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(54) **Title**: SOLID PREPARATION

(57) **Abstract**: The present invention provides solid preparation superior in disintegration property and preservation stability. The present invention relates to a solid preparation containing (1) compound (A) or a salt thereof, (2) metformin or a salt thereof, and (3) crospovidone. It also relates to compound (A) or a salt thereof superior in dissolution property.

DESCRIPTION

SOLID PREPARATION

[Technical Field]

[0001]

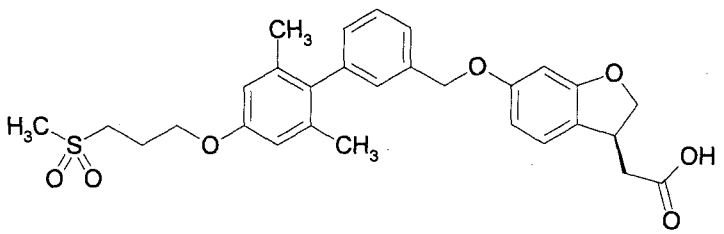
The present invention relates to a solid preparation containing [(3S)-6-({2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid (sometimes to be abbreviated as "compound (A)" in the present specification) or a salt thereof and metformin or a salt thereof and the like. In addition, it relates to compound (A) or a salt thereof and the like superior in dissolution property.

[0002]

[Background of the Invention]

Compound (A) is a compound represented by the following formula:

[0003]



[0004]

Compound (A) and a salt thereof have been reported as a GPR40 receptor agonist useful as an insulin secretagogue or a prophylactic or therapeutic drug for diabetes and the like (patent document 1).

However, a solid preparation containing compound (A) or a salt thereof and metformin or a salt thereof has not been reported.

[Document List]

[patent document]

[0005]

patent document 1: US-A-2010/0004312

[Summary of Invention]

[Problems to be Solved by the Invention]

[0006]

The present inventors have studied a solid preparation containing compound (A) or a salt thereof and metformin or a salt thereof. As a result, they could not obtain preferable disintegration property, and the disintegration property varied among individual preparations.

Moreover, compound (A) or a salt thereof in a solid preparation sometimes showed poor dissolution property.

[0007]

The present inventors have conducted intensive studies in an attempt to solve the aforementioned problems and found that a solid preparation containing compound (A) or a salt thereof, metformin or a salt thereof, and crospovidone is superior in disintegration property, shows small variation in the disintegration property among respective preparations, and shows superior dissolution property in a particular range of the average particle size of compound (A). Further studies have resulted in the completion of the present invention.

[0008]

Accordingly, the present invention provides the following.

[1] A solid preparation comprising

(1) [(3S)-6-({2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid or a salt thereof,

(2) metformin or a salt thereof, and

(3) crospovidone

(hereinafter sometimes to be abbreviated as the solid preparation of the present invention),

[2] the solid preparation of the above-mentioned [1], wherein said metformin or a salt thereof is metformin hydrochloride,

[3] the solid preparation of the above-mentioned [1] or [2], further comprising hydroxypropylcellulose,

[4] the solid preparation of the above-mentioned [1], [2] or [3], further comprising microcrystalline cellulose and

magnesium stearate,

[5] [(3S)-6-({2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid or a salt thereof, which has an average particle size of less than 35 μm,

[6] a solid preparation comprising [(3S)-6-({2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid or a salt thereof of the above-mentioned [5],

[1-1] a method of improving disintegration property of a solid preparation comprising

(1) [(3S)-6-({2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid or a salt thereof, and

(2) metformin or a salt thereof, comprising adding crospovidone to the solid preparation,

[1-2] a method of ameliorating variation in disintegration property of a solid preparation comprising

(1) [(3S)-6-({2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid or a salt thereof, and

(2) metformin or a salt thereof, comprising adding crospovidone to the solid preparation,

[1-3] a method of improving preservation stability of a solid preparation comprising

(1) [(3S)-6-({2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid or a salt thereof,

(2) metformin or a salt thereof, and

(3) crospovidone,

comprising adding hydroxypropylcellulose to the solid preparation,

[1-4] a solid preparation comprising

(1) [(3S)-6-({2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-

benzofuran-3-yl]acetic acid or a salt thereof, and

(2) hydroxypropylcellulose.

[Effect of the Invention]

[0009]

The solid preparation of the present invention is useful as a therapeutic drug for diabetes and the like, and superior in disintegration property. The solid preparation of the present invention shows small variation in disintegration property of respective preparations. Moreover, the solid preparation of the present invention further containing hydroxypropylcellulose is superior in preservation stability. Specifically, in the solid preparation, the production of a decomposition product or analogue of the active ingredient (particularly, compound (A)) during the steps of a preparation production method and a long-term (e.g., 2 weeks) preservation process is suppressed.

Moreover, according to the present invention, the dissolution property of a solid preparation containing compound (A) or a salt thereof can be improved, and the amount of the active ingredient absorbed in the body can be increased, whereby the efficacy thereof can be improved.

[0010]

[Detailed Description of the Invention]

The present invention is explained in detail in the following.

[0011]

Compound (A) or a salt thereof can be produced by a known method, for example, the method described in WO2008/001931 or a method analogous thereto.

[0012]

Examples of the salt of compound (A) include a pharmacologically acceptable salt, such as a salt with inorganic acid, a salt with organic acid, a salt with basic or acidic amino acid and the like.

[0013]

Preferable examples of the salt with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like.

[0014]

Preferable examples of the salt with organic acid include salts with benzoic acid, formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

[0015]

Preferable examples of the salt with basic amino acid include salts with arginine, lysine, ornithine and the like, and preferable examples of the salt with acidic amino acid include salts with aspartic acid, glutamic acid and the like.

[0016]

As compound (A) or a salt thereof, free form of compound (A) is preferable.

[0017]

Compound (A) may be a solvate (e.g., hydrate) or non-solvate (e.g., non-hydrate).

[0018]

Compound (A) is preferably a hydrate, more preferably 0.5 hydrate.

[0019]

Compound (A) may be labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I) and the like.

[0020]

Furthermore, a deuterium-converted compound wherein ^{1}H has been converted to $^{2}H(D)$ is also encompassed in the compound (A).

[0021]

The average particle size of compound (A) or a salt thereof is preferably about 5 - about 45 μm, more preferably about 10 - about 40 μm, particularly preferably about 15 -

about 35 μm. With such average particle size, a solid preparation superior in the dissolution property of compound (A) or a salt thereof can be obtained.

The average particle size of compound (A) or a salt thereof is less than 35 μm, preferably less than 30μm. While the lower limit of the aforementioned average particle size is not particularly limited as long as it does not influence the manufacturability, it is preferably not less than about 1 μm, more preferably not less than about 5 μm, particularly preferably not less than about 10 μm. By adopting such average particle size, a solid preparation containing compound (A) or a salt thereof shows superior dissolution property.

[0022]

The above-mentioned preferable average particle size is applied to compound (A) used as a starting material for producing the solid preparation of the present invention (containing a pulverized product obtained by pulverization in the process for producing a solid preparation, a mixed pulverized product obtained by pulverization together with an excipient and the like). In other words, the average particle size of compound (A) may vary due to the coagulation of compound (A) and the like in the process of producing the solid preparation of the present invention, or in the process of preserving the solid preparation after production.

[0023]

In the present specification, the average particle size means a particle size at which particles are divided into 50% each of crude particles and fine granules in weight distribution or number distribution (preferably number distribution). The average particle size can be measured using a known measurement device, for example, a laser diffraction particle distribution apparatus (e.g., HELOS&RODOS (trade name) (manufactured by SYMPATEC)) and the like.

Compound (A) having a desired average particle size can also be produced by pulverizing compound (A) having a large

average particle size together with, where necessary, an excipient such as microcrystalline cellulose and the like. Here, pulverization is performed according to a known method and using, for example, a cutter mill, a hammer mill, a jet mill and the like.

[0024]

Particularly, when a solid preparation is produced using compound (A) having a weak binding force and a comparatively large average particle size, an effort is necessary to achieve a sufficient preparation hardness, such as use of a large amount of an additive such as a binder and the like, and the like. When the average particle size of compound (A) is made smaller, the use of a large amount of an additive such as a binder and the like becomes unnecessary, and the content of the drug in the solid preparation can be increased.

[0025]

Compound (A) having the above-mentioned desired average particle size preferably shows dispersibility of "particles of 0.1 μm or below in not more than 10% of the total amount, and particles of 1000 μm or more in not more than 10% of the total amount", wherein the dispersibility is preferably measured by a laser diffraction particle distribution apparatus.

[0026]

In the solid preparation of the present invention, the content of compound (A) or a salt thereof is generally 0.5 - 90 wt%, preferably 1 - 30 wt%, more preferably 1 - 20 wt%, particularly preferably 1 - 10 wt%.

[0027]

The solid preparation of the present invention contains metformin or a salt thereof.

[0028]

In the solid preparation of the present invention, metformin or a salt thereof is preferably metformin hydrochloride.

[0029]

In the solid preparation of the present invention, the content of metformin or a salt thereof is generally 50 - 95 wt%, preferably 55 - 90 wt%, more preferably 60 - 85 wt%, particularly preferably 60 - 80 wt%.

[0030]

The solid preparation of the present invention contains crospovidone.

[0031]

In the solid preparation of the present invention, the content of crospovidone and is generally 0.5 - 20 wt%, preferably 1 - 15 wt%, more preferably 1 - 10 wt%.

[0032]

The solid preparation of the present invention may contain a pharmaceutically acceptable carrier in addition to the above-mentioned components, as long as it does not inhibit the effect of the present invention. As the pharmaceutically acceptable carrier in the present specification, various organic or inorganic carrier substances conventionally used as preparation materials can be used. They are appropriately added as, for example, excipient, binder, glidant, lubricant, colorant, pH adjuster, surfactant, stabilizer, acidulant, flavor, coating agent or coating additive in an appropriate amount.

[0033]

Examples of the excipient include microcrystalline cellulose, sugar alcohols such as D-mannitol, xylitol, sorbitol, maltitol, erythritol, lactitol and the like; saccharides such as lactose, sucrose, glucose, maltose and the like; starches such as cornstarch, potato starch, wheat starch, rice starch, partly pregelatinized starch, pregelatinized starch, porous starch and the like; light anhydrous silicic acid, dextrin, carboxymethylstarch, gelatin, magnesium oxide, calcium hydrogen phosphate, anhydrous calcium hydrogen phosphate, calcium carbonate and calcium sulfate; and microcrystalline cellulose is more preferable.

[0034]

The content of the excipient in the solid preparation of the present invention is preferably 1 - 90 wt%, more preferably 2 - 80 wt%.

