among these, polyoxyethylene(21) lauryl ether and polyoxyethylene(25) lauryl ether are preferable. Especially, polyoxyethylene(25) lauryl ether (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) is preferably usable in a candesartan cilexetil-containing preparation according to the present invention.

[0021]

A candesartan cilexetil-containing preparation according to the present invention may contain at least one kind of pharmacologically acceptable additives among commonly used diluents, disintegrants and binders.

[0022]

Usable diluents include, for example, crystalline cellulose, starches such as corn starch, lactose, powdered sugar, granulated sugar, glucose, mannitol, light anhydrous silicic acid, talc, magnesium oxide, magnesium carbonate, calcium carbonate, anhydrous dibasic calcium phosphate, tribasic calcium phosphate, xylitol, sorbitol, and the like. These diluents may be used independently or in a combination of two or more.

[0023]

Usable disintegrants include, for example, crystalline cellulose, sodium carboxymethyl starch, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, crosslinked polyvinylpyrrolidone, low substituted hydroxypropylcellulose, starches and the like. These disintegrants may be used independently or in a combination of two or more.

[0024]

Usable binders are pharmacologically acceptable binders including, for example, sucrose, gelatin, powdered acacia, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose (carmellose), crystalline cellulose·carboxymethylcellulose sodium, polyvinylpyrrolidone, pullulan, dextrin, tragacanth, sodium alginate, pregelatinized starch, polyvinyl alcohol and the like. These binders may be used independently or in a combination of two or more.

[0025]

An additive which is at least one kind among these diluents, disintegrants and binders is contained preferably in the range of 500 parts by weight or greater and 10000 parts by weight or less, more preferably in the range of 700 parts by weight or greater and 8000 parts by weight or less, and still more preferably in the range of 900 parts by weight or greater and 7000 parts by weight or less, with respect to 100 parts by weight of candesartan cilexetil.

[0026]

Candesartan cilexetil may be combined with, in addition to a pharmacologically acceptable additive such as a diluent, a disintegrant, a binder or the like, any of other commonly used pharmacologically acceptable additives including, for example, lubricants, fluidizer, antistatic agents, surfactants, flavoring agents, wetting agents, fillers, bulking agents, adsorbents, preservatives (e.g., antiseptics), buffers, disintegration extenders, colorants and the like.

[0027]

Usable lubricants include, for example, magnesium stearate, light anhydrous

silicic acid, talc, calcium stearate, sodium stearyl fumarate, sucrose esters of fatty acid, L-leucine, and the like. Usable antistatic agents include, for example, light anhydrous silicic acid and the like. Usable surfactants include, for example, anionic surfactants such as sodium alkylsulfate; nonionic surfactants such as polyoxyethylene sorbitan fatty acid ester, polyoxyethylene fatty acid ester, polyoxyethylene castor oil derivative; and the like. Usable flavoring agents include, for example, fragrances; sweetening agents such as sucrose, lactose, mannitol, xylitol, saccharin, saccharin sodium, aspartame, stevioside, sucralose, acesulfame potassium, thaumatin, erythritol; and the like. Usable wetting agents include, for example, polyethylene glycol (macrogol), glycerin, propylene glycol, and the like. These commonly used additives other than the diluents, disintegrants and binders may also be used independently or in a combination of two or more.

[0028]

According to the present invention, a stable candesartan cilexetil-containing preparation in which generation of related substances is inhibited during a production process or storage thereof can be obtained by incorporation of lauromacrogol.

[0029]

(Production method)

A candesartan cilexetil-containing preparation according to the present invention can be produced by a method known in the pharmaceutical field. For example, tablet can be produced by performing respective operations such as mixing, granulation, drying, particle size regulation, and tableting with respect to candesartan cilexetil, lauromacrogol, an additive such as a diluent, a disintegrant, a binder or the

like using commonly used solvent according to a method well known in the art. Between the particle size regulation and the tableting, a disintegrant, a lubricant or the like may be mixed. Among these operations, granulation may be performed by use of an apparatus such as, for example, an agitation granulator, a fluidized-bed granulator, a biaxial granulator or the like. Tableting may be performed by use of a commercially available tableting machine.

