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(54) Title: SOLID PREPARATION

(57) Abstract: The problem of the present invention is provision of a solid preparation containing N-methyl-N- (1-methylethyl) - 6, 7, 8, 9-tetrahydropyrazino [2, 3-f] [1, 4] oxazepin-3-amine or a salt thereof, which may release the compound in a sustained manner. A solid preparation containing N-methyl-N- (1- methylethyl) -6, 7,8, 9-tetrahydropyrazino [2, 3-f] [1,4] oxazepin-3- amine or a salt thereof, and a hydrophilic gel-forming polymer.

DESCRIPTION

Title of the Invention: SOLID PREPARATION

[Technical field]

[0001]

The present invention relates to a solid preparation containing N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, which may release the compound in a sustained manner.

[0002]

(Background of the invention)

N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine and salts thereof exhibit serotonin 5-HT_{2C} receptor-activating action, and are known to be useful as prophylactic or therapeutic agents for lower urinary tract symptoms, obesity, and/or organ prolapse (patent document 1).

Patent document 2 discloses a nifedipine-containing dry coated tablet comprising a core containing nifedipine and a hydrophilic gel-forming polymer substance and exhibiting delayed release of nifedipine, and an outer shell formed by compression coating the core, which contains nifedipine, a hydrophilic gel-forming polymer substance, and a disintegration-suppressive substance composed of a water-insoluble polymer that forms a pH-independent matrix with nifedipine and the hydrophilic gel-forming polymer substance.

Patent document 3 discloses a dry coated tablet comprising a core containing 8-80% by weight of nifedipine, 15-80% by weight of a hydrophilic gel-forming polymer substance composed of a cellulose derivative and the like, and 2-30% by weight of a disintegration-suppressive substance composed of a water-insoluble polymer, and an outer shell containing 5-50% by weight of nifedipine, 30-90% by weight of a hydrophilic gel-forming polymer substance composed of a cellulose derivative and the like, and 5-50% by weight of a disintegration-suppressive substance composed of a water-insoluble polymer.

Patent document 4 discloses a dry coated tablet comprising a core containing nifedipine and a hydrophilic gel-forming polymer substance, and an outer shell containing nifedipine, a hydrophilic gel-forming polymer substance, and a disintegration-suppressive substance composed of a water-insoluble polymer.

[Document List]

[Patent documents]

[0003]

patent document 1: WO 2010/147226

patent document 2: JP-A-9-143073

patent document 3: JP-A-2004-2348

patent document 4: JP-A-2009-120600

[SUMMARY OF THE INVENTION]

[Problems to be Solved by the Invention]

[0004]

Since N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine and salts thereof have high solubility and a short half-life, three doses per day are anticipated to avoid an adverse event in a typical rapid release tablet.

From the viewpoints of the convenience for patients and medication compliance, a preparation capable of reducing the number of doses is desired.

Thus, an object of the present invention is to provide a preparation which may release N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in a sustained manner, which may permit administration once or twice per day.

In addition, a preparation containing N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof as an active ingredient has a problem of the stability of the active ingredient, since it is influenced by an increase in the amount of additive. Therefore, the amount of the additive to be used is desirably small.

Thus, another object of the present invention is to provide a preparation that may reduce the amount of additive to be used, which in turn may suppress a decrease in the stability of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof.

[Means of Solving the Problems]

[0005]

The present inventor has conducted intensive studies in an attempt to solve the aforementioned problems and found that N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine and a salt thereof may be released in a sustained manner by using a hydrophilic gel-forming polymer.

The present inventor has also found that, in a solid preparation (such as a tablet) comprising a core, an outer shell, a hydrophilic gel-forming polymer in the core and the outer shell, and N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in the core and/or the outer shell, the release behavior of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof may be controlled by adjusting the content thereof in the core and/or the outer shell, whereby the compound may be released in a sustained manner.

The present inventor has further found that use of a hydrophilic gel-forming polymer may enable maintenance of moldability even when the amount of additives other than the hydrophilic gel-forming polymer is reduced. It has been found that the chemical stability of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine and salts thereof is affected when the amount of additive is increased. Therefore, the reduction of stability of the compound may be expected to be suppressed by decreasing the additives.

The present inventor has conducted further studies based on the above findings and completed the present invention.

[0006]

Accordingly, the present invention provides the following.

[1] A solid preparation comprising N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, and a hydrophilic gel-forming polymer.

[2] The solid preparation of the above-mentioned [1], comprising (1) a core comprising N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, and a first hydrophilic gel-forming polymer; and (2) an outer shell comprising N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, and a second hydrophilic gel-forming polymer.

[2-1] The solid preparation of the above-mentioned [1], comprising (1) a core comprising N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, and a first hydrophilic gel-forming polymer; and (2) an outer shell comprising a second hydrophilic gel-forming polymer and not comprising N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof.

[3] The solid preparation of the above-mentioned [2] or [2-1], wherein the first hydrophilic gel-forming polymer and the second hydrophilic gel-forming polymer are the same or different and each is selected from the group consisting of polyethylene oxide, hydroxypropyl methyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, carboxyvinyl polymer, methyl cellulose, and sodium carboxymethyl cellulose.

[4] The solid preparation of the above-mentioned [2], wherein, in the preparation, the content (by weight) of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in the core is the same as or higher than the content (by weight) of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in the outer shell.

[Effects of the invention]

[0007]

The present invention can provide a preparation containing N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof as an active ingredient, which may release the compound in a sustained manner by using a hydrophilic gel-forming polymer.

In particular, according to the present invention, a solid preparation (such as a tablet) comprising a core, an outer shell, a hydrophilic gel-forming polymer in the core and the outer shell, and N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in the core and/or the outer shell, which may release the compound in a sustained manner, can be provided by adjusting the content of the compound in the core and/or the outer shell.

Furthermore, the present invention can provide a preparation that may be administered once or twice per day.

In addition, the present invention can provide a preparation that may exhibit good moldability due to the use of a hydrophilic gel-forming polymer, even when the amount of an additive other than the hydrophilic gel-forming polymer is reduced and, since the amount of the additive to be used may be reduced, the present invention can provide a preparation that may suppress lowering of the stability of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine and a salt thereof.

[Brief explanation of the drawings]

[0008]

Fig. 1 shows the results of Experimental Example 1.

Fig. 2 shows the results of Experimental Example 2.

Fig. 3 shows the results of Experimental Example 3.

Fig. 4 shows the results of Experimental Example 4.

Fig. 5 shows the results of Experimental Example 5.

Fig. 6 shows the results of Experimental Example 6.

Fig. 7 shows the results of Experimental Example 7.

Fig. 8 shows the results of Experimental Example 8.