[0035]

The binder only needs to be an additive capable of binding particles during dry or wet granulation and direct tableting and, for example, hydroxypropylcellulose [e.g., grade: L, SL, SSL (trade name); Nippon Soda Co., Ltd.], hydroxypropylmethylcellulose [e.g., hypromellose 2910, TC-5 (grade: MW, E, EW, R, RW) (trade name); Shin-Etsu Chemical Co., Ltd.], povidone (polyvinylpyrrolidone), copolyvidone and the like can be mentioned. Hydroxypropylcellulose is preferable.

[0036]

In the solid preparation of the present invention, the content of the binder is preferably 0.5 - 15 wt%, more preferably 1 - 10 wt%.

[0037]

Examples of the glidant include talc, light anhydrous silicic acid, hydrated silicon dioxide and magnesium aluminometasilicate.

Examples of the lubricant include stearic acid, magnesium stearate, calcium stearate, sucrose ester of fatty acid, talc, waxes, DL-leucine, sodium lauryl sulfate, magnesium lauryl sulfate, macrogol 6000 and light anhydrous silicic acid, and magnesium stearate is preferable.

[0038]

Preferable examples of the colorant include food colors such as Food Color Yellow No. 5, Food Color Red No. 2, Food Color Blue No. 2 and the like; food lake colors, red ferric oxide, yellow ferric oxide and the like.

[0039]

Preferable examples of the pH adjuster include citric acid or a salt thereof, phosphoric acid or a salt thereof, carbonic acid or a salt thereof, tartaric acid or a salt thereof, fumaric acid or a salt thereof, acetic acid or a salt

thereof, amino acid or a salt thereof and the like.

[0040]

Preferable examples of the surfactant include sodium lauryl sulfate, polysorbate 80, polyoxyethylene(160)polyoxypropylene(30)glycol and the like.

[0041]

Preferable examples of the stabilizer include succinic acid, tartaric acid, citric acid, lactic acid, fumaric acid, malic acid, ascorbic acid, acetic acid, acidic amino acid (e.g., glutamic acid, aspartic acid), inorganic salts of these acids (e.g., alkali metal salt, alkaline earth metal salt), salts with inorganic bases (e.g., ammonium) of these acids, salts with organic bases (e.g., meglumine) of these acids, salts with basic amino acid (e.g., arginine, lysine, ornithine) of these acids, hydrates thereof, solvates thereof and the like.

[0042]

Preferable examples of the acidulant include ascorbic acid, citric acid, tartaric acid, malic acid and the like.

[0043]

Preferable examples of the flavor include menthol, peppermint oil, lemon oil, vanillin and the like.

[0044]

Preferable examples of the coating agent include sugar coating agent, aqueous film coating agent, enteric film coating agent, sustained-release film coating agent and the like.

[0045]

As the sugar coating agent, for example, purification sucrose can be mentioned, and one or more kinds selected from talc, precipitated calcium carbonate, gelatin, gum arabic, pullulan, carnauba wax and the like may be used in combination.

[0046]

Examples of the aqueous film coating agent include cellulose polymers such as hydroxypropylcellulose [e.g., grade: L, SL, SSL (trade name); Nippon Soda Co., Ltd.], hydroxypropylmethylcellulose [e.g., hypromellose 2910, TC-5

(grade: MW, E, EW, R, RW) (trade name); Shin-Etsu Chemical Co., Ltd.], hydroxyethylcellulose, methylhydroxyethylcellulose and the like; synthesis polymers such as polyvinyl acetaldiethylaminoacetate, aminoalkylmethacrylate copolymer E [Eudragit E (trade name)], polyvinylpyrrolidone and the like; polysaccharides such as pullulan and the like; and the like.

[0047]

Examples of the enteric film coating agent include cellulose polymers such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, cellulose acetate phthalate and the like; acrylic acid polymers such as methacrylic acid copolymer L [Eudragit L (trade name)], methacrylic acid copolymer LD [Eudragit L-30D55 (trade name)], methacrylic acid copolymer S [Eudragit S (trade name)] and the like; naturally occurring substances such as shellac and the like; and the like.

[0048]

Examples of the sustained-release film coating agent include cellulose polymers such as ethylcellulose and the like; acrylic acid polymers such as aminoalkyl methacrylate copolymer RS [Eudragit RS (trade name)], ethyl acrylate·methacrylic acid methyl copolymer suspension [Eudragit NE (trade name)] and the like; and the like.

[0049]

Preferable examples of the coating additive include light shielding agents such as titanium oxide and the like; glidants such as talc and the like; colorants such as red ferric oxide, yellow ferric oxide and the like; plasticizers such as macrogol 6000, triethyl citrate, castor oil, polysorbates and the like; organic acids such as citric acid, tartaric acid, malic acid, ascorbic acid and the like; and the like.

[0050]

The above-mentioned additive may be a mixture of two or more kinds at an appropriate ratio.

[0051]

The solid preparation of the present invention preferably further contains hydroxypropylcellulose to improve preservation stability of the preparation.

[0052]

Here, the improvement of the preservation stability of a solid preparation means, for example, the production of a decomposition product or analogue of the active ingredient (particularly, compound (A)) in the preparation is suppressed when the solid preparation is preserved for a long term (e.g., 2 weeks). Here, the preservation conditions may be severe conditions (40°C, 75%RH).

[0053]

As hydroxypropylcellulose, for example, those commercially available as grades: L, SL, SSL are used, with preference given to SSL.

[0054]

When the solid preparation of the present invention contains hydroxypropylcellulose, the content of the hydroxypropylcellulose in the solid preparation is generally 1 - 30 wt%, preferably 2 - 25 wt%, more preferably 3 - 20 wt%, particularly preferably 3 - 10 wt%.

[0055]

The solid preparation of the present invention preferably further contains microcrystalline cellulose to optimize physicochemical property of the preparation (e.g., manufacturability, tablet disintegration property, tablet hardness).

[0056]

When the solid preparation of the present invention contains microcrystalline cellulose, the content of the microcrystalline cellulose in the solid preparation is generally 1 - 30 wt%, preferably 2 - 25 wt%, more preferably 3 - 20 wt%.

[0057]

The solid preparation of the present invention may

further contain magnesium stearate to optimize physicochemical property of the preparation (e.g., manufacturability, tablet disintegration property, tablet hardness).

[0058]

When the solid preparation of the present invention contains magnesium stearate, the content of the magnesium stearate in the solid preparation is generally 0.01 - 10 wt%, preferably 0.1 - 5 wt%, more preferably 0.15 - 2 wt%.

[0059]

The solid preparation of the present invention is preferably the following preparation.

[solid preparation 1]

A solid preparation comprising

(1) compound (A) or a salt thereof,

(2) metformin or a salt thereof,

(3) crospovidone,

(4) excipient (preferably, microcrystalline cellulose),

(5) binder (preferably, hydroxypropylcellulose), and

(6) lubricant (preferably, magnesium stearate).

[solid preparation 2]

A solid preparation comprising

(1) compound (A) or a salt thereof,

(2) metformin or a salt thereof,

(3) crospovidone,

(4) microcrystalline cellulose,

(5) hydroxypropylcellulose, and

(6) magnesium stearate.

[0060]

The contents of the components of the solid preparation of the present invention are preferably the following contents. The solid preparation of the present invention may contain components other than the following components.

(1) compound (A) or a salt thereof: 1 - 10 wt%

(2) metformin or a salt thereof: 60 - 80 wt%

(3) crospovidone: 1 - 10 wt%

(4) microcrystalline cellulose: 3 - 20 wt%

(5) hydroxypropylcellulose: 3 - 10 wt%

(6) magnesium stearate: 0.15 - 2 wt%

[0061]

The contents of the components of the solid preparation of the present invention are more preferably the following contents. The solid preparation of the present invention may contain components other than the following components.

(1) compound (A) or a salt thereof: 1 - 5 wt%

(2) metformin or a salt thereof: 70 - 80 wt%

(3) crospovidone: 1 - 5 wt%

(4) microcrystalline cellulose: 5 - 15 wt%

(5) hydroxypropylcellulose: 3 - 10 wt%

(6) magnesium stearate: 0.15 - 2 wt%

[0062]

Examples of the dosage form of the solid preparation of the present invention include granule, tablet (e.g., uncoated tablet, film-coated tablet) and the like. Of these, tablet is preferable.

[0063]

The solid preparation of the present invention can be produced by a method conventionally used in the pharmaceutical field.

[0064]

The solid preparation of the present invention can be specifically produced by appropriately combining operations such as granulation, mixing, tableting (compression molding), coating and the like.

[0065]

For granulation, for example, a granulation machine such as an agitating granulator, a fluid bed granulator, a dry granulating machine and the like is used.

[0066]

For mixing, for example, a mixer such as a V-type mixer, a tumbler mixer and the like is used.

[0067]

Tableting (compression molding) is performed by punching using, for example, a single punch tableting machine, a rotary tableting machine and the like, at a pressure of generally 0.3 - 35 kN/cm^2.

[0068]

Coating is performed using, for example, a film coating apparatus together with the aforementioned coating agent and coating additive.

[0069]

The solid preparation of the present invention is preferably film-coated for the purpose of improving easy administrability, preparation strength and the like.

[0070]

Preferable examples of the coating agent and coating additive used for film coating include those similar to the ones used for the aforementioned additive.

[0071]

When the solid preparation of the present invention is film-coated, the film coating layer can be formed in a proportion of generally 1 - 10 parts by weight, preferably 2 - 6 parts by weight, per 100 parts by weight of said solid preparation.

[0072]

Specifically, the solid preparation of the present invention can be produced according to the following production steps. Each starting material used in the following production steps is used in such amount as to achieve the aforementioned content per finally obtained solid preparation.

Compound (A) or a salt thereof and metformin or a salt thereof are mixed together with other additives (e.g., excipient, binder, disintegrant) as necessary in an appropriate mixer, and the mixture is granulated using an aqueous solution of a binder (e.g., hydroxypropylcellulose and the like), and sieved when desired. To the obtained sieved powder are added crospovidone,

lubricant (e.g., magnesium stearate and the like) and/or other additive, the mixture is molded and dried when desired to give the solid preparation of the present invention. Furthermore, a film coating solution is sprayed when desired to give a film-coated tablet. Mixing and granulation can be performed using, for example, a fluid bed dryer granulator and the like. Molding can be performed by tableting using, for example, a rotary tableting machine.

[0073]

A film-coated tablet can be produced by, for example, coating a uncoated tablet obtained by the above-mentioned method, by spraying an aqueous solution of a film coating agent (e.g., a mixture of film coating base such as hypromellose 2910 and the like; plasticizer such as macrogol 6000 and the like; and colorant such as titanium oxide, red ferric oxide, yellow ferric oxide and the like) by a film coating machine and the like.

[0074]

The solid preparation of the present invention is preferably produced by a fluid bed granulation method. A solid preparation produced by a fluid bed granulation method, particularly a tablet, shows a remarkable effect of the present invention.