[0030]

In this embodiment, lauromacrogol is incorporated at a ratio of 2.4 parts by weight or less with respect to 100 parts by weight of the candesartan cilexetil-containing preparation. Preferably, lauromacrogol is incorporated at a ratio of 0.01 parts by weight or greater and 2.4 parts by weight or less with respect to 100 parts by weight of the candesartan cilexetil-containing preparation.

[0031]

In this embodiment, uncoated tablets or post-granulation uncoated granules may be coated. Coating is preferably performed by use of a film coating machine, a fluidized-bed granulator or the like. Coating can be performed with a coating agent well known in the art. Usable coating agents include, for example, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, aminoalkyl methacrylate copolymer E, aminoalkyl methacrylate copolymer RS, methacrylic acid copolymer L, methacrylic acid copolymer LD, methacrylic acid copolymer S, dried methacrylic acid copolymer LD, ethyl acrylate-methyl methacrylate

copolymer dispersion, sucrose and the like.

[0032]

According to a method for producing a candesartan cilexetil-containing preparation in this embodiment, lauromacrogol is incorporated. Thus, a candesartan cilexetil-containing preparation in which generation of related substances is inhibited during a production process or storage thereof can be produced.

Examples

[0033]

The above-described candesartan cilexetil-containing preparation according to the present invention will be described in more detail by way of specific production methods and test results thereof.

[0034]

(Example 1)

After mixing 10.0 g of candesartan cilexetil, 464 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose and 0.25 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such

that the tablets would each have a weight of 125.0 mg and a thickness of 2.6 mm. Thus, the tablets were obtained.

[0035]

(Example 2)

After mixing 10.0 g of candesartan cilexetil, 464 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose and 0.10 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.6 mm (at the same tableting pressure as that in Example 1). Thus, the tablets were obtained.

[0036]

(Example 3)

After mixing 10.0 g of candesartan cilexetil, 464 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose and 0.05 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size

regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.6 mm (at the same tableting pressure as that in Example 1). Thus, the tablets were obtained.

[0037]

(Example 4)

After mixing 10.0 g of candesartan cilexetil, 463 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose and 1.00 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.5 mm (at a tableting pressure higher than that in Examples 1 through 3). Thus, the tablets were obtained.

[0038]

(Example 5)

After mixing 10.0 g of candesartan cilexetil, 463.5 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex

Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose and 0.50 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.5 mm (at the same tableting pressure as that in Example 4). Thus, the tablets were obtained.

[0039]

(Example 6)

After mixing 10.0 g of candesartan cilexetil, 464 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose and 0.25 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.5 mm (at the same tableting pressure as that in Example 4). Thus, the tablets were obtained.

[0040]

(Example 7)

After mixing 10.0 g of candesartan cilexetil, 464 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose and 0.10 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.5 mm (at the same tableting pressure as that in Example 4). Thus, the tablets were obtained.

[0041]

(Example 8)

After mixing 10.0 g of candesartan cilexetil, 464 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose and 0.05 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such

that the tablets would each have a weight of 125.0 mg and a thickness of 2.5 mm (at the same tableting pressure as that in Example 4). Thus, the tablets were obtained.

[0042]

(Example 9)

After mixing 60.0 g of candesartan cilexetil, 399 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose, 15.0 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) and 0.15 g of food yellow No. 5 was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.5 mm (at the same tableting pressure as that in Example 4). Thus, the tablets were obtained.

[0043]

(Example 10)

After mixing 60.0 g of candesartan cilexetil, 404 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose, 10.0 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) and 0.15 g of food yellow No. 5 was sprayed thereto, and granulation and drying were performed.

The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.5 mm (at the same tableting pressure as that in Example 4). Thus, the tablets were obtained.

[0044]

(Example 11)

After mixing 60.0 g of candesartan cilexetil, 409 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose, 5.00 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) and 0.15 g of food yellow No. 5 was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.5 mm (at the same tableting pressure as that in Example 4). Thus, the tablets were obtained.