Fig. 9 shows the results of Experimental Example 9.

Fig. 10 shows the results of Experimental Example 10.

Fig. 11 shows the results of Experimental Example 11.

Fig. 12 shows the results of Experimental Example 12.

[Description of Embodiments]

[0009]

The present invention is described in detail below.

The solid preparation of the present invention contains N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof as an active ingredient.

[0010]

Examples of the salt of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine include inorganic acid salts, organic acid salts, and basic or acidic amino acid salts.

Examples of the inorganic acid salt include hydrochloride, hydrobromate, nitrate, sulfate, and phosphate.

Examples of the organic acid salt include formate, acetate, trifluoroacetate, fumarate, oxalate, tartrate, maleate, citrate, succinate, malate, methanesulfonate, benzenesulfonate, and p-toluenesulfonate.

Examples of the basic amino acid salt include salts with arginine, lysine, and ornithine.

Examples of the acidic amino acid salt include aspartate and glutamate.

Of these, a pharmacologically acceptable salt is preferable.

As a salt of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine, N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine hydrochloride is especially preferable.

[0011]

The amount of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or salt thereof in a free form in the solid preparation of the present invention is generally 1-1000 mg, preferably 5-800 mg, more preferably 10-500 mg.

The amount of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or salt thereof in a free form in the solid preparation of the present invention is generally 0.5-85% by weight, preferably 1-75% by weight, more preferably 1-65% by weight, relative to the weight of the bare preparation (uncoated tablet).

[0012]

The solid preparation of the present invention characteristically contains a hydrophilic gel-forming polymer.

[0013]

In the present invention, the viscosity (25°C, 1% aqueous solution) of the hydrophilic gel-forming polymer is generally not less than 100 cP, preferably not less than 5500 cP, more preferably not less than 7500 cP. In the present invention, the viscosity (25°C, 1% aqueous solution) of the hydrophilic gel-forming polymer is generally not more than 500,000 cP.

In the present invention, the hydrophilic gel-forming polymer is not particular limited as long as it has the above-mentioned viscosity. Examples include polyethylene oxide (for example, Polyox™ WSR 303 produced by The Dow Chemical Company, or PEO-20NF produced by Sumitomo Seika Chemicals Co., Ltd.), hydroxypropyl methyl cellulose (for example, METOLOSE 90SH-100000SR produced by Shin-etsu Chemical Co., Ltd.), carboxymethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, carboxyvinyl polymer (for example, Carbopol 971PNF produced by the Lubrizol Corporation), methyl cellulose, and sodium carboxymethyl cellulose. Polyethylene oxide, hydroxypropyl methyl cellulose, and carboxyvinyl polymer are preferable, and polyethylene oxide is especially preferable.

[0014]

In the solid preparation of the present invention, it is preferable to use a highly viscous hydrophilic gel-forming polymer (such as polyethylene oxide) as the hydrophilic gel-forming polymer, because it may control dissolution of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or salt thereof.

[0015]

In the solid preparation of the present invention, the content of the hydrophilic gel-forming polymer is generally 15-95% by weight, preferably 25-85% by weight, more preferably 35-75% by weight, relative to the weight of the bare preparation (uncoated tablet).

[0016]

In the present description, the "bare preparation (uncoated tablet)" refers to a preparation (tablet) prior to coating when the solid preparation is to be coated as described below, or a solid preparation (tablet) itself when the solid preparation is not coated.

[0017]

For example, the solid preparation of the present invention is a tablet.

Specific examples of the solid preparation of the present invention include the following embodiments (A), (B) and (C).

(A) A single-layered solid preparation (e.g., tablet) containing N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, and a hydrophilic gel-forming polymer (hereinafter also referred to as a single-layered tablet of the present invention).

(B) A solid preparation (e.g., tablet) comprising:

(1) a core containing N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, and a first hydrophilic gel-forming polymer; and

(2) an outer shell containing N-methyl-N-(1-methylethyl)-

6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, and a second hydrophilic gel-forming polymer.

(C) A solid preparation (e.g., tablet) comprising:

(1) a core containing N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, and a first hydrophilic gel-forming polymer; and

(2) an outer shell containing a second hydrophilic gel-forming polymer, and not containing N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof.

(Hereinafter (B) and (C) are also referred to as a dry coated tablet of the present invention.)

[0018]

In the single-layered tablet of the present invention, the contents of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof and the hydrophilic gel-forming polymer are as indicated above.

[0019]

The single-layered tablet of the present invention may be film-coated, as described below.

When the single-layered tablet of the present invention is film-coated, the content of the hydrophilic gel-forming polymer is the content thereof in the uncoated tablet before film coating.

[0020]

In the present invention, a shell of a hydrophilic gel-forming polymer and free of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine and a salt thereof may be formed on the outside of the single-layered tablet. This embodiment is to be described later as a dry coated tablet with a shell not containing N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof.

[0021]

In the dry coated tablet of the present invention, the core may be a tablet (in the DESCRIPTION, a tablet as a core is referred to as a core tablet).

In the dry coated tablet of the present invention, the content of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or salt thereof in a free form in the core is generally 0.5-1000 mg, preferably 2.5-800 mg, more preferably 5-500 mg.

In the dry coated tablet of the present invention, the content of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or salt thereof in a free form in the outer shell is generally 0-500 mg, preferably 0-400 mg, more preferably 0-250 mg.

[0022]

The dry coated tablet of the present invention may contain N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in both the core and the outer shell, or only in the core.

For example, a dry coated tablet containing N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in the core and not containing N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in the outer shell is also encompassed in the solid preparation of the present invention.

[0023]

In the dry coated tablet of the present invention, the content (by weight) of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in the core is preferably equal to or higher than the content (by weight) of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in the outer shell, since further delayed and sustained release of the active ingredient can be expected.

[0024]

The dry coated tablet of the present invention is a solid preparation (such as a tablet) comprising a core, an outer shell, a hydrophilic gel-forming polymer in the core and the outer shell, and the active ingredient in the core and/or the outer shell, which may control the release behavior of the active ingredient by adjusting the content of the active ingredient in the core and/or the outer shell, thereby releasing the active ingredient in a sustained manner.

When measured according to the Paddle Method described in the Japanese Pharmacopoeia 16th Edition (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 100 rpm, 900 mL), the dissolution ratio of the active ingredient is generally 0-30% after 2 hr; 15-55% after 6 hr; 35-80% after 9 hr, preferably 5-25% after 2 hr; 20-50% after 6 hr; 40-75% after 9 hr, more preferably 5-20%% after 2 hr; 25-45% after 6 hr; 45-70% after 9 hr.