The solid preparation of the present invention is preferably a tablet containing granules (e.g., granules obtained by the above-mentioned granulation) at preferably 70 - 100 wt%, more preferably 85 - 98 wt%, further preferably 80 - 95 wt%.

[0075]

The "granule" here means particles having almost the same size and shape, which are obtained by granulating a starting material in the form of powder, bulk, solution, molten liquid and the like by a wet granulation method, a dry granulation method, a heating granulation method and the like (preferably, dry granulation method).

[0076]

The granules generally have a particle size of not less than 1000 μm for not more than 20%, not more than 150 μm for not more than 65% (on (remaining on sieves) with 16M sieves: not more than 20%; pass (pass through sieves) with 100M sieves: not more than 65%), preferably not less than 1000 μm for not more than 5%, not more than 150 μm for not more than 55% (on with 16M sieves: not more than 5%; pass with 100 M sieves: not more than 55%). Here, the particle size is, for example, a value obtained by measuring the weight of the granules remaining on the standard sieves after passage therethrough.

[0077]

The granules may have different sizes and shapes during the process of formulation (e.g., tableting step) to give the solid preparation of the present invention.

[0078]

The weight of the solid preparation of the present invention (e.g., the weight per tablet) is generally 50 - 2000 mg, preferably 70 - 1800 mg, more preferably 80 - 1500 mg.

[0079]

The solid preparation of the present invention has superior effects as a medicament, and shows low toxicity and fewer side effects, it is useful in mammals (e.g., human, bovine, horse, swine, dog, cat, monkey, mouse, rat, particularly human) for the prophylaxis or treatment of, for example, diabetes [e.g., type 1 diabetes, type 2 diabetes, type 1.5 diabetes (LADA (Latent Autoimmune Diabetes in Adults)), gestational diabetes, diabetes with impaired insulin secretion, obese diabetes, IGT (impaired glucose tolerance), IFG (Impaired Fasting Glucose), IFG (Impaired Fasting Glycaemia)], diabetic complications [e.g., neuropathy, nephropathy, retinopathy, cataract, macroangiopathy, arteriosclerosis, osteopenia, hyperosmolar diabetic coma, infections (e.g., respiratory infection, urinary tract infection, gastrointestinal infection, dermal soft tissue infection, inferior limb infection), diabetic gangrene, xerostomia, hypacusis, cerebrovascular

disorder, peripheral blood circulation disorder], obesity, hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, hypoHDL-emia, postprandial hyperlipemia), arteriosclerosis (e.g., atherosclerosis), hypertension, myocardial infarction, angina pectoris, cerebrovascular disorder (e.g., cerebral infarction, cerebral apoplexy), insulin resistance syndrome, syndrome X, dysmetabolic syndrome and the like.

[0080]

In addition, the solid preparation of the present invention is also useful for secondary prevention (e.g., secondary prevention of cardiovascular event such as myocardial infarction and the like) or suppression of progression [e.g., suppression of progression from impaired glucose tolerance to diabetes; suppression of progression from diabetes to diabetic complications (preferably diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, arteriosclerosis)], both of the above-mentioned various diseases.

[0081]

The solid preparation of the present invention can be administered orally and safely to a mammal.

[0082]

The dose of the solid preparation of the present invention only needs to contain an effective amount of compound (A) or a salt thereof as a pharmaceutically active ingredient. For example, for administration to an adult (body weight 60 kg), the effective amount is generally 1 mg - 500 mg, preferably 1 mg - 400 mg, more preferably 10 mg - 250 mg, further preferably 10 mg - 200 mg (further more preferably 12.5 mg, 25 mg, 50 mg, 100 mg), once per day, as compound (A) free form (anhydride).

The dose of the solid preparation of the present invention only needs to contain an effective amount of metformin or a salt thereof as a pharmaceutically active ingredient. For example, for administration to an adult (body weight 60 kg), the effective amount is generally 300 mg - 2000 mg, preferably 400

mg - 1500 mg, more preferably 500 - 1000 mg (further more preferably 500 mg, 850 mg, 1000 mg), once per day, as hydrochloride.

[0083]

The size of the solid preparation of the present invention varies depending on the shape of the solid preparation (round, caplet, oblong etc.).

[0084]

Particularly preferable specific examples of the solid preparation of the present invention include

"a solid preparation containing, per tablet, compound (A) or a salt thereof at 12.5 mg as a free form (anhydride) and metformin or a salt thereof at 500 mg as hydrochloride";

"a solid preparation containing, per tablet, compound (A) or a salt thereof at 12.5 mg as a free form (anhydride) and metformin or a salt thereof at 850 mg as hydrochloride";

"a solid preparation containing, per tablet, compound (A) or a salt thereof at 12.5 mg as a free form (anhydride) and metformin or a salt thereof at 1000 mg as hydrochloride";

"a solid preparation containing, per tablet, compound (A) or a salt thereof at 25 mg as a free form (anhydride) and metformin or a salt thereof at 500 mg as hydrochloride";

"a solid preparation containing, per tablet, compound (A) or a salt thereof at 25 mg as a free form (anhydride) and metformin or a salt thereof at 850 mg as hydrochloride";

"a solid preparation containing, per tablet, compound (A) or a salt thereof at 25 mg as a free form (anhydride) and metformin or a salt thereof at 1000 mg as hydrochloride";

"a solid preparation containing, per tablet, compound (A) or a salt thereof at 50 mg as a free form (anhydride) and metformin or a salt thereof at 500 mg as hydrochloride";

"a solid preparation containing, per tablet, compound (A) or a salt thereof at 50 mg as a free form (anhydride) and metformin or a salt thereof at 850 mg as hydrochloride";

"a solid preparation containing, per tablet, compound (A) or a

salt thereof at 50 mg as a free form (anhydride) and metformin or a salt thereof at 1000 mg as hydrochloride";

"a solid preparation containing, per tablet, compound (A) or a salt thereof at 100 mg as a free form (anhydride) and metformin or a salt thereof at 500 mg as hydrochloride";

"a solid preparation containing, per tablet, compound (A) or a salt thereof at 100 mg as a free form (anhydride) and metformin or a salt thereof at 850 mg as hydrochloride";

"a solid preparation containing, per tablet, compound (A) or a salt thereof at 100 mg as a free form (anhydride) and metformin or a salt thereof at 1000 mg as hydrochloride".

[0085]

The solid preparation of the present invention can be used in combination with one or more other kinds of medicaments (hereinafter sometimes to be abbreviated as "concomitant drug").

[0086]

Specific examples of the concomitant drug include one or more medicaments selected from a therapeutic agent for diabetes, a therapeutic agent for diabetic complications, a therapeutic agent for hyperlipidemia, an antihypertensive agent, an antiobesity agent, a diuretic, an antithrombotic agent and the like.

[0087]

Examples of the therapeutic agent for diabetes include insulin preparations (e.g., animal insulin preparation extracted from the pancreas of bovine, swine; human insulin preparation synthesized by genetic engineering using Escherichia coli or yeast; zinc insulin; protamine zinc insulin; fragment or derivative of insulin (e.g., INS-1), oral insulin preparation), insulin sensitizers (e.g., pioglitazone or a salt thereof (preferably hydrochloride), rosiglitazone or a salt thereof (preferably maleate), metaglidasen, AMG-131, balaglitazone, MBX-2044, rivoglitazone, aleglitazar, chiglitazar, lobeglitazone, PLX-204, PN-2034, GFT-505, THR-0921, compound described in WO2007/013694, WO2007/018314, WO2008/093639 or WO2008/099794),

α-glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate), insulin secretagogues (e.g., sulfonylurea (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, glipizide, glybuzole), repaglinide, nateglinide, mitiglinide or a calcium salt hydrate thereof), dipeptidyl peptidase IV inhibitors (e.g., alogliptin or a salt thereof (preferably benzoate), trelagliptin or a salt thereof (preferably succinate), vildagliptin, sitagliptin, saxagliptin, BI1356, GRC8200, MP-513, PF-00734200, PHX1149, SK-0403, ALS2-0426, TA-6666, TS-021, KRP-104), β3 agonists (e.g., N-5984), GLP-1 receptor agonists (e.g., GLP-1, GLP-1MR agent, liraglutide, exenatide, AVE-0010, BIM-51077, Aib(8,35)hGLP-1(7,37)NH2, CJC-1131, albiglutide), amylin agonists (e.g., pramlintide), phosphotyrosine phosphatase inhibitors (e.g., sodium vanadate), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitor, glucose-6-phosphatase inhibitor, glucagon antagonist, FBPase inhibitor), SGLT2 (sodium-glucose cotransporter 2) inhibitors (e.g., depagliflozin, AVE2268, TS-033, YM543, TA-7284, remogliflozin, ASP1941), SGLT1 inhibitors, 11β-hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498, INCB-13739), adiponectin or agonist thereof, IKK inhibitors (e.g., AS-2868), leptin resistance improving drugs, somatostatin receptor agonists, glucokinase activators (e.g., piragliatin, AZD1656, AZD6370, TTP-355, compound described in WO2006/112549, WO2007/028135, WO2008/047821, WO2008/050821, WO2008/136428 or WO2008/156757), GIP (Glucose-dependent insulinotropic peptide), GPR119 agonists (e.g., PSN821), FGF21, FGF analogue and the like.

[0088]

Examples of the therapeutic agents for diabetic complications include aldose reductase inhibitors (e.g., tolrestat, epalrestat, zopolrestat, fidarestat, CT-112, ranirestat (AS-3201), lidorestat), neurotrophic factors and increasing drugs thereof (e.g., NGF, NT-3, BDNF, neurotrophin production/secretion promoting agent described in WO01/14372

(e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(2-methylphenoxy)propyl]oxazole), compound described in WO2004/039365), PKC inhibitors (e.g., ruboxistaurin mesylate), AGE inhibitors (e.g., ALT946, N-phenacylthiazolium bromide (ALT766), EXO-226, pyridorin, pyridoxamine), GABA receptor agonists (e.g., gabapentin, pregabalin), serotonin noradrenaline reuptake inhibitors (e.g., duloxetine), sodium channel inhibitors (e.g., lacosamide), active oxygen scavengers (e.g., thioctic acid), cerebral vasodilators (e.g., tiapride, mexiletine), somatostatin receptor agonists (e.g., BIM23190), apoptosis signal regulating kinase-1 (ASK-1) inhibitors and the like.