[0045]

(Example 12)

After mixing 60.0 g of candesartan cilexetil, 411.5 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose, 2.50 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) and 0.15 g of food yellow No. 5 was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.5 mm (at the same tableting pressure as that in Example 4). Thus, the tablets were obtained.

[0046]

(Example 13)

After mixing 60.0 g of candesartan cilexetil, 413 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose, 1.00 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) and 0.15 g of food yellow No. 5 was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by

Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.5 mm (at the same tableting pressure as that in Example 4). Thus, the tablets were obtained.

[0047]

(Example 14)

After mixing 60.0 g of candesartan cilexetil, 413.5 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose, 0.50 g of lauromacrogol (produced by Nikko Chemicals Co., Ltd.; trade name: BL-25) and 0.15 g of food yellow No. 5 was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.5 mm (at the same tableting pressure as that in Example 4). Thus, the tablets were obtained.

[0048]

(Comparative example 1)

After mixing 10.0 g of candesartan cilexetil, 464 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose was sprayed thereto, and granulation and drying were performed. The particle size of

resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.6 mm (at the same tableting pressure as that in Example 1). Thus, the tablets were obtained.

[0049]

(Comparative example 2)

After mixing 12.0 g of candesartan cilexetil, 483.6 g of lactose hydrate, 120 g of corn starch, and 48.0 g of stearic acid by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 30 g of hydroxypropylcellulose was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 24.0 g of carmellose calcium, and 2.40 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 120.0 mg and a thickness of 2.5 mm (at the same tableting pressure as that in Example 1). Thus, the tablets were obtained.

[0050]

(Comparative example 3)

After mixing 10.0 g of candesartan cilexetil, 464 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 25 g of hydroxypropylcellulose was

sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 20.0 g of croscarmellose sodium, and 6.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 125.0 mg and a thickness of 2.5 mm (at the same tableting pressure as that in Example 4). Thus, the tablets were obtained.

[0051]

(Comparative example 4)

After mixing 10.0 g of candesartan cilexetil, 477 g of lactose hydrate, and 100 g of corn starch by use of a fluidized-bed granulator (produced by Powrex Corporation), an aqueous solution containing 20 g of hydroxypropylcellulose and 13.0 g of macrogol 6000 was sprayed thereto, and granulation and drying were performed. The particle size of resultant granules was regulated through a No. 22 sieve. The obtained particle-size regulated granules, 28.0 g of carmellose calcium, and 2.00 g of magnesium stearate were mixed by a V blender (produced by Fuji Paudal Co., Ltd.). The resultant mixture was tableted by a rotary tableting machine (produced by Kikusui Seisakusho Ltd.) such that the tablets would each have a weight of 130.0 mg and a thickness of 2.6 mm (at the same tableting pressure as that in Example 4). Thus, the tablets were obtained.

[0052]

(Purity)

On the tablets in Examples 1 through 8 and Comparative examples 1 through

4, the purity was evaluated. The purity evaluation was performed as follows. The tablets were stored at 40°C at 75% RH for 2 weeks, and then a test was performed in conformity to the candesartan cilexetil tablet purity test described in the Japanese Pharmacopoeia Sixteenth Edition. Thus, the purity was measured. The measurement results are shown in FIG. 1 and FIG. 2.

[0053]

As can be seen from the results shown in FIG. 1 and FIG. 2, a smaller amount of related substances is detected in Examples 1 through 8 than in Comparative examples 1 and 3, in which lauromacrogol is not incorporated. It is also seen regarding Examples 1 through 8 that when the amount of lauromacrogol is larger, the detected amount of related substances is smaller. A low-melting fatty oil-like substance, such as macrogol 6000, is incorporated to inhibit the generation of related substances in the conventional art, as is described in Patent Literature 1. Patent Literature 1 describes that in order to inhibit the generation of related substances, macrogol 6000 is incorporated at a ratio of 5 parts by weight with respect to 100 parts by weight of the candesartan cilexetil-containing preparation in the example. Patent Literature 7 describes that in order to inhibit the generation of related substances, stearic acid is incorporated at a ratio of 3.1 parts by weight or 6.2 parts by weight with respect to 100 parts by weight of the candesartan cilexetil-containing preparation in the example. In Comparative example 2, stearic acid as stabilizing agent in the conventional art is incorporated. In Comparative example 4, macrogol is incorporated. In these comparative examples, the detected amount of related substances is smaller than in Comparative examples 1 and 3 with no incorporation of stabilizing agent. However,