In another embodiment, it is generally 10-45% after 2 hr; 40-80% after 6 hr; 60-100% after 9 hr, preferably 15-40% after 2 hr; 45-75% after 6 hr; 65-95% after 9 hr, more preferably 20-35% after 2 hr; 50-70% after 6 hr; 70-95% after 9 hr.

[0025]

Examples of the first and second hydrophilic gel-forming polymers in the dry coated tablet of the present invention include those recited above as the hydrophilic gel-forming polymer in the solid preparation of the present invention.

The first hydrophilic gel-forming polymer and the second hydrophilic gel-forming polymer may be identical or different.

In the dry coated tablet of the present invention, each of the first and second hydrophilic gel-forming polymers is preferably polyethylene oxide.

[0026]

In the dry coated tablet of the present invention, the content of the first hydrophilic gel-forming polymer in the core is generally 0.01-90% by weight, preferably 5-70% by

weight, more preferably 10-50% by weight, relative to the weight of the core.

In the dry coated tablet of the present invention, the content of the second hydrophilic gel-forming polymer in the outer shell is generally 20-100% by weight, preferably 30-95% by weight, more preferably 40-90% by weight, relative to the weight of the outer shell.

[0027]

The dry coated tablet of the present invention may be film-coated as described below.

When the dry coated tablet of the present invention is film-coated, the content of the hydrophilic gel-forming polymer is the content of the preparation (uncoated tablet) prior to film coating.

[0028]

In the dry coated tablet of the present invention, the weight ratio of the core and the outer shell (core:outer shell) is generally 1:1.5-3.5, preferably 1:1.5-3.0, more preferably 1:2-2.5, still more preferably about 1:2.

[0029]

The solid preparation (single-layered tablet, dry coated tablet) of the present invention may further contain an additive conventionally used in the field of preparations.

Examples of the additive include excipients (e.g., mannitol, spray-dried mannitol, starch, lactose, sucrose, calcium carbonate, calcium phosphate, and crystalline cellulose), binders (e.g., starch, gum arabic, alginic acid, gelatin, polyvinyl pyrrolidone, and hydroxypropyl cellulose (having low viscosity preventing function as a hydrophilic gel-forming polymer, e.g., HPC-SL and HPC-L, produced by Nippon Soda Co., Ltd.), and lubricants (e.g., stearic acid, magnesium stearate, calcium stearate, and talc).

[0030]

The use of a hydrophilic gel-forming polymer in the present invention may reduce the amount of additives other than

the hydrophilic gel-forming polymer.

In the solid preparation of the present invention, the content of the total amount of the additive other than the hydrophilic gel-forming polymer is generally 5-95% by weight, preferably 15-75% by weight, more preferably 25-65% by weight, relative to the weight of the uncoated tablet.

[0031]

The solid preparation (single-layered tablet, dry coated tablet) of the present invention can be produced using the above-mentioned various components and according to a conventional method in the technical field of preparations.

[0032]

The single-layered tablet of the present invention can be produced, for example, by blending N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, a hydrophilic gel-forming polymer (e.g., polyethylene oxide, hydroxypropyl methyl cellulose, carboxyvinyl polymer, etc.), and additive to be optionally added (for example, excipient (e.g., mannitol), lubricant (e.g., magnesium stearate), binder), and compression-molding (tableting) the mixture.

[0033]

The dry coated tablet of the present invention can be produced, for example, according to the following method.

N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, a hydrophilic gel-forming polymer (e.g., polyethylene oxide, hydroxypropyl methyl cellulose, carboxyvinyl polymer, etc.), and additive to be optionally added (for example, excipient (e.g., mannitol), lubricant (e.g., magnesium stearate), binder), and compression-molding the mixture to give a core (core tablet).

Separately, N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, a hydrophilic gel-forming polymer (e.g., polyethylene

oxide, hydroxypropyl methyl cellulose, carboxyvinyl polymer, etc.), and additive to be optionally added (for example, excipient (e.g., mannitol), lubricant (e.g., magnesium stearate), binder) are blended to give an outer shell blended powder (i.e., a powder mixture of components forming the outer shell).

The core tablet and the outer shell blended powder are compression-molded to give a dry coated tablet.

[0034]

A dry coated tablet not contain N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in the outer shell can be produced by not adding N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or salt thereof during the process of producing the outer shell blended powder in the above-mentioned production method.

[0035]

Blending can be performed using a mixer such as V-mixer or tumbler mixer. Compression molding can be performed by tableting using, for example, a single-punch tablet press, rotary tablet press, or the like.

[0036]

The solid preparation (single-layered tablet, dry coated tablet) of the present invention may be coated as necessary by a conventional method in the technical field of preparations. For example, the following film coating bases and coating additives can be used.

Examples of the film coating base include hydroxypropyl methyl cellulose (TC-5E, TC-5R; produced by Shin-etsu Chemical Co., Ltd.), hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, methyl cellulose, and hydroxyethyl methyl cellulose.

Examples of the coating additive include light-blocking agents such as titanium oxide; fluidizing agents such as talc, sterile talc; colorants such as ferric oxide and yellow ferric

oxide; plasticizers such as polyethylene glycol (e.g., Macrogol 6000), triethyl citrate, castor oil, and polysorbates; and organic acids such as citric acid, tartaric acid, malic acid, and ascorbic acid.

[0037]

When the solid preparation of the present invention is film-coated, the amount of the film coating is generally 1%-8%, preferably 2%-6%, relative to the weight of the bare preparation (uncoated tablet).

[0038]

The weight of the solid preparation of the present invention is generally 100 mg - 1,500 mg, preferably 200 mg - 1,000 mg.

[0039]

The size of the single-layered tablet of the present invention is generally 6 mm - 20 mm, preferably 8 mm - 15 mm.

The size of the dry coated tablet of the present invention is generally 4.5 mm - 17 mm, preferably 5 mm - 12 mm, and the size of the core (core tablet) of the dry coated tablet is generally 7.5 mm - 20 mm, preferably 8 mm - 15 mm.

[0040]

The shape of the solid preparation of the present invention is not particularly limited, and it may be any shape such as round, caplet-shaped, donut-shaped, oblong-shaped and the like.

[0041]

The solid preparation of the present invention may be useful as an agent for ameliorating, preventing, or treating all serotonin 5-HT_{2C} related diseases such as lower urinary tract symptoms (e.g., stress incontinence) in mammalian animals (such as human, monkey, cattle, horse, pig, mouse, rat, hamster, rabbit, cat, dog, sheep, and goat). The solid preparation of the present invention can be orally administered safely.