[0089]

Examples of the therapeutic agent for hyperlipidemia include HMG-CoA reductase inhibitors (e.g., pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, rosuvastatin, pitavastatin or salts thereof (e.g., sodium salt, calcium salt)), squalene synthase inhibitors (e.g., compound described in WO97/10224, for example, N-[[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetic acid), fibrate compounds (e.g., bezafibrate, clofibrate, simfibrate, clinofibrate), anion exchange resins (e.g., colestyramine), probucol, nicotinic acid drugs (e.g., nicomol, niceritrol, niaspan), ethyl icosapentate, phytosterol (e.g., soysterol, γ-oryzanol), cholesterol absorption inhibitors (e.g., Zetia), CETP inhibitors (e.g., dalcetrapib, anacetrapib), ω-3 fatty acid preparations (e.g., ω-3-acid ethyl esters 90) and the like.

[0090]

Examples of the antihypertensive agent include angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril, etc.), angiotensin II antagonists (e.g., candesartan cilexetil, candesartan, losartan, losartan potassium, eprosartan, valsartan, telmisartan, irbesartan, tasosartan, olmesartan,

olmesartan medoxomil, azilsartan, azilsartan medoxomil and the like), calcium antagonists (e.g., manidipine, nifedipine, amlodipine, efonidipine, nicardipine, cilnidipine and the like), β blockers (e.g., metoprolol, atenolol, propranolol, carvedilol, pindolol and the like), clonidine and the like.

[0091]

Examples of the antiobesity agent include monoamine uptake inhibitors (e.g., phentermine, sibutramine, mazindol, fluoxetine, tesofensine), serotonin 2C receptor agonists (e.g., lorcaserin), serotonin 6 receptor antagonists, histamine H3 receptor antagonists, GABA modulators (e.g., topiramate), neuropeptide Y antagonists (e.g., velneperit), cannabinoid receptor antagonists (e.g., rimonabant, taranabant), ghrelin antagonists, ghrelin receptor antagonists, ghrelin acylation enzyme inhibitors, opioid receptor antagonists (e.g., GSK-1521498), orexin receptor antagonists, melanocortin 4 receptor agonists, 11β-hydroxysteroid dehydrogenase inhibitors (e.g., AZD-4017), pancreatic lipase inhibitors (e.g., orlistat, cetilistat), β3 agonists (e.g., N-5984), diacylglycerol acyltransferase 1 (DGAT1) inhibitors, acetyl-CoA carboxylase (ACC) inhibitors, stearoyl-CoA desaturase inhibitors, microsomal triglyceride transfer protein inhibitors (e.g., R-256918), sodium-glucose cotransporter inhibitors (e.g., JNJ-28431754, remogliflozin), NFκB inhibitors (e.g., HE-3286), PPAR agonists (e.g., GFT-505, DRF-11605), phosphotyrosine phosphatase inhibitors (e.g., sodium vanadate, trodusquemine), GPR119 agonists (e.g., PSN-821), glucokinase activators (e.g., AZD-1656), leptin, leptin derivative (e.g., metreleptin), CNTF (ciliary neurotrophic factor), BDNF (brain-derived neurotrophic factor), cholecystokinin agonists, glucagon-like peptide-1 (GLP-1) preparation (e.g., animal GLP-1 preparation extracted from bovine or swine pancreas; human GLP-1 preparation synthesized by genetic engineering using Escherichia coli or yeast; fragment or derivative of GLP-1 (e.g., exenatide, liraglutide), amylin preparation (e.g., pramlintide, AC-2307), neuropeptide Y

agonists (e.g., PYY3-36, derivatives of PYY3-36, obinepitide, TM-30339, TM-30335), oxyntomodulin preparation: FGF21 preparations (e.g., animal FGF21 preparation extracted from bovine or swine pancreas; human FGF21 preparation synthesized by genetic engineering using Escherichia coli or yeast; fragment or derivative of FGF21), anorexigenic agents (e.g., P-57) and the like.

[0092]

Examples of the diuretic include xanthine derivatives (e.g., theobromine sodium salicylate, theobromine calcium salicylate), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide), antialdosterone preparations (e.g., spironolactone, triamterene), carbonic anhydrase inhibitors (e.g., acetazolamide), chlorobenzenesulfonamide agents (e.g., chlortalidone, mefruside, indapamide), azosemide, isosorbide, ethacrynic acid, piretanide, bumetanide, furosemide and the like.

[0093]

Examples of the antithrombotic agent include heparins (e.g., heparin sodium, heparin calcium, enoxaparin sodium, dalteparin sodium), warfarins (e.g., warfarin potassium), anti-thrombin drugs (e.g., argatroban, dabigatran), FXa inhibitors (e.g., rivaroxaban), apixaban, edoxaban, YM150, compound described in WO02/06234, WO2004/048363, WO2005/030740, WO2005/058823 or WO2005/113504), thrombolytic agents (e.g., urokinase, tisokinase, alteplase, nateplase, monteplase, pamiteplase), platelet aggregation inhibitors (e.g., ticlopidine hydrochloride, clopidogrel, prasugrel, E5555, SHC530348, cilostazol, ethyl icosapentate, beraprost sodium, sarpogrelate hydrochloride) and the like.

[0094]

Of the above-mentioned concomitant drugs, insulin sensitizers (preferably pioglitazone hydrochloride), insulin

preparation, α-glucosidase inhibitors (preferably voglibose, acarbose), sulfonylureas (preferably glimepiride), dipeptidyl peptidase IV inhibitor (preferably, alogliptin benzoate) and the like are preferable.

[0095]

When the solid preparation of the present invention and a concomitant drug are used in combination, the administration time of these is not limited, and they may be administered simultaneously to an administration subject, or may be administered in a staggered manner.

[0096]

In addition, the solid preparation of the present invention and the concomitant drug may be administered as separate preparations to an administration subject, or they may be administered to an administration subject as a single preparation containing the solid preparation of the present invention and the concomitant drug.

[0097]

The dose of the concomitant drug can be appropriately determined based on the clinically employed dose of each drug. In addition, the mixing ratio of the solid preparation of the present invention and the concomitant drug can be appropriately determined according to the administration subject, administration route, target disease, condition, combination and the like. For example, when the administration subject is a human, the concomitant drug may be used in an amount of 0.01 to 100 parts by weight per 1 part by weight of the solid preparation of the present invention.

[0098]

Use of the concomitant drug in this way provides superior effects such as 1) enhanced effect of the action of one or more medicaments selected from compound (A) or a salt thereof, metformin or a salt thereof, and a concomitant drug (synergistic effect of medicament actions), 2) reduction effect of the dose of one or more medicaments selected from compound (A) or a salt

thereof, metformin or a salt thereof, and a concomitant drug (reduction effect of medicament dose as compared to single drug administration), 3) reduction effect of secondary action of one or more medicaments selected from compound (A) or a salt thereof, metformin or a salt thereof, and a concomitant drug, and the like.

[0099]

The present invention also provides a method of ameliorating (decreasing) variation in the disintegration property of a solid preparation comprising compound (A) or a salt thereof, and metformin or a salt thereof, which comprises adding crospovidone to the solid preparation. The solid preparation can be produced in the same manner as the solid preparation of the present invention, and can be used for the treatment of diabetes and the like. The amount of crospovidone to be added is the same as the content of crospovidone in the solid preparation of the present invention. The variation in the disintegration property means, for example, variation in the disintegration property per tablet as shown in the below-mentioned Experimental Examples.

To be specific, the variation in the disintegration property of the solid preparation of in the present invention means variation in the disintegration time by the disintegration test method according to the Japanese Pharmacopoeia, that is, a standard deviation of the disintegration time when the disintegration test is performed plural times. For example, the standard deviation of the disintegration time by the disintegration test method (test solution is water, no disc) is preferably within 0.3 min.

[0100]

The present invention also provides compound (A) or a salt thereof having an average particle size of less than 35 μm, and a (solid) preparation containing compound (A) or a salt thereof having an average particle size of less than 35 μm. The (solid) preparation can be produced in the same manner as

the solid preparation of the present invention, and can be used for the treatment of diabetes and the like.

In addition, the (solid) preparation may further contain metformin or a salt thereof (preferably metformin hydrochloride). In another embodiment, the (solid) preparation may further contain alogliptin or a salt thereof (preferably alogliptin benzoate).

Poor dissolution property decreases the amount of the active ingredient to be absorbed in the body, and lowers its efficacy.

By setting the average particle size of compound (A) or a salt thereof to about 5 - about 45 μm, preferably about 10 - about 40 μm, more preferably about 15 - about 35 μm, a (solid) preparation showing superior dissolution property of compound (A) or a salt thereof can be obtained.

By setting the average particle size of compound (A) or a salt thereof to less than 35 μm, preferably less than 30 μm, a (solid) preparation showing superior dissolution property of compound (A) or a salt thereof can be obtained. While the lower limit of the aforementioned average particle size is not particularly limited as long as it does not influence the productivity, it is preferably not less than about 1 μm, more preferably not less than about 5 μm, particularly preferably not less than about 10 μm.

[0101]

The present invention also provides a preparation comprising compound (A) or a salt thereof and hydroxypropylcellulose. The solid preparation can be produced in the same manner as the solid preparation of the present invention, and can be used for the treatment of diabetes and the like.

As shown in the below-mentioned Experimental Examples, a mixture of compound (A) and a salt thereof and polyvinylpyrrolidone (PVP) produced many analogs. However, a mixture containing hydroxypropylcellulose instead of PVP

suppressed production of analogue.

Thus, a solid preparation comprising compound (A) or a salt thereof and hydroxypropylcellulose can suppress the production of an analogue as compared to the use of other binders (e.g., PVP, hypromellose etc.).

[Examples]

[0102]

The present invention is explained in more detail in the following by referring to Examples, Comparative Examples, and Experimental Examples, which are not to be construed as limitative.

As additives for pharmaceutical preparations in the following Examples, Comparative Examples, and Experimental Examples, the Japanese Pharmacopoeia 16th edition, the Japanese Pharmaceutical Codex or Japanese Pharmaceutical Excipients 2003 compatible products were used.

[0103]

Example 1

[(3S)-6-({2',6'-Dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid 0.5 hydrate (sometimes to be abbreviated as compound (A') in the present specification) (25.4 g), metformin hydrochloride (500 g), and microcrystalline cellulose (21.6 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed dryer, and the mixture was granulated while spraying a 7(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade SSL) solution (400 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. The granulated powder (517.5 g) was measured, and mixed with microcrystalline cellulose (18 g) (manufactured by Asahi Kasei, CEOLUS KG-802), crospovidone (47.7 g) (manufactured by BASF, Kollidon CL-F), and magnesium

stearate (1.8 g) in a plastic bag to give a mixed powder. Using a tableting machine, the mixed powder was tableted at tableting pressure 14kN to give preparation 1 (tablet, long diameter 13.5 mm×short diameter 8.5 mm, 650 mg per tablet). The composition of preparation 1 per tablet is shown in Table 1.