stearic acid should be incorporated at a ratio of 6.7 parts by weight with respect to 100 parts by weight of the candesartan cilexetil-containing preparation to inhibit the generation of related substances at the same level as Example 3, as is shown in Comparative example 2. In Comparative example 4, macrogol 6000 should be incorporated at a ratio of 2.0 parts by weight with respect to 100 parts by weight of the candesartan cilexetil-containing preparation to inhibit the generation of related substances at the same level as Example 4 or 5 in which lauromacrogol is contained at a ratio of 0.16 parts by weight or less with respect to 100 parts by weight of the candesartan cilexetil-containing preparation. Stearic acid or macrogol needs to be incorporated in a larger amount than in Examples 1 through 8 in which lauromacrogol is incorporated. From these results, it is understood that the candesartan cilexetil-containing preparations in Examples 1 through 8, owing to containing lauromacrogol, can significantly inhibit generation of related substances with a smaller amount of the stabilizing agent than in the conventional art.

[0054]

(Hardness)

Next, on the tablets in Examples 9 through 14, the relationship between the amount of lauromacrogol and the hardness of the tablets was examined. The hardness was measured as follows. The hardness of three tablets in each example was measured by a Schleuniger tablet hardness tester (MODEL 6D), and the average value thereof was set as the hardness of the tablets in the corresponding example. For measuring the hardness of tablets with a score therein, all such tablets were each set such that the surface with the score was directed upward and thus the score was

perpendicular to the direction in which the hardness tester would push the tablet. The results of the hardness measurement on the tablets in Examples 9 through 14 are shown in FIG. 3. In addition, the amounts of lauromacrogol of the Examples with respect to 100 parts by weight of the candesartan cilexetil-containing preparation are shown in FIG. 3.

[0055]

As is clear from FIG. 3, regarding Examples 9 through 14, when the amount of lauromacrogol is larger, the hardness of the tablet is lower.

[0056]

(Dissolution)

On the tablets in Examples 9 through 14, the relationship between the amount of lauromacrogol and the dissolution of candesartan cilexetil was examined. The dissolution of candesartan cilexetil was measured as follows. A test was performed in conformity to the description on the dissolution of candesartan cilexetil tablet in the Japanese Pharmacopoeia Sixteenth Edition, and the dissolution rate (%) in 45 minutes of candesartan cilexetil was measured. The results of the dissolution measurement of candesartan cilexetil on the tablets in Examples 9 through 14 are shown in FIG. 4. In addition, the amounts of lauromacrogol of the Examples with respect to 100 parts by weight of the candesartan cilexetil-containing preparation are shown in FIG. 4.

[0057]

As is clear from FIG. 4, regarding Examples 9 through 14, when the amount of lauromacrogol is larger, the dissolution of candesartan cilexetil from the tablet is

lower.

CLAIMS

[Claim 1]

A candesartan cilexetil-containing preparation, comprising candesartan cilexetil and lauromacrogol.

[Claim 2]

The candesartan cilexetil-containing preparation according to claim 1, wherein the lauromacrogol is contained at a ratio of 2.4 parts by weight or less with respect to 100 parts by weight of the candesartan cilexetil-containing preparation.

[Claim 3]

The candesartan cilexetil-containing preparation according to claim 2, wherein the lauromacrogol is selected from polyoxyethylene(2) lauryl ether, polyoxyethylene(4.2) lauryl ether, polyoxyethylene(9) lauryl ether, polyoxyethylene(21) lauryl ether, and polyoxyethylene(25) lauryl ether.

[Claim 4]

The candesartan cilexetil-containing preparation according to claim 2, wherein the lauromacrogol is polyoxyethylene(25) lauryl ether.