[0042]

While the dose of N-methyl-N-(1-methylethyl)-6,7,8,9-

tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in the solid preparation of the present invention varies depending on the administration subject, symptom, and the like, for oral administration to a patient with lower urinary tract symptom (adult; body weight about 60 kg), it is generally an amount of about 0.01667 - about 16.67 mg/kg body weight, preferably about 0.08333 - about 13.33 mg/kg body weight, more preferably about 0.1667 - about 8.333 mg/kg body weight, which can be administered one to several times per day according to the symptoms.

[0043]

The solid preparation of the present invention may release the active ingredient in a sustained manner, which may reduce the number of doses per day (one or two doses/day). As a result, increased convenience for patients and improved medication compliance are expected.

[0044]

The solid preparation of the present invention can be used in combination with an active ingredient other than N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof (hereinafter abbreviated as a "concomitant drug"). In this case, the time of administration of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or salt thereof and that of the concomitant drug are not limited, and they may be administered simultaneously or in a staggered manner to the administration subject. Furthermore, the solid preparation of the present invention and a concomitant drug may be administered as two kinds of preparations containing each active ingredient, or may be administered as a single preparation containing both active ingredients.

The dose of the concomitant drug can be appropriately determined based on the dose employed in clinical situations.

Examples of the concomitant drug include other therapeutic drugs for stress incontinence.

[Examples]

[0045]

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

As the preparation additives (e.g., polyethylene oxide, mannitol, magnesium stearate, hydroxypropyl cellulose, crystalline cellulose, carboxyvinyl polymer, yellow ferric oxide, spray-dried mannitol, hydroxypropyl methyl cellulose, talc) used in the following Examples, the Japanese Pharmacopoeia 16th Edition compatible products, Japanese Pharmaceutical Excipients 2003 compatible products, the United States Pharmacopeia (USP) compatible products, and the National Formulary (NF) compatible products were used.

In the following Examples, dissolution tests were performed according to the Paddle Method described in the Japanese Pharmacopoeia 16th Edition. The dissolution test, 2nd fluid used as the test liquid can be prepared according to a known method. The amount of the dissolution test, 2nd fluid used as the test liquid is generally 900 mL.

Compound X used in the following Formulation Examples is N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine. The dissolution property of the preparations obtained in Examples 1-27 was evaluated by the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 50 rpm, 900 mL) by using a Varian dissolution tester. The dissolution property of the preparations obtained in Examples 34-39 was evaluated using a dissolution tester manufactured by Toyama Sangyo Co., Ltd. and according to the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 100 rpm, 900 mL).

[0046]

Example 1

Compound X hydrochloride (5.82 g), polyethylene oxide (Polyox™ WSR 303, 2.5 g), mannitol (0.095 g), and magnesium

stearate (0.085 g) were blended and tableted with a 7 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (170 mg per tablet).

Polyethylene oxide (Polyox™ WSR 303, 15 g), mannitol (1.83 g), and magnesium stearate (0.17 g) were blended to produce an outer shell blended powder. The core tablet and 340 mg of the outer shell blended powder were tableted with a 11 mmϕ punch by using an autograph tablet press (AG-IS, Shimadzu) to produce dry coated tablets (510 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 1.

[0047]

[Table 1]

Table 1 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	116.4
	Polyethylene oxide (Polyox™ WSR 303)	50
	Mannitol	1.9
	Magnesium stearate	1.7
	Subtotal (core tablet)	170
Outer shell	Polyethylene oxide (Polyox™ WSR 303)	300
	Mannitol	36.6
	Magnesium stearate	3.4
	Subtotal (outer shell)	340
Total		510

[0048]

Example 2

Compound X hydrochloride (5.82 g), polyethylene oxide (Polyox™ WSR 303, 2.5 g), mannitol (0.095 g), and magnesium stearate (0.085 g) were blended and tableted with a 7 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (170 mg per tablet).

Polyethylene oxide (Polyox™ WSR 303, 12.5 g), mannitol (4.33 g), and magnesium stearate (0.17 g) were blended to produce an outer shell blended powder. The core tablet and 340 mg of the outer shell blended powder were tableted with a 11

mmϕ punch by using an autograph tablet press (AG-IS, Shimadzu) to produce dry coated tablets (510 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 2.

[0049]

[Table 2]

Table 2 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	116.4
	Polyethylene oxide (Polyox™ WSR 303)	50
	Mannitol	1.9
	Magnesium stearate	1.7
	Subtotal (core tablet)	170
Outer shell	Polyethylene oxide (Polyox™ WSR 303)	250
	Mannitol	86.6
	Magnesium stearate	3.4
	Subtotal (outer shell)	340
Total		510

[0050]

Example 3

Compound X hydrochloride (5.82 g), polyethylene oxide (Polyox™ WSR 303, 17.5 g), mannitol (1.925 g), and magnesium stearate (0.255 g) were blended to produce a powder mixture. 510 mg of the powder mixture was pressed into a tablet with a 11 mmϕ punch by using an autograph tablet press (AG-IS, Shimadzu) to produce single-layered tablets (510 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 3.

[0051]

[Table 3]

Table 3 Composition of one single-layered tablet

Additive	Dosage (mg/tablet)
Compound X hydrochloride	116.4
Polyethylene oxide (Polyox™ WSR 303)	350
Mannitol	38.5
Magnesium stearate	5.1
Total	510

[0052]

Example 4

Compound X hydrochloride (5.82 g), polyethylene oxide (Polyox™ WSR 303, 2.5 g), mannitol (0.095 g), and magnesium stearate (0.085 g) were blended and tableted with a 7 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (170 mg per tablet).

Polyethylene oxide (Polyox™ WSR 303, 10 g), mannitol (6.83 g), and magnesium stearate (0.17 g) were blended to produce an outer shell blended powder. The core tablet and 340 mg of the outer shell blended powder were tableted with a 11 mmϕ punch by using an autograph tablet press (AG-IS, Shimadzu) to produce dry coated tablets (510 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 4.

[0053]

[Table 4]

Table 4 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	116.4
	Polyethylene oxide (Polyox™ WSR 303)	50
	Mannitol	1.9
	Magnesium stearate	1.7
	Subtotal (core tablet)	170
Outer shell	Polyethylene oxide (Polyox™ WSR 303)	200
	Mannitol	136.6
	Magnesium stearate	3.4
	Subtotal (outer shell)	340
Total		510

[0054]

Example 5

Compound X hydrochloride (5.82 g), polyethylene oxide

(Polyox™ WSR 303, 2.5 g), mannitol (0.095 g), and magnesium stearate (0.085 g) were blended and tableted with a 7 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (170 mg per tablet).

Polyethylene oxide (Polyox™ WSR 303, 7.5 g), mannitol (9.33 g), and magnesium stearate (0.17 g) were blended to produce an outer shell blended powder. The core tablet and 340 mg of the outer shell blended powder were tableted with a 11 mmϕ punch by using an autograph tablet press (AG-IS, Shimadzu) to produce dry coated tablets (510 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 5.