[0104]

Table 1

blending composition of preparation 1

component	weight (mg)
compound (A')	25.43
metformin hydrochloride	500
microcrystalline cellulose (PH101)	21.57
hydroxypropylcellulose (SSL)	28
microcrystalline cellulose (KG802)	20
crospovidone (CL-F)	53
magnesium stearate	2
total	650

[0105]

Example 2

Compound (A') (2696 g), metformin hydrochloride (53000 g), and microcrystalline cellulose (2286 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed dryer (WSG-60, POWREX CORPORATION), and the mixture was granulated while spraying a 8(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade SSL) solution (37100 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-7S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. One more batch of the same sieved powder was produced. The sieved powder (103500 g) was measured, crospovidone (3600 g) (manufactured by BASF, Kollidon CL-F), microcrystalline cellulose (9540 g) (manufactured by Asahi Kasei, CEOLUS KG-802),

and magnesium stearate (360 g) were added and they were mixed in a tumbler mixer (TM-400S, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted at tableting pressure 14kN to give a tablet (long diameter 13.5 mm×short diameter 8.5 mm, 650 mg per tablet).

OPADRY Red 03F45081 (1008 g) (manufactured by COLORCON JAPAN; containing hypromellose 2910, macrogol 6000, titanium oxide and red ferric oxide) and OPADRY Yellow 03F42240 (2016 g) (manufactured by COLORCON JAPAN; containing hypromellose 2910, macrogol 6000, titanium oxide and yellow ferric oxide) were suspended in purified water (27220 g) to prepare a coating solution. In a coating machine (DRC-1200DS, POWREX CORPORATION), the coating solution was sprayed on the tablet (109200 g) obtained above until the tablet weight increased by 18 mg per tablet, and a 5(w/w)% macrogol 6000 solution (672 g) was further sprayed to give preparation 2 (film-coated tablet). The composition of preparation 2 per tablet is shown in Table 2.

[0106]

Table 2

blending composition of preparation 2

component	weight (mg)
compound (A')	25.43
metformin hydrochloride	500
microcrystalline cellulose (PH101)	21.57
hydroxypropylcellulose (SSL)	28
crospovidone (CL-F)	20
microcrystalline cellulose (KG802)	53
magnesium stearate	2
subtotal	650
OPADRY Red 03F45081	6
OPADRY Yellow 03F42240	12
macrogol 6000	0.2
total	668.2

[0107]

Example 3

The sieved powder (11.5 g) obtained in Example 2 was

mixed with microcrystalline cellulose (0.4 g) (manufactured by Asahi Kasei, CEOLUS KG-802), crospovidone (1.06 g) (manufactured by BASF, Kollidon CL-F), and magnesium stearate (0.04 g) in a glass bottle to give a mixed powder. Using a tableting machine, the mixed powder was tableted at tableting pressure 14kN to give preparation 3 (tablet, long diameter 13.5 mm×short diameter 8.5 mm, 650 mg per tablet). The composition of preparation 3 per tablet is shown in Table 3.

[0108]

Table 3

blending composition of preparation 3

component	weight (mg)
compound (A')	25.43
metformin hydrochloride	500
microcrystalline cellulose (PH101)	21.57
hydroxypropylcellulose(SSL)	28
microcrystalline cellulose (KG802)	20
crospovidone (CL-F)	53
magnesium stearate	2
total	650

[0109]

Example 4

The sieved powder (11.5 g) obtained in Example 2 was mixed with crospovidone (0.4 g) (manufactured by BASF, Kollidon CL-F), microcrystalline cellulose (1.06 g) (manufactured by Asahi Kasei, CEOLUS KG-802), and magnesium stearate (0.04 g) in a glass bottle to give a mixed powder. Using a tableting machine, the mixed powder was tableted at tableting pressure 14kN to give preparation 4 (tablet, long diameter 13.5 mm×short diameter 8.5 mm, 650 mg per tablet). The composition of preparation 4 per tablet is shown in Table 4.

[0110]

[Table 4]

blending composition of preparation 4

component	weight (mg)
compound (A')	25.43
metformin hydrochloride	500
microcrystalline cellulose (PH101)	21.57
hydroxypropylcellulose(SSL)	28
crospovidone (CL-F)	20
microcrystalline cellulose (KG802)	53
magnesium stearate	2
total	650

[0111]

Example 5

Compound (A') (1602 g), metformin hydrochloride (53550 g), and microcrystalline cellulose (2178 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed dryer (WSG-60, POWREX CORPORATION), and the mixture was granulated while spraying a 8(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade SSL) solution (37800 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-7S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. One more batch of the same sieved powder was produced. The sieved powder (104400 g) was measured, crospovidone (3488 g) (manufactured by BASF, Kollidon CL-F), microcrystalline cellulose (8938 g) (manufactured by Asahi Kasei, CEOLUS KG-802), and magnesium stearate (327 g) were added and they were mixed in a tumbler mixer (TM-400S, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted to give a tablet (long diameter 17.5 mm×short diameter 9.5 mm, 1075 mg per tablet).

OPADRY Red 03F45081 (1000 g) (manufactured by COLORCON JAPAN; containing hypromellose 2910, macrogol 6000, titanium oxide and red ferric oxide) and OPADRY Yellow 03F42240 (2000 g) (manufactured by COLORCON JAPAN; containing hypromellose 2910, macrogol 6000, titanium oxide and yellow ferric oxide) were suspended in purified water (27000 g) to prepare a coating solution. In a coating machine (DRC-1200DS, POWREX CORPORATION), the coating solution was sprayed on the tablet (107500 g) obtained above until the tablet weight increased by 18 mg per tablet, and a 5(w/w)% macrogol 6000 solution (500 g) was further sprayed to give preparation 5 (film-coated tablet). The composition of preparation 5 per tablet is shown in Table 5.

[0112]

[Table 5]

blending composition of preparation 5

component	weight (mg)
compound (A')	25.43
metformin hydrochloride	850
microcrystalline cellulose (PH101)	34.57
hydroxypropylcellulose (SSL)	48
crospovidone (CL-F)	32
microcrystalline cellulose (KG802)	82
magnesium stearate	3
subtotal	1075
OPADRY Red 03F45081	10
OPADRY Yellow 03F42240	20
macrogol 6000	0.25
total	1105.25

[0113]

Example 6

Compound (A') (1373 g), metformin hydrochloride (54000 g), and microcrystalline cellulose (2137 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed dryer (WSG-60, POWREX CORPORATION), and the mixture was granulated while spraying a 8(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade SSL) solution (37800 g). The granules were dried to give a granulated powder. Compound (A')

used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-7S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. One more batch of the same sieved powder was produced. The sieved powder (105900 g) was measured, crospovidone (3591 g) (manufactured by BASF, Kollidon CL-F), microcrystalline cellulose (9167 g) (manufactured by Asahi Kasei, CEOLUS KG-802), and magnesium stearate (378 g) were added and they were mixed in a tumbler mixer (TM-400S, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted to give a tablet (long diameter 19.0 mm×short diameter 10.5 mm, 1260 mg per tablet).

OPADRY Red 03F45081 (1056 g) (manufactured by COLORCON JAPAN; containing hypromellose 2910, macrogol 6000, titanium oxide and red ferric oxide) and OPADRY Yellow 03F42240 (2112 g) (manufactured by COLORCON JAPAN; containing hypromellose 2910, macrogol 6000, titanium oxide and yellow ferric oxide) were suspended in purified water (28510 g) to prepare a coating solution. In a coating machine (DRC-1200DS, POWREX CORPORATION), the coating solution was sprayed on the tablet (110900 g) obtained above until the tablet weight increased by 36 mg per tablet, and a 5(w/w)% macrogol 6000 solution (528 g) was further sprayed to give preparation 6 (film-coated tablet). The composition of preparation 6 per tablet is shown in Table 6.

[0114]

[Table 6]

blending composition of preparation 6

component	weight (mg)
compound (A')	25.43
metformin hydrochloride	1000
microcrystalline cellulose (PH101)	39.57
hydroxypropylcellulose (SSL)	56
crospovidone (CL-F)	38
microcrystalline cellulose (KG802)	97
magnesium stearate	4
subtotal	1260
OPADRY Red 03F45081	12
OPADRY Yellow 03F42240	24
macrogol 6000	0.30
total	1296.3

[0115]

Example 7

Compound (A') (25.4 g), metformin hydrochloride (500 g), and microcrystalline cellulose (21.6 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed dryer, and the mixture was granulated while spraying a 7(w/w)% polyvinylpyrrolidone (manufactured by BASF, Kollidon K30)solution (400 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. The granulated powder (517.5 g) was measured, and mixed with microcrystalline cellulose (18 g) (manufactured by Asahi Kasei, CEOLUS KG-802), crospovidone (47.7 g) (manufactured by BASF, Kollidon CL-F), and magnesium stearate (1.8 g) in a plastic bag to give a mixed powder. Using a tableting machine, the mixed powder was tableted at tableting pressure 14kN to give preparation 7 (tablet, long diameter 13.5 mm×short diameter 8.5 mm, 650 mg per tablet). The composition of preparation 7 per tablet is shown in Table 7.

[0116]

[Table 7]

blending composition of preparation 7

component	weight (mg)
compound (A')	25.43
metformin hydrochloride	500
microcrystalline cellulose (PH101)	21.57
polyvinylpyrrolidone (K30)	28
microcrystalline cellulose (KG802)	20
crospovidone (CL-F)	53
magnesium stearate	2
total	650

[0117]

Example 8

Compound (A') (489.6 g), metformin hydrochloride (19000 g) and microcrystalline cellulose (745.4 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed granulation dryer (FD-WSG-30, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (12980 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.2 mmϕ punching screen to give a sieved powder. The sieved powder (14380 g) was measured, and mixed with microcrystalline cellulose (1261 g) (manufactured by Asahi Kasei, CEOLUS KG-802), crospovidone (494.0 g) (manufactured by BASF, Kollidon CL-F), and magnesium stearate (52.00 g) in a tumbler mixer (TM-60, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted to give a tablet (long diameter 19.0 mm×short diameter 10.5 mm, 1245 mg per tablet).

OPADRY Red 03F45081 (168 g) (manufactured by COLORCON JAPAN) and OPADRY Yellow 03F42240 (336 g) (manufactured by

COLORCON JAPAN) were suspended in purified water (4536 g) to prepare a coating solution. In a coating machine (DRC-650DS, POWREX CORPORATION), the coating solution was sprayed on the tablet (8715 g) obtained above until the tablet weight increased by 36 mg per tablet, and a 5(w/w)% macrogol 6000 solution (42.0 g) was further sprayed to give preparation 8 (film-coated tablet). The composition of preparation 8 per tablet is shown in Table 8.