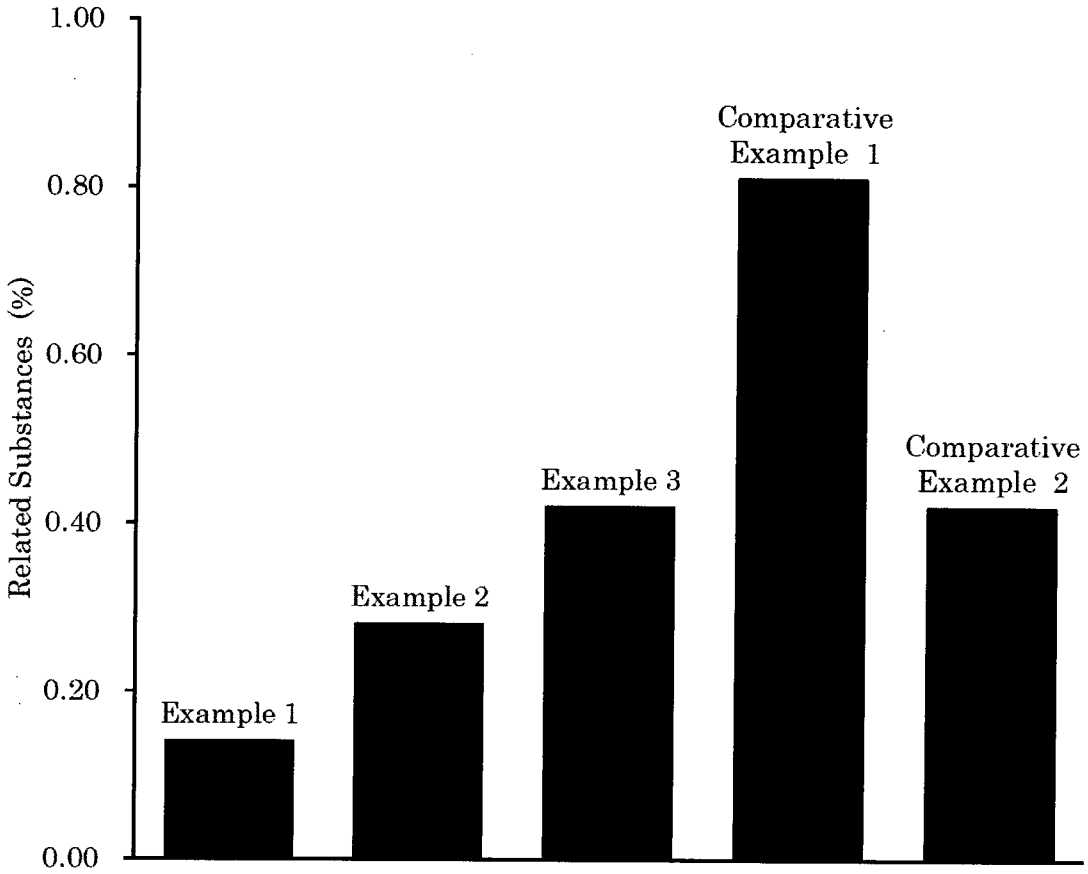
[Claim 5]

The candesartan cilexetil-containing preparation according to claim 1, further comprising at least one kind of pharmacologically acceptable additives among a diluent, a disintegrant and a binder.