[0055]

[Table 5]

Table 5 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	116.4
	Polyethylene oxide (Polyox™ WSR 303)	50
	Mannitol	1.9
	Magnesium stearate	1.7
	Subtotal (core tablet)	170
Outer shell	Polyethylene oxide (Polyox™ WSR 303)	150
	Mannitol	186.6
	Magnesium stearate	3.4
	Subtotal (outer shell)	340
Total		510

[0056]

Example 6

Compound X hydrochloride (5.238 g), polyethylene oxide (Polyox™ WSR 303, 2.5 g), mannitol (0.677 g), and magnesium stearate (0.085 g) were blended and tableted with a 7 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (170 mg per tablet).

Compound X hydrochloride (0.582 g), polyethylene oxide (Polyox™ WSR 303, 12.5 g), mannitol (3.748 g), and magnesium stearate (0.17 g) were blended to produce an outer shell blended powder. The core tablet and 340 mg of the outer shell blended powder were tableted with a 11 mmϕ punch by using an autograph tablet press (AG-IS, Shimadzu) to produce dry coated tablets (510 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 6.

[0057]

[Table 6]

Table 6 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	104.76
	Polyethylene oxide (Polyox™ WSR 303)	50
	Mannitol	13.54
	Magnesium stearate	1.7
	Subtotal (core tablet)	170
Outer shell	Compound X hydrochloride	11.64
	Polyethylene oxide (Polyox™ WSR 303)	250
	Mannitol	74.96
	Magnesium stearate	3.4
	Subtotal (outer shell)	340
Total		510

[0058]

Example 7

Compound X hydrochloride (4.074 g), polyethylene oxide (Polyox™ WSR 303, 2.5 g), mannitol (1.841 g), and magnesium stearate (0.085 g) were blended and tableted with a 7 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (170 mg per tablet).

Compound X hydrochloride (1.746 g), polyethylene oxide (Polyox™ WSR 303, 12.5 g), mannitol (2.584 g), and magnesium stearate (0.17 g) were blended to produce an outer shell blended powder. The core tablet and 340 mg of the outer shell

blended powder were tableted with a 11 mmϕ punch by using an autograph tablet press (AG-IS, Shimadzu) to produce dry coated tablets (510 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 7.

[0059]

[Table 7]

Table 7 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	81.48
	Polyethylene oxide (Polyox™ WSR 303)	50
	Mannitol	36.82
	Magnesium stearate	1.7
	Subtotal (core tablet)	170
Outer shell	Compound X hydrochloride	34.92
	Polyethylene oxide (Polyox™ WSR 303)	250
	Mannitol	51.68
	Magnesium stearate	3.4
	Subtotal (outer shell)	340
Total		510

[0060]

Example 8

Compound X hydrochloride (4.074 g), polyethylene oxide (Polyox™ WSR 303, 2.5 g), mannitol (0.356 g), and magnesium stearate (0.07 g) were blended and tableted with a 6.5 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (140 mg per tablet).

Compound X hydrochloride (1.746 g), polyethylene oxide (Polyox™ WSR 303, 12.5 g), mannitol (0.109 g), and magnesium stearate (0.145 g) were blended to produce an outer shell blended powder. The core tablet and 290 mg of the outer shell blended powder were tableted with a 10.5 mmϕ punch by using an autograph tablet press (AG-IS, Shimadzu) to produce dry coated tablets (430 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 8.

[0061]

[Table 8]

Table 8 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	81.48
	Polyethylene oxide (Polyox™ WSR 303)	50
	Mannitol	7.12
	Magnesium stearate	1.4
	Subtotal (core tablet)	140
Outer shell	Compound X hydrochloride	34.92
	Polyethylene oxide (Polyox™ WSR 303)	250
	Mannitol	2.18
	Magnesium stearate	2.9
	Subtotal (outer shell)	290
Total		430

[0062]

Example 9

Compound X hydrochloride (4.074 g), polyethylene oxide (Polyox™ WSR 303, 1.75 g), mannitol (0.116 g), and magnesium stearate (0.06 g) were blended and tableted with a 6.5 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (120 mg per tablet).

Compound X hydrochloride (1.746 g), polyethylene oxide (Polyox™ WSR 303, 10 g), mannitol (0.134 g), and magnesium stearate (0.12 g) were blended to produce an outer shell blended powder. The core tablet and 240 mg of the outer shell blended powder were tableted with a 10 mmϕ punch by using an autograph tablet press (AG-IS, Shimadzu) to produce dry coated tablets (360 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 9.

[0063]

[Table 9]

Table 9 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	81.48
	Polyethylene oxide (Polyox™ WSR 303)	35
	Mannitol	2.32
	Magnesium stearate	1.2
	Subtotal (core tablet)	120
Outer shell	Compound X hydrochloride	34.92
	Polyethylene oxide (Polyox™ WSR 303)	200
	Mannitol	2.68
	Magnesium stearate	2.4
	Subtotal (outer shell)	240
Total		360

[0064]

Example 10

Compound X hydrochloride (3.492 g), polyethylene oxide (Polyox™ WSR 303, 1.5 g), mannitol (0.057 g), and magnesium stearate (0.051 g) were blended and tableted with a 6 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (102 mg per tablet).

Compound X hydrochloride (2.328 g), polyethylene oxide (Polyox™ WSR 303, 7.5 g), mannitol (0.072 g), and magnesium stearate (0.1 g) were blended to produce an outer shell blended powder. The core tablet and 200 mg of the outer shell blended powder were tableted with a 9.5 mmϕ punch by using an autograph tablet press (AG-IS, Shimadzu) to produce dry coated tablets (302 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 10.

[0065]

[Table 10]

Table 10 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	69.84
	Polyethylene oxide (Polyox™ WSR 303)	30
	Mannitol	1.14
	Magnesium stearate	1.02
	Subtotal (core tablet)	102
Outer shell	Compound X hydrochloride	46.56
	Polyethylene oxide (Polyox™ WSR 303)	150
	Mannitol	1.44
	Magnesium stearate	2
	Subtotal (outer shell)	200
Total		302

[0066]

Example 11

Compound X hydrochloride (2.91 g), polyethylene oxide (Polyox™ WSR 303, 1.25 g), mannitol (0.0475 g), and magnesium stearate (0.0425 g) were blended and tableted with a 5.5 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (85 mg per tablet).

Compound X hydrochloride (2.91 g), polyethylene oxide (Polyox™ WSR 303, 6 g), and magnesium stearate (0.09 g) were blended to produce an outer shell blended powder. The core tablet and 180 mg of the outer shell blended powder were tableted with a 9 mmϕ punch by using an autograph tablet press (AG-IS, Shimadzu) to produce dry coated tablets (265 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 11.