[0118]

[Table 8]

blending composition of preparation 8

component	weight (mg)
compound (A')	25.43
metformin hydrochloride	1000
microcrystalline cellulose (PH101)	39.57
hydroxypropylcellulose	41
microcrystalline cellulose (KG802)	97
crospovidone	38
magnesium stearate	4
subtotal (mg)	1245
OPADRY Red 03F45081	12
OPADRY Yellow 03F42240	24
macrogol 6000	0.3
total (mg)	1281.3

[0119]

Example 9

Compound (A') (515.3 g), metformin hydrochloride (17000 g) and microcrystalline cellulose (684.7 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed granulation dryer (FD-WSG-30, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (11660 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained

granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.2 mmϕ punching screen to give a sieved powder. The sieved powder (14180 g) was measured, and mixed with microcrystalline cellulose (1230 g) (manufactured by Asahi Kasei, CEOLUS KG-802), crospovidone (480.0 g) (manufactured by BASF, Kollidon CL-F), and magnesium stearate (45.00 g) in a tumbler mixer (TM-60, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted to give a tablet (long diameter 17.5 mm×short diameter 9.5 mm, 1062 mg per tablet).

OPADRY Red 03F45081 (160.0 g) (manufactured by COLORCON JAPAN) and OPADRY Yellow 03F42240 (320.0 g) (manufactured by COLORCON JAPAN) were suspended in purified water (4320 g) to prepare a coating solution. In a coating machine (DRC-650DS, POWREX CORPORATION), the coating solution was sprayed on the tablets (8496 g) obtained above until the tablet weight increased by 30 mg per tablet, and a 5(w/w)% macrogol 6000 solution (40.0 g) was further sprayed to give preparation 9 (film-coated tablet). The composition of preparation 9 per tablet is shown in Table 9.

[0120]

[Table 9]

blending composition of preparation 9

component	weight (mg)
compound (A')	25.43
metformin hydrochloride	850
microcrystalline cellulose (PH101)	34.57
hydroxypropylcellulose	35
microcrystalline cellulose (KG802)	82
crospovidone	32
magnesium stearate	3
subtotal (mg)	1062
OPADRY Red 03F45081	10
OPADRY Yellow 03F42240	20
macrogol 6000	0.25
total (mg)	1092.25

[0121]

Example 10

Compound (A') (979.0 g), metformin hydrochloride (19000 g) and microcrystalline cellulose (807.0 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed granulation dryer (FD-WSG-30, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (13300 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.2 mmϕ punching screen to give a sieved powder. The sieved powder (14200 g) was measured, and mixed with microcrystalline cellulose (1325 g) (manufactured by Asahi Kasei, CEOLUS KG-802), crospovidone (500.0 g) (manufactured by BASF, Kollidon CL-F), and magnesium stearate (50.00 g) in a tumbler mixer (TM-60, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted to give a tablet (long diameter 13.5 mm×short diameter 8.5 mm, 643 mg per tablet).

OPADRY Red 03F45081 (156 g) (manufactured by COLORCON JAPAN) and OPADRY Yellow 03F42240 (321.0 g) (manufactured by COLORCON JAPAN) were suspended in purified water (4212 g) to prepare a coating solution. In a coating machine (DRC-650DS, POWREX CORPORATION), the coating solution was sprayed on the tablets (8359 g) obtained above until the tablet weight increased by 18 mg per tablet, and a 5(w/w)% macrogol 6000 solution (52.0 g) was further sprayed to give preparation 10 (film-coated tablet). The composition of preparation 10 per tablet is shown in Table 10.

[0122]

[Table 10]

blending composition of preparation 10

component	weight (mg)
compound (A')	25.43
metformin hydrochloride	500
microcrystalline cellulose (PH101)	21.57
hydroxypropylcellulose	21
microcrystalline cellulose (KG802)	53
crospovidone	20
magnesium stearate	2
subtotal (mg)	643
OPADRY Red 03F45081	6
OPADRY Yellow 03F42240	12
macrogol 6000	0.2
total (mg)	661.2

[0123]

Comparative Example 1

The sieved powder (11.5 g) obtained in Example 2 was mixed with microcrystalline cellulose (0.4 g) (manufactured by Asahi Kasei, CEOLUS KG-802), croscarmellose sodium (1.06 g) (manufactured by FMC, Ac-Di-Sol), and magnesium stearate (0.04 g) in a glass bottle to give a mixed powder. Using a tableting machine, the mixed powder was tableted at tableting pressure 14kN to give comparison preparation 1 (tablet, long diameter 13.5 mm×short diameter 8.5 mm, 650 mg per tablet). The composition of comparison preparation 1 per tablet is shown in Table 11.

[0124]

[Table 11]

blending composition of comparison preparation 1

component	weight (mg)
compound (A')	25.43
metformin hydrochloride	500
microcrystalline cellulose (PH101)	21.57
hydroxypropylcellulose(SSL)	28
microcrystalline cellulose (KG802)	20
croscarmellose sodium	53
magnesium stearate	2
total	650

[0125]

Comparative Example 2

The sieved powder (11.5 g) obtained in Example 2 was mixed with microcrystalline cellulose (0.4 g) (manufactured by Asahi Kasei, CEOLUS KG-802), sodium starch glycolate (1.06 g) (manufactured by DMV, Primojel), and magnesium stearate (0.04 g) in a glass bottle to give a mixed powder. Using a tableting machine, the mixed powder was tableted at tableting pressure 14kN to give comparison preparation 2 (tablet, long diameter 13.5 mm×short diameter 8.5 mm, 650 mg per tablet). The composition of comparison preparation 2 per tablet is shown in Table 12.

[0126]

[Table 12]

blending composition of comparison preparation 2

component	weight (mg)
compound (A')	25.43
metformin hydrochloride	500
microcrystalline cellulose (PH101)	21.57
hydroxypropylcellulose(SSL)	28
microcrystalline cellulose (KG802)	20
sodium starch glycolate	53
magnesium stearate	2
total	650

[0127]

Experimental Example 1

The disintegration time of the preparations obtained in Examples 3 and 4, and Comparative Examples 1 and 2 was measured according to the disintegration test method of the Japanese Pharmacopoeia (16th edition) (test solution: water, no disc, (each numerical value of N=6 and mean thereof)). The results are shown in Table 13.

[0128]

[Table 13]

preparation disintegration time (min)

	Example 3	Example 4	Comparative Example 1	Comparative Example 2
N=1	3.8	4.6	5.5	4.2
N=2	4.1	4.7	5.9	4.9
N=3	4.2	4.8	6.0	4.9
N=4	4.3	5.1	6.5	5.4
N=5	4.5	5.1	6.7	7.0
N=6	4.5	5.2	6.9	7.8
mean	4.2	4.9	6.3	5.7
standard deviation	0.2	0.2	0.5	1.3

[0129]

As shown in Table 13, the preparations of Examples 3 and 4 showed superior disintegration property. The preparations of Examples 3 and 4 showed suppressed variation in the disintegration property of respective preparations. That is, it has been clarified that a preparation containing crospovidone is superior in disintegration property and shows small variation in the disintegration property of respective preparations, as compared to a preparation containing croscarmellose sodium or sodium starch glycolate.

[0130]

Experimental Example 2

The preparations obtained in Example 1 and Example 7 were preserved in an open glass bottle under the conditions of 60°C, 75%RH for 2 weeks, and the total analog of compound (A') in the preparations was quantified by high performance liquid chromatography. The results are shown in Table 14.

[0131]

[Table 14]

stability test result of compound (A') (production of analog)

	Example 1	Example 7
Initial	1.36%	1.44%
60°C 75%RH 2 weeks	1.46%	5.40%

[0132]

As shown in Table 14, the preparation of Example 1 showed preservation stability superior to that of the preparation of Example 7. That is, it has been clarified that a preparation containing hydroxypropylcellulose is superior in the preservation stability as compared to a preparation containing polyvinylpyrrolidone, since the former showed suppression of the production of analogue of the active ingredient as compared to the latter. Moreover, since production of analogue is suppressed at the time point of Initial, it has been clarified that the production of analogue during the preparation production step is also suppressed in a preparation containing hydroxypropylcellulose.

[0133]

Experimental Example 3

Compound (A') and the additives described in Table 15 were mixed in a mortar, and preserved in an open glass bottle under the conditions of 40°C, 75%RH for 2 weeks and in a closed glass bottle under the conditions of 60°C for 2 weeks. The total analog of compound (A') after preservation was quantified by high performance liquid chromatography. The results are shown in Table 15.

[0134]

[Table 15]

compound (A') stability test results 2 (production of analog)

additive	blending weight ratio (drug substance/ additive)	total analog (%)		
		initial	40°C 75%RH-2W glass bottle opened	60°C-2W glass bottle closed
none	-	0.51	0.49	0.52
hydroxypropyl-cellulose (HPC)	1/5	0.52	0.53	0.58
hypromellose (HPMC)	1/5	0.54	0.79	1.13
polyvinyl-pyrrolidone	1/5	0.57	1.12	1.51

[0135]

As shown in Table 15, the mixture of compound (A') and hydroxypropylcellulose showed superior preservation stability. That is, it has been clarified that hydroxypropylcellulose is superior to hypromellose and polyvinylpyrrolidone in the suppressive effect on the production of compound (A') analogue.

[0136]

Example 1A

Compound (A') (17230 g), D-mannitol (37040 g) and microcrystalline cellulose (6700 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed dryer (WSG-60, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (33500 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 21.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-7S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. The sieved powder (57340 g) was measured, croscarmellose sodium (3050 g) (manufactured by FMC, Ac-Di-Sol), and magnesium stearate (610 g) were added and they were mixed in a tumbler mixer (TM-400S, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted at tableting pressure 6kN to give a tablet (long diameter 8 mm×short diameter 4.5 mm, 100 mg per tablet).

OPADRY White 03F480011 (4850 g) (manufactured by COLORCON JAPAN; containing hypromellose 2910, macrogol 6000 and titanium oxide) was suspended in purified water (43650 g) to prepare a coating solution. In a coating machine (DRC-1200DS, POWREX CORPORATION), the coating solution was sprayed on the tablets (55000 g) obtained above until the tablet weight increased by 5 mg per tablet, and a 5(w/w)% macrogol 6000 solution (550 g) was

further sprayed to give preparation 1A (film-coated tablet). The composition of preparation 1A per tablet is shown in Table 16.

[0137]

[Table 16]

blending composition of preparation 1A

component	weight (mg)
compound (A')	25.43
D-mannitol	55.57
microcrystalline cellulose (PH101)	10
hydroxypropylcellulose	3
croscarmellose sodium	5
magnesium stearate	1
subtotal	100
OPADRY White 03F480011	5
macrogol 6000	0.05
total	105.05

[0138]

Example 2A

Compound (A') (19320 g), D-mannitol (34540 g) and microcrystalline cellulose (6650 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed dryer (WSG-60, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (33260 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 23.1 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-7S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. The sieved powder (57580 g) was measured, croscarmellose sodium (3063 g) (manufactured by FMC, Ac-Di-Sol), and magnesium stearate (612.5 g) were added and they were mixed in a tumbler mixer (TM-400S, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was

tableted at tableting pressure 7kN to give a tablet (long diameter 10.5 mm×short diameter 5.5 mm, 175 mg per tablet).