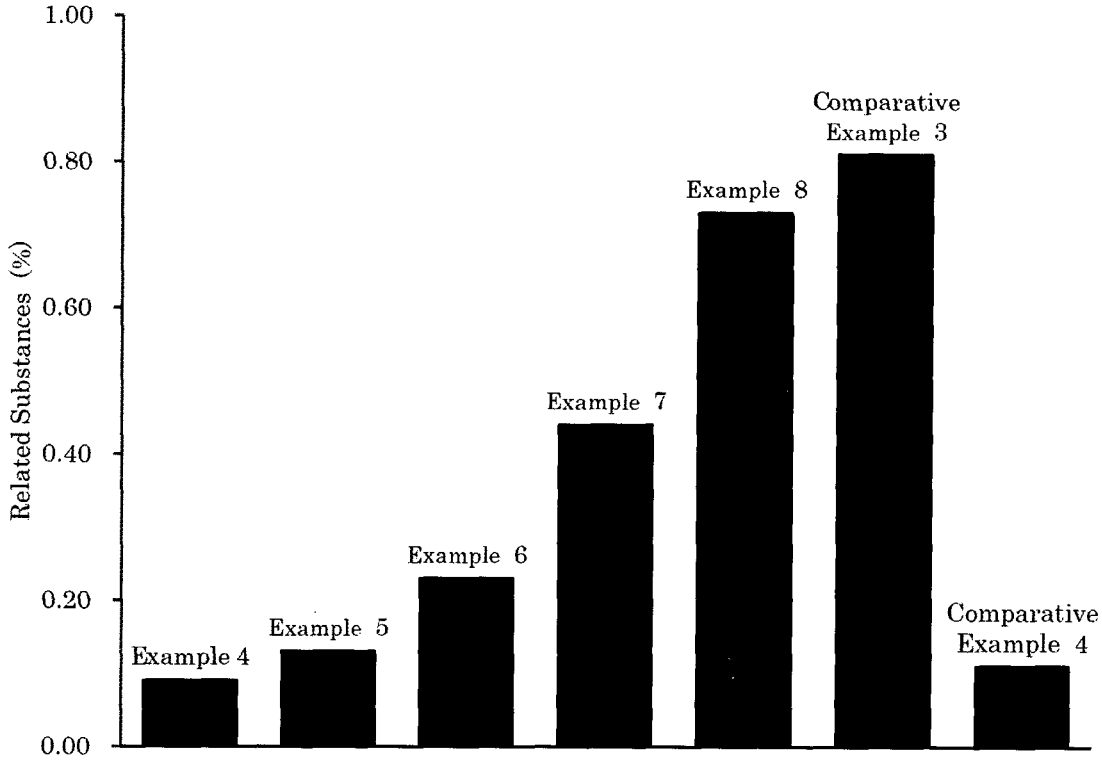
[Claim 6]

The candesartan cilexetil-containing preparation according to claim 5, wherein the additive is contained in the range of 500 parts by weight or greater and 10000 parts by weight or less with respect to 100 parts by weight of candesartan cilexetil.

[Fig.1]


1.00
0.80
0.60
0.40
0.20
0.00
Related Substances (%)
Example 1
Example 2
Example 3
Comparative Example 1
Comparative Example 2

[Fig.2]


1.00
0.80
0.60
0.40
0.20
0.00
Related Substances (%)
Example 4
Example 5
Example 6
Example 7
Example 8
Comparative Example 3
Comparative Example 4

[Fig.3]

	Example 9	Example 10	Example 11	Example 12	Example 13	Example 14
Amount of Lauromacrogol (Parts by Wight)	2.40	1.60	0.80	0.40	0.16	0.08
INITIAL (kg)	2.7	3.1	3.5	5.4	7.3	6.7
25°C, 75% 1W (kg)	1.9	2.1	2.4	3.4	5.4	3.7
40°C, 75% 1W (kg)	1.3	1.6	2.0	3.7	5.3	4.8

[Fig.4]

	Example 9	Example 10	Example 11	Example 12	Example 13	Example 14
Amount of Lauromacrogol (Parts by Wight)	2.40	1.60	0.80	0.40	0.16	0.08
INITIAL (%)	78.4 - 85.4	77.3 - 87.0	—	82.3 - 85.6	89.4 - 90.6	94.2 - 97.0

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2013/083279

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. A61K31/4184(2006.01)i, A61K9/20(2006.01)i, A61K47/34(2006.01)i, A61P9/12(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. A61K31/4184, A61K9/20, A61K47/34, A61P9/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan 1922-1996
Published unexamined utility model applications of Japan 1971-2014
Registered utility model specifications of Japan 1996-2014
Published registered utility model applications of Japan 1994-2014

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAplus/REGISTRY(STN), JSTPlus/JMEDPlus/JST580(JDreamIII)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PA	JP 2013-224265 A (ASAHI KASEI CHEMICALS CORPORATION) 2013.10.31, the whole document (No Family)	1-6
X	JP 5-194218 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 1993.08.03, Claim 1, [0014] & US 5534534 A & EP 782852 A1 & EP 546358 A2	1-6
A	JP 2009-107944 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 2009.05.21, the whole document (No Family)	1-6

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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