[0067]

[Table 11]

Table 11 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	58.2
	Polyethylene oxide (Polyox™ WSR 303)	25
	Mannitol	0.95
	Magnesium stearate	0.85
	Subtotal (core tablet)	85
Outer shell	Compound X hydrochloride	58.2
	Polyethylene oxide (Polyox™ WSR 303)	120
	Magnesium stearate	1.8
	Subtotal (outer shell)	180
Total		265

[0068]

Example 12

Compound X hydrochloride (4.074 g), hydroxypropyl methyl cellulose (METOLOSE 90SH-100000SR, 1.75 g), mannitol (0.116 g), and magnesium stearate (0.06 g) were blended and tableted with a 6.5 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (120 mg per tablet).

Compound X hydrochloride (1.746 g), hydroxypropyl methyl cellulose (METOLOSE 90SH-100000SR, 10 g), mannitol (0.134 g), and magnesium stearate (0.12 g) were blended to produce an outer shell blended powder. The core tablet and 240 mg of the outer shell blended powder were tableted with a 10 mmϕ punch by using an autograph tablet press (AG-IS, Shimadzu) to produce dry coated tablets (360 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 12.

[0069]

[Table 12]

Table 12 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	81.48
	Hydroxypropyl methyl cellulose (METOLOSE 90SH-100000SR)	35
	Mannitol	2.32
	Magnesium stearate	1.2
	Subtotal (core tablet)	120
Outer shell	Compound X hydrochloride	34.92
	Hydroxypropyl methyl cellulose (METOLOSE 90SH-100000SR)	200
	Mannitol	2.68
	Magnesium stearate	2.4
	Subtotal (outer shell)	240
Total		360

[0070]

Example 13

Compound X hydrochloride (366.8 g) and crystalline cellulose (22.5 g) were charged in a fluid bed granulator (LAB-1, Powrex Corp.), granulated while spraying an aqueous solution obtained by dissolving hydroxypropyl cellulose (HPC-L, 18.9 g) in purified water, and dried to produce a granulated powder. The granulated powder (362.8 g) was blended with polyethylene oxide (Polyox™ WSR 303, 152 g) and magnesium stearate (5.2 g) and tableted with a 7 mmϕ punch by using a rotary tablet press (Correct 19K, Kikusui Seisakusho) to produce core tablets (130 mg per tablet).

Compound X hydrochloride (279.2 g), mannitol (60.8 g) and crystalline cellulose (20.8 g) were charged in a fluid bed granulator (LAB-1, Powrex Corp.), granulated while spraying an aqueous solution obtained by dissolving hydroxypropyl cellulose (HPC-L, 17.6 g) in purified water, and dried to produce a granulated powder. The granulated powder (189.2 g) was blended

with polyethylene oxide (Polyox™ WSR 303, 880 g), and magnesium stearate (10.8 g) to produce an outer shell blended powder. The core tablet and 270 mg of the outer shell blended powder were tableted with a 10 mmϕ punch by using a rotary tablet press (manufactured by Kikusui Seisakusho) to produce dry coated tablets (400 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 13.

[0071]

[Table 13]

Table 13 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	81.5
	Polyethylene oxide (Polyox™ WSR 303)	38
	Magnesium stearate	1.3
	Hydroxypropyl cellulose (HPC-L)	4.2
	Crystalline cellulose	5
	Subtotal (core tablet)	130
Outer shell	Compound X hydrochloride	34.9
	Polyethylene oxide (Polyox™ WSR 303)	220
	Mannitol	7.6
	Magnesium stearate	2.7
	Hydroxypropyl cellulose (HPC-L)	2.2
	Crystalline cellulose	2.6
	Subtotal (outer shell)	270
Total		400

[0072]

Example 14

Compound X hydrochloride (1.746 g), polyethylene oxide (Polyox™ WSR 303, 2.74 g), mannitol (4.724 g), and magnesium stearate (0.09 g) were blended and tableted with a 6 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (93 mg per tablet).

Compound X hydrochloride (1.746 g), polyethylene oxide (Polyox™ WSR 303, 13 g), mannitol (4.754 g), and magnesium

stearate (0.2 g) were blended to produce an outer shell blended powder. The core tablet and 197 mg of the outer shell blended powder were tableted with a 9 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce dry coated tablets (290 mg per tablet) containing compound X hydrochloride (30 mg as compound X) shown in Table 14.

[0073]

[Table 14]

Table 14 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	17.46
	Polyethylene oxide (Polyox™ WSR 303)	27.4
	Mannitol	47.24
	Magnesium stearate	0.9
	Subtotal (core tablet)	93
Outer shell	Compound X hydrochloride	17.46
	Polyethylene oxide (Polyox™ WSR 303)	130
	Mannitol	47.54
	Magnesium stearate	2
	Subtotal (outer shell)	197
Total		290

[0074]

Example 15

Compound X hydrochloride (2.094 g), polyethylene oxide (Polyox™ WSR 303, 3.3 g), mannitol (5.696 g), and magnesium stearate (0.11 g) were blended and tableted with a 6 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (112 mg per tablet).

Compound X hydrochloride (1.398 g), polyethylene oxide (Polyox™ WSR 303, 17.55 g), mannitol (4.622 g), and magnesium stearate (0.23 g) were blended to produce an outer shell blended powder. The core tablet and 238 mg of the outer shell

blended powder were tableted with a 9 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce dry coated tablets (350 mg per tablet) containing compound X hydrochloride (30 mg as compound X) shown in Table 15.

[0075]

[Table 15]

Table 15 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	20.94
	Polyethylene oxide (Polyox™ WSR 303)	33
	Mannitol	56.96
	Magnesium stearate	1.1
	Subtotal (core tablet)	112
Outer shell	Compound X hydrochloride	13.98
	Polyethylene oxide (Polyox™ WSR 303)	175.5
	Mannitol	46.22
	Magnesium stearate	2.3
	Subtotal (outer shell)	238
Total		350

[0076]

Example 16

Compound X hydrochloride (2.445 g), polyethylene oxide (Polyox™ WSR 303, 3.8 g), mannitol (5.705 g), hydroxypropyl cellulose (HPC-L, 0.42 g), crystalline cellulose (0.5 g), and magnesium stearate (0.13 g) were blended and tableted with a 7 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (130 mg per tablet).