OPADRY White 03F480011 (3983 g) (manufactured by COLORCON JAPAN; containing hypromellose 2910, macrogol 6000 and titanium oxide) was suspended in purified water (35400 g) to prepare a coating solution. In a coating machine (DRC-1200DS, POWREX CORPORATION), the coating solution was sprayed on the tablets (55000 g) obtained above until the tablet weight increased by 9 mg per tablet, and a 5(w/w)% macrogol 6000 solution (522 g) was further sprayed to give preparation 2A (film-coated tablet). The composition of preparation 2A per tablet is shown in Table 17.

[0139]

[Table 17]

blending composition of preparation 2A

component	weight (mg)
compound (A')	50.85
D-mannitol	90.9
microcrystalline cellulose (PH101)	17.5
hydroxypropylcellulose	5.25
croscarmellose sodium	8.75
magnesium stearate	1.75
subtotal	175
OPADRY White 03F480011	9
macrogol 6000	0.09
total	184.09

[0140]

Example 3A

Compound (A') (694.9 g), alogliptin benzoate (hereinafter compound III) (228.6 g), mannitol (3046 g) (manufactured by Rocket Japan, D-mannitol), and microcrystalline cellulose (453.1 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed granulation dryer (FD-5S, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (2430 g). The granules were dried to give a granulated powder. Compound (A') used here was a

pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. The sieved powder (3892 g) was measured, mixed with microcrystalline cellulose (460.0 g) (manufactured by Asahi Kasei, CEOLUS PH-101), croscarmellose sodium (207.0 g) (manufactured by FMC, Ac-Di-Sol), and magnesium stearate (41.40 g) in a tumbler mixer (TM-1S, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted to give a tablet (diameter 8.0 mm, 200 mg per tablet).

Hypromellose 2910 (256.3 g) (manufactured by Shin-Etsu Chemical Co., Ltd., Metolose TC-5) was dissolved in purified water (1854 g), and a dispersion of titanium oxide (28.80 g) (manufactured by Freund Corporation), yellow ferric oxide (1.440 g) (manufactured by UNIVAR) and red ferric oxide (1.440 g) (manufactured by Kohnstamm, ferric oxide red) in purified water (738.0 g) was mixed with the hypromellose 2910 solution to prepare a coating solution. In a coating machine (DRC-500DS, POWREX CORPORATION), the coating solution was sprayed on the tablets (3600 g) obtained above until the tablet weight increased by 8 mg per tablet to give preparation 3A. The composition of preparation 3A per tablet is shown in Table 18.

[0141]

[Table 18]

blending composition of preparation 3A

component	weight (mg)
compound (A')	25.43
compound III	8.5
mannitol	113.09
microcrystalline cellulose (PH101)	36.78
hydroxypropylcellulose	5.4
croscarmellose sodium	9
magnesium stearate	1.8
subtotal (mg)	200
hypromellose 2910	7.12
titanium oxide	0.8
yellow ferric oxide	0.04
red ferric oxide	0.04
total (mg)	208

[0142]

Example 4A

Compound (A') (694.9 g), compound III (457.2 g), mannitol (2818 g) (manufactured by Rocket Japan, D-mannitol), and microcrystalline cellulose (453.1 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed granulation dryer (FD-5S, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (2430 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. The sieved powder (3892 g) was measured, mixed with microcrystalline cellulose (460.0 g) (manufactured by Asahi Kasei, CEOLUS PH-101), croscarmellose sodium (207.0 g) (manufactured by FMC, Ac-Di-Sol), and magnesium stearate (41.40 g) in a tumbler mixer (TM-1S, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a

tableting machine, the mixed powder was tableted to give a tablet (diameter 8.0 mm, 200 mg per tablet).

Hypromellose 2910 (256.3 g) (manufactured by Shin-Etsu Chemical Co., Ltd., Metolose TC-5) was dissolved in purified water (1854 g), and a dispersion of titanium oxide (28.80 g) (manufactured by Freund Corporation), yellow ferric oxide (1.440 g) (manufactured by UNIVAR) and red ferric oxide (1.440 g) (manufactured by Kohnstamm, ferric oxide red) in purified water (738.0 g) was mixed with the hypromellose 2910 solution to prepare a coating solution. In a coating machine (DRC-500DS, POWREX CORPORATION), the coating solution was sprayed on the tablets (3600 g) obtained above until the tablet weight increased by 8 mg per tablet to give preparation 4A. The composition of preparation 4A per tablet is shown in Table 19.

[0143]

[Table 19]

blending composition of preparation 4A

component	weight (mg)
compound (A')	25.43
compound III	17
mannitol	104.59
microcrystalline cellulose (PH101)	36.78
hydroxypropylcellulose	5.4
croscarmellose sodium	9
magnesium stearate	1.8
subtotal (mg)	200
hypromellose 2910	7.12
titanium oxide	0.8
yellow ferric oxide	0.04
red ferric oxide	0.04
total (mg)	208

[0144]

Example 5A

Compound (A') (694.9 g), compound III (914.3 g), mannitol (2360 g) (manufactured by Rocket Japan, D-mannitol), and microcrystalline cellulose (453.1 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed granulation dryer (FD-5S, POWREX CORPORATION), and the

mixture was granulated while spraying a 6(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (2430 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. The sieved powder (3892 g) was measured, mixed with microcrystalline cellulose (460.0 g) (manufactured by Asahi Kasei, CEOLUS PH-101), croscarmellose sodium (207.0 g) (manufactured by FMC, Ac-Di-Sol), and magnesium stearate (41.40 g) in a tumbler mixer (TM-1S, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted to give a tablet (diameter 8.0 mm, 200 mg per tablet).

Hypromellose 2910 (256.3 g) (manufactured by Shin-Etsu Chemical Co., Ltd., Metolose TC-5) was dissolved in purified water (1854 g), and a dispersion of titanium oxide (28.80 g) (manufactured by Freund Corporation), yellow ferric oxide (1.440 g) (manufactured by UNIVAR) and red ferric oxide (1.440 g) (manufactured by Kohnstamm, ferric oxide red) in purified water (738.0 g) was mixed with the hypromellose 2910 solution to prepare a coating solution. In a coating machine (DRC-500DS, POWREX CORPORATION), the coating solution was sprayed on the tablets (3600 g) obtained above until the tablet weight increased by 8 mg per tablet to give preparation 5A. The composition of preparation 5A per tablet is shown in Table 20.

[0145]

[Table 20]

blending composition of preparation 5A

component	weight (mg)
compound (A')	25.43
compound III	34
mannitol	87.59
microcrystalline cellulose (PH101)	36.78
hydroxypropylcellulose	5.4
croscarmellose sodium	9
magnesium stearate	1.8
subtotal (mg)	200
hypromellose 2910	7.12
titanium oxide	0.8
yellow ferric oxide	0.04
red ferric oxide	0.04
total (mg)	208

[0146]

Example 6A

Compound (A') (1390 g), compound III (228.6 g), mannitol (2351 g) (manufactured by Rocket Japan, D-mannitol), and microcrystalline cellulose (453.1 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed granulation dryer (FD-5S, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (2430 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. The sieved powder (3892 g) was measured, mixed with microcrystalline cellulose (460.0 g) (manufactured by Asahi Kasei, CEOLUS PH-101), croscarmellose sodium (207.0 g) (manufactured by FMC, Ac-Di-Sol), and magnesium stearate (41.40 g) in a tumbler mixer (TM-1S, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a

tableting machine, the mixed powder was tableted to give a tablet (diameter 8.0 mm, 200 mg per tablet).

Hypromellose 2910 (256.3 g) (manufactured by Shin-Etsu Chemical Co., Ltd., Metolose TC-5) was dissolved in purified water (1854 g), and a dispersion of titanium oxide (28.80 g) (manufactured by Freund Corporation), yellow ferric oxide (1.440 g) (manufactured by UNIVAR) and red ferric oxide (1.440 g) (manufactured by Kohnstamm, ferric oxide red) in purified water (738.0 g) was mixed with the hypromellose 2910 solution to prepare a coating solution. In a coating machine (DRC-500DS, POWREX CORPORATION), the coating solution was sprayed on the tablets (3600 g) obtained above until the tablet weight increased by 8 mg per tablet to give preparation 6A. The composition of preparation 6A per tablet is shown in Table 21.

[0147]

[Table 21]

blending composition of preparation 6A

component	weight (mg)
compound (A')	50.85
compound III	8.5
mannitol	87.67
microcrystalline cellulose (PH101)	36.78
hydroxypropylcellulose	5.4
croscarmellose sodium	9
magnesium stearate	1.8
subtotal (mg)	200
hypromellose 2910	7.12
titanium oxide	0.8
yellow ferric oxide	0.04
red ferric oxide	0.04
total (mg)	208

[0148]

Example 7A

Compound (A') (1390.0 g), compound III (457.2 g), mannitol (2123 g) (manufactured by Rocket Japan, D-mannitol), and microcrystalline cellulose (453.1 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed granulation dryer (FD-5S, POWREX CORPORATION), and the

mixture was granulated while spraying a 6(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (2430 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. The sieved powder (3892 g) was measured, mixed with microcrystalline cellulose (460.0 g) (manufactured by Asahi Kasei, CEOLUS PH-101), croscarmellose sodium (207.0 g) (manufactured by FMC, Ac-Di-Sol), and magnesium stearate (41.40 g) in a tumbler mixer (TM-1S, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted to give a tablet (diameter 8.0 mm, 200 mg per tablet).

Hypromellose 2910 (256.3 g) (manufactured by Shin-Etsu Chemical Co., Ltd., Metolose TC-5) was dissolved in purified water (1854 g), and a dispersion of titanium oxide (28.80 g) (manufactured by Freund Corporation), yellow ferric oxide (1.440 g) (manufactured by UNIVAR) and red ferric oxide (1.440 g) (manufactured by Kohnstamm, ferric oxide red) in purified water (738.0 g) was mixed with the hypromellose 2910 solution to prepare a coating solution. In a coating machine (DRC-500DS, POWREX CORPORATION), the coating solution was sprayed on the tablets (3600 g) obtained above until the tablet weight increased by 8 mg per tablet to give preparation 7A. The composition of preparation 7A per tablet is shown in Table 22.