Compound X hydrochloride (1.047 g), polyethylene oxide (Polyox™ WSR 303, 22 g), mannitol (3.203 g), hydroxypropyl cellulose (HPC-L, 0.22 g), crystalline cellulose (0.26 g), and magnesium stearate (0.27 g) were blended to produce an outer shell blended powder. The core tablet and 270 mg of the outer

shell blended powder were tableted with a 10 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce dry coated tablets (400 mg per tablet) containing compound X hydrochloride (30 mg as compound X) shown in Table 16.

[0077]

[Table 16]

Table 16 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	24.45
	Polyethylene oxide (Polyox™ WSR 303)	38
	Mannitol	57.05
	Hydroxypropyl cellulose (HPC-L)	4.2
	Crystalline cellulose	5
	Magnesium stearate	1.3
	Subtotal (core tablet)	130
Outer shell	Compound X hydrochloride	10.47
	Polyethylene oxide (Polyox™ WSR 303)	220
	Mannitol	32.03
	Hydroxypropyl cellulose (HPC-L)	2.2
	Crystalline cellulose	2.6
	Magnesium stearate	2.7
	Subtotal (outer shell)	270
Total		400

[0078]

Example 17

Compound X hydrochloride (2.793 g), polyethylene oxide (Polyox™ WSR 303, 4.4 g), mannitol (6.607 g), hydroxypropyl cellulose (HPC-L, 0.45 g), crystalline cellulose (0.6 g), and magnesium stearate (0.15 g) were blended and tableted with a 7 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (150 mg per tablet).

Compound X hydrochloride (0.699 g), polyethylene oxide (Polyox™ WSR 303, 26 g), mannitol (3.431 g), hydroxypropyl

cellulose (HPC-L, 0.25 g), crystalline cellulose (0.31 g), and magnesium stearate (0.31 g) were blended to produce an outer shell blended powder. The core tablet and 310 mg of the outer shell blended powder were tableted with a 10 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce dry coated tablets (460 mg per tablet) containing compound X hydrochloride (30 mg as compound X) shown in Table 17.

[0079]

[Table 17]

Table 17 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	27.93
	Polyethylene oxide (Polyox™ WSR 303)	44
	Mannitol	66.07
	Hydroxypropyl cellulose (HPC-L)	4.5
	Crystalline cellulose	6
	Magnesium stearate	1.5
	Subtotal (core tablet)	150
Outer shell	Compound X hydrochloride	6.99
	Polyethylene oxide (Polyox™ WSR 303)	260
	Mannitol	34.31
	Hydroxypropyl cellulose (HPC-L)	2.5
	Crystalline cellulose	3.1
	Magnesium stearate	3.1
	Subtotal (outer shell)	310
Total		460

[0080]

Example 18

Compound X hydrochloride (3.144 g), polyethylene oxide (Polyox™ WSR 303, 5 g), mannitol (7.496 g), hydroxypropyl cellulose (HPC-L, 0.51 g), crystalline cellulose (0.68 g), and magnesium stearate (0.17 g) were blended and tableted with a 8 mmϕ punch by using a manual tablet press (HANDTAB, manufactured

by Ichihashi Seiki) to produce core tablets (170 mg per tablet).

Compound X hydrochloride (0.348 g), polyethylene oxide (Polyox™ WSR 303, 30 g), mannitol (3.672 g), hydroxypropyl cellulose (HPC-L, 0.28 g), crystalline cellulose (0.35 g), and magnesium stearate (0.35 g) were blended to produce an outer shell blended powder. The core tablet and 350 mg of the outer shell blended powder were tableted with a 11 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce dry coated tablets (520 mg per tablet) containing compound X hydrochloride (30 mg as compound X) shown in Table 18.

[0081]

[Table 18]

Table 18 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	31.44
	Polyethylene oxide (Polyox™ WSR 303)	50
	Mannitol	74.96
	Hydroxypropyl cellulose (HPC-L)	5.1
	Crystalline cellulose	6.8
	Magnesium stearate	1.7
	Subtotal (core tablet)	170
Outer shell	Compound X hydrochloride	3.48
	Polyethylene oxide (Polyox™ WSR 303)	300
	Mannitol	36.72
	Hydroxypropyl cellulose (HPC-L)	2.8
	Crystalline cellulose	3.5
	Magnesium stearate	3.5
	Subtotal (outer shell)	350
Total		520

[0082]

Example 19

Compound X hydrochloride (1.746 g), polyethylene oxide (Polyox™ WSR 303, 7.87 g), mannitol (4.739 g), and magnesium

stearate (0.145 g) were blended to produce a powder mixture. 290 mg of the powder mixture was tableted with a 9 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce single-layered tablets (290 mg per tablet) containing compound X hydrochloride (30 mg as compound X) shown in Table 19.

[0083]

[Table 19]

Table 19 Composition of one single-layered tablet

Additive	Dosage (mg/tablet)
Compound X hydrochloride	34.92
Polyethylene oxide (Polyox™ WSR 303)	157.4
Mannitol	94.78
Magnesium stearate	2.9
Total	290

[0084]

Example 20

Compound X hydrochloride (8.15 g), polyethylene oxide (PEO-20NF, 3.8 g), hydroxypropyl cellulose (HPC-L, 0.42 g), crystalline cellulose (0.5 g), and magnesium stearate (0.13 g) were blended and tableted with a 7 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (130 mg per tablet).

Compound X hydrochloride (3.49 g), polyethylene oxide (PEO-20NF, 22g), mannitol (0.76 g), hydroxypropyl cellulose (HPC-L, 0.22 g), crystalline cellulose (0.26 g), and magnesium stearate (0.27 g) were blended to produce an outer shell blended powder. The core tablet and 270 mg of the outer shell blended powder were tableted with a 10 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce dry coated tablets (400 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 20.

[0085]

[Table 20]

Table 20 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	81.5
	Polyethylene oxide (PEO-20NF)	38
	Hydroxypropyl cellulose (HPC-L)	4.2
	Crystalline cellulose	5
	Magnesium stearate	1.3
	Subtotal (core tablet)	130
Outer shell	Compound X hydrochloride	34.9
	Polyethylene oxide (PEO-20NF)	220
	Mannitol	7.6
	Hydroxypropyl cellulose (HPC-L)	2.2
	Crystalline cellulose	2.6
	Magnesium stearate	2.7
	Subtotal (outer shell)	270
Total		400

[0086]

Example 21

Compound X hydrochloride (8.15 g), carboxyvinyl polymer (Carbopol 971PNF, 3.8 g), hydroxypropyl cellulose (HPC-L, 0.42 g), crystalline cellulose (0.5 g), and magnesium stearate (0.13 g) were blended and tableted with a 7 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (130 mg per tablet).