[0149]

[Table 22]

blending composition of preparation 7A

component	weight (mg)
compound (A')	50.85
compound III	17
mannitol	79.17
microcrystalline cellulose (PH101)	36.78
hydroxypropylcellulose	5.4
croscarmellose sodium	9
magnesium stearate	1.8
subtotal (mg)	200
hypromellose 2910	7.12
titanium oxide	0.8
yellow ferric oxide	0.04
red ferric oxide	0.04
total (mg)	208

[0150]

Example 8A

Compound (A') (1390 g), compound III (914.3 g), mannitol (1666 g) (manufactured by Rocket Japan, D-mannitol), and microcrystalline cellulose (453.1 g) (manufactured by Asahi Kasei, CEOLUS PH-101) were measured and placed in a fluidized-bed granulation dryer (FD-5S, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (2430 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 25.6 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. The sieved powder (3892 g) was measured, mixed with microcrystalline cellulose (460.0 g) (manufactured by Asahi Kasei, CEOLUS PH-101), croscarmellose sodium (207.0 g) (manufactured by FMC, Ac-Di-Sol), and magnesium stearate (41.40 g) in a tumbler mixer (TM-1S, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a

tableting machine, the mixed powder was tableted to give a tablet (diameter 8.0 mm, 200 mg per tablet).

Hypromellose 2910 (256.3 g) (manufactured by Shin-Etsu Chemical Co., Ltd., Metolose TC-5) was dissolved in purified water (1854 g), and a dispersion of titanium oxide (28.80 g) (manufactured by Freund Corporation), yellow ferric oxide (1.440 g) (manufactured by UNIVAR) and red ferric oxide (1.440 g) (manufactured by Kohnstamm, ferric oxide red) in purified water (738.0 g) was mixed with the hypromellose 2910 solution to prepare a coating solution. In a coating machine (DRC-500DS, POWREX CORPORATION), the coating solution was sprayed on the tablets (3600 g) obtained above until the tablet weight increased by 8 mg per tablet to give preparation 8A. The composition of preparation 8A per tablet is shown in Table 23.

[0151]

[Table 23]

blending composition of preparation 8A

component	weight (mg)
compound (A')	50.85
compound III	34
mannitol	62.17
microcrystalline cellulose (PH101)	36.78
hydroxypropylcellulose	5.4
croscarmellose sodium	9
magnesium stearate	1.8
subtotal (mg)	200
hypromellose 2910	7.12
titanium oxide	0.8
yellow ferric oxide	0.04
red ferric oxide	0.04
total (mg)	208

[0152]

Example 9A

Compound (A') (1477 g), D-mannitol (2574 g) and microcrystalline cellulose (500.2 g) were cast into a fluidized-bed granulation dryer (FD-5S, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% aqueous hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L)

solution (2501 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 14.3 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. The sieved powder (3995 g) was measured, and mixed with croscarmellose sodium (212.5 g), and magnesium stearate (42.50 g) in a tumbler mixer (TM-15, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted to give a tablet (long diameter 10.5 mm×short diameter 5.5 mm, 175 mg per tablet).

OPADRY White 03F48001 (540.0 g) (manufactured by COLORCON JAPAN) was suspended in purified water (4860 g) to prepare a coating solution. In a coating machine (DRC-500, POWREX CORPORATION), the coating solution was sprayed on the tablets (2975 g) obtained above until the tablet weight increased by 9 mg per tablet to give preparation 9A (film-coated tablet). The composition of preparation 9A per tablet is shown in Table 24.

[0153]

[Table 24]

blending composition of preparation 9A

component	weight (mg)
compound (A')	50.85
D-mannitol	90.9
microcrystalline cellulose	17.5
hydroxypropylcellulose	5.25
croscarmellose sodium	8.75
magnesium stearate	1.75
OPADRY White 03F480011	9
total (mg)	184

[0154]

Example 10A

Compound (A') (1477 g), D-mannitol (2574 g) and

microcrystalline cellulose (500.2 g) were cast into a fluidized-bed granulation dryer (FD-5S, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% aqueous hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (2501 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 23.1 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. The sieved powder (3995 g) was measured, and mixed with croscarmellose sodium (212.5 g), and magnesium stearate (42.50 g) in a tumbler mixer (TM-15, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted to give a tablet (long diameter 10.5 mm×short diameter 5.5 mm, 175 mg per tablet).

OPADRY White 03F48001 (540.0 g) (manufactured by COLORCON JAPAN) was suspended in purified water (4860 g) to prepare a coating solution. In a coating machine (DRC-500, POWREX CORPORATION), the coating solution was sprayed on the tablets (2975 g) obtained above until the tablet weight increased by 9 mg per tablet to give preparation 10A (film-coated tablet). The composition of preparation 10A per tablet is shown in Table 25.

[0155]

[Table 25]

blending composition of preparation 10A

component	weight (mg)
compound (A')	50.85
D-mannitol	90.9
microcrystalline cellulose	17.5
hydroxypropylcellulose	5.25
croscarmellose sodium	8.75
magnesium stearate	1.75
OPADRY White 03F480011	9
total (mg)	184

[0156]

Example 11A

Compound (A') (1477 g), D-mannitol (2574 g) and microcrystalline cellulose (500.2 g) were cast into a fluidized-bed granulation dryer (FD-5S, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% aqueous hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (2501 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 33.4 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. The sieved powder (3995 g) was measured, and mixed with croscarmellose sodium (212.5 g), and magnesium stearate (42.50 g) in a tumbler mixer (TM-15, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted to give a tablet (long diameter 10.5 mm×short diameter 5.5 mm, 175 mg per tablet).

OPADRY White 03F48001 (540.0 g) (manufactured by COLORCON JAPAN) was suspended in purified water (4860 g) to prepare a coating solution. In a coating machine (DRC-500, POWREX CORPORATION), the coating solution was sprayed on the tablets

(2975 g) obtained above until the tablet weight increased by 9 mg per tablet to give preparation 11A (film-coated tablet). The composition of preparation 11A per tablet is shown in Table 26.

[0157]

[Table 26]

blending composition of preparation 11A

component	weight (mg)
compound (A')	50.85
D-mannitol	90.9
microcrystalline cellulose	17.5
hydroxypropylcellulose	5.25
croscarmellose sodium	8.75
magnesium stearate	1.75
OPADRY White 03F480011	9
total (mg)	184

[0158]

Comparative Example 1A

Compound (A') (1477 g), D-mannitol (2574 g) and microcrystalline cellulose (500.2 g) were cast into a fluidized-bed granulation dryer (FD-5S, POWREX CORPORATION), and the mixture was granulated while spraying a 6(w/w)% aqueous hydroxypropylcellulose (Nippon Soda Co., Ltd., grade L) solution (2501 g). The granules were dried to give a granulated powder. Compound (A') used here was a pulverized product by PINMILL, which had an average particle size of 42.5 μm as measured by a laser diffraction particle size analyzer and according to a dry method. A part of the obtained granulated powder was crushed by a Power Mill grinding machine (P-3S, Showa Kagakukikai Co., Ltd.) using a 1.5 mmϕ punching screen to give a sieved powder. The sieved powder (3995 g) was measured, and mixed with croscarmellose sodium (212.5 g), and magnesium stearate (42.50 g) in a tumbler mixer (TM-15, Showa Kagakukikai Co., Ltd.) to give a mixed powder. Using a tableting machine, the mixed powder was tableted to give a tablet (long diameter 10.5 mm×short diameter 5.5 mm, 175 mg per

tablet).

OPADRY White 03F48001 (540.0 g) (manufactured by COLORCON JAPAN) was suspended in purified water (4860 g) to prepare a coating solution. In a coating machine (DRC-500, POWREX CORPORATION), the coating solution was sprayed on the tablets (2975 g) obtained above until the tablet weight increased by 9 mg per tablet to give comparison preparation 1A (film-coated tablet). The composition of comparison preparation 1A per tablet is shown in Table 27.

[0159]

[Table 27]

blending composition of comparison preparation 1A

component	weight (mg)
compound (A')	50.85
D-mannitol	90.9
microcrystalline cellulose	17.5
hydroxypropylcellulose	5.25
croscarmellose sodium	8.75
magnesium stearate	1.75
OPADRY White 03F480011	9
total (mg)	184

[0160]

Experimental Example 1A

The film-coated tablets of Example 9A, Example 10A, Example 11A, and Comparative Example 1A were subjected to the measurement of the dissolution property of compound (A') according to the Japanese Pharmacopoeia Paddle Method (rotation number 50 rpm, 37°C, phosphate buffer containing 0.1% sodium lauryl sulfate (pH 6.8), 900 mL, n=6). The results are shown in Table 28. The respective values in the Table show the average of the dissolution ratio(%) of 6 film-coated tablets.

[0161]

[Table 28]

	Example 9A (14.3 μm)	Example 10A (23.1 μm)	Example 11A (33.4 μm)	Comparative Example 1A (42.5 μm)
Time	Average	Average	Average	Average
0	0	0	0	0
5	18.1	20.1	17.3	10.2
10	52.3	52.4	49.3	34.9
15	70.3	66.9	62.8	53.2
20	86	81.3	75.4	62.2
30	92.5	88.2	83.5	69.9
45	96.4	94.3	90.6	77.4
60	97.1	96.5	95.6	88.4

[0162]

As shown in Table 28, the preparations of Examples 9A, 10A and 11A were superior to the preparation of Comparative Example 1A in the dissolution property of compound (A'). That is, it has been clarified that compound (A) or a salt thereof having an average particle size of less than 35 μm (e.g., 14.3 - 33.4 μm) is superior in the dissolution property from a preparation.

INDUSTRIAL APPLICABILITY

[0163]

According to the present invention, a solid preparation containing compound (A) or a salt thereof, metformin or a salt thereof and crospovidone, which is superior in the disintegration property and preservation stability, can be provided. In addition, according to the present invention, compound (A) or a salt thereof having superior dissolution property can be provided.

[0164]

This application is based on a patent application No. 2012-161025 filed in Japan, the contents of which are incorporated in full herein.

CLAIMS

1. A solid preparation comprising
(1) [(3S)-6-({2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid or a salt thereof,
(2) metformin or a salt thereof, and
(3) crospovidone.

2. The solid preparation according to claim 1, wherein said metformin or a salt thereof is metformin hydrochloride.

3. The solid preparation according to claim 1 or 2, further comprising hydroxypropylcellulose.

4. The solid preparation according to claim 3, further comprising microcrystalline cellulose and magnesium stearate.

5. [(3S)-6-({2',6'-Dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid or a salt thereof, which has an average particle size of less than 35 μm.

6. A solid preparation comprising [(3S)-6-({2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid or a salt thereof according to claim 5.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2013/070126

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14
ADD.

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)
A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/001931 A2 (TAKEDA PHARMACEUTICAL [JP]; YASUMA TSUNEO [JP]; NEGORO NOBUYUKI [JP];) 3 January 2008 (2008-01-03) claims 1-15 page 57 pages 60-61 -----	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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"P" document published prior to the international filing date but later than the priority date claimed

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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
12 November 2013	05/12/2013

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2013/070126

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