Compound X hydrochloride (3.49 g), carboxyvinyl polymer (Carbopol 971PNF, 22 g), mannitol (0.76 g), hydroxypropyl cellulose (HPC-L, 0.22 g), crystalline cellulose (0.26 g), and magnesium stearate (0.27 g) were blended to produce an outer shell blended powder. The core tablet and 270 mg of the outer shell blended powder were tableted with a 10 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce dry coated tablets (400 mg per tablet) containing compound X hydrochloride (100 mg as compound X) shown in Table 21.

[0087]

[Table 21]

Table 21 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	81.5
	Carboxyvinyl polymer (Carbopol 971 PNF)	38
	Hydroxypropyl cellulose (HPC-L)	4.2
	Crystalline cellulose	5
	Magnesium stearate	1.3
	Subtotal (core tablet)	130
Outer shell	Compound X hydrochloride	34.9
	Carboxyvinyl polymer (Carbopol 971 PNF)	220
	Mannitol	7.6
	Hydroxypropyl cellulose (HPC-L)	2.2
	Crystalline cellulose	2.6
	Magnesium stearate	2.7
	Subtotal (outer shell)	270
Total		400

[0088]

Example 22

Compound X hydrochloride (97.9 g), mannitol (329 g), and polyethylene oxide (PEO-20NF, 44 g) were charged in a fluid bed granulator (MP-01, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The granulated powder (353.1 g) was blended with polyethylene oxide (PEO-20NF, 33 g) and magnesium stearate (3.9 g) and tableted with a 6.5 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to give core tablets (130 mg per tablet).

Compound X hydrochloride (36.7 g), mannitol (128.9 g), and polyethylene oxide (PEO-20NF, 385 g) were charged in a fluid bed granulator (MP-01, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The granulated powder (393.3 g) was blended with polyethylene oxide (PEO-20NF, 275 g) and magnesium stearate (6.75 g) to

produce an outer shell blended powder. The core tablet and 270 mg of the outer shell blended powder were tableted with a 10 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to produce dry coated tablets (400 mg per tablet) containing compound X hydrochloride (30 mg as compound X). The dry coated tablets were charged in a coating pan (DRC-300, Powrex Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methylcellulose (TC-5E) in purified water and dispersing yellow ferric oxide therein, and dried to produce film-coated dry coated tablets shown in Table 22.

[0089]

[Table 22]

Table 22 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	24.45
	Polyethylene oxide (PEO-20NF)	22
	Mannitol	82.25
	Magnesium stearate	1.3
	Subtotal (core tablet)	130
Outer shell	Compound X hydrochloride	10.47
	Polyethylene oxide (PEO-20NF)	220
	Mannitol	36.83
	Magnesium stearate	2.7
	Subtotal (outer shell)	270
Film	Hydroxypropyl methyl cellulose	15.4
	Yellow ferric oxide	0.4
	Subtotal (film)	16
Total		416

[0090]

Example 23

Compound X hydrochloride (87.3 g), mannitol (300.7 g), and polyethylene oxide (PEO-20NF, 36.25 g) were charged in a fluid bed granulator (MP-01, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The granulated powder (339.4 g) was blended with polyethylene

oxide (PEO-20NF, 29 g) and magnesium stearate (3.6 g) and tableted with a 5.5 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to give core tablets (93 mg per tablet).

Compound X hydrochloride (69.84 g), mannitol (190.2 g), and polyethylene oxide (PEO-20NF, 260 g) were charged in a fluid bed granulator (MP-1, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The granulated powder (455 g) was blended with polyethylene oxide (PEO-20NF, 227.5 g) and magnesium stearate (7 g) to produce an outer shell blended powder. The core tablet and 197 mg of the outer shell blended powder were tableted with a 9 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to produce dry coated tablets (290 mg per tablet) containing compound X hydrochloride (30 mg as compound X). The dry coated tablets were charged in a coating pan (DRC-300, Powrex Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methyl cellulose (TC-5E) in purified water and dispersing yellow ferric oxide therein, and dried to produce film-coated dry coated tablets shown in Table 23.

[0091]

[Table 23]

Table 23 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	17.46
	Polyethylene oxide (PEO-20NF)	14.5
	Mannitol	60.14
	Magnesium stearate	0.9
	Subtotal (core tablet)	93
Outer shell	Compound X hydrochloride	17.46
	Polyethylene oxide (PEO-20NF)	130
	Mannitol	47.54
	Magnesium stearate	2
	Subtotal (outer shell)	197
Film	Hydroxypropyl methyl cellulose	11.31
	Yellow ferric oxide	0.29
	Subtotal (film)	11.6
Total		301.6

[0092]

Example 24

Compound X hydrochloride (104.8 g), mannitol (284.4 g), and polyethylene oxide (PEO-20NF, 236.1 g) were charged in a fluid bed granulator (MP-01, Powrex Corp.), granulated while spraying purified water, and dried to obtain a granulated powder. The granulated powder (521 g) was blended with polyethylene oxide (PEO-20NF, 196.75 g) and magnesium stearate (7.25 g), and tableted with a 9 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to produce uncoated tablets (290 mg per tablet) containing compound X hydrochloride (30 mg as compound X). The uncoated tablets were charged in a coating pan (DRC-300, Powrex Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methyl cellulose (TC-5E) in purified water and dispersing yellow ferric oxide therein, and dried to produce film-coated single-layered tablets shown in Table 24.

[0093]

[Table 24]

Table 24 Composition of one single-layered tablet

Additive		Dosage (mg/tablet)
Uncoated tablet	Compound X hydrochloride	34.92
	Polyethylene oxide (PEO-20NF)	157.4
	Mannitol	94.78
	Magnesium stearate	2.9
	Subtotal (uncoated tablet)	290
Film	Hydroxypropyl methyl cellulose	11.31
	Yellow ferric oxide	0.29
	Subtotal (film)	11.6
Total		301.6

[0094]

Example 25

Compound X hydrochloride (0.815 g), polyethylene oxide (Polyox™ WSR 303, 2.3 g), mannitol (9.855 g), and magnesium

stearate (0.13 g) were blended and tableted with a 7 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (130 mg per tablet).

Compound X hydrochloride (0.349 g), polyethylene oxide (Polyox™ WSR 303, 22 g), mannitol (4.381 g), and magnesium stearate (0.27 g) were blended to produce an outer shell blended powder. The core tablet and 270 mg of the outer shell blended powder were tableted with a 10 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce dry coated tablets (400 mg per tablet) containing compound X hydrochloride (10 mg as compound X) shown in Table 25.

[0095]

[Table 25]

Table 25 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	8.15
	Polyethylene oxide (Polyox™ WSR 303)	22
	Mannitol	98.55
	Magnesium stearate	1.3
	Subtotal (core tablet)	130
Outer shell	Compound X hydrochloride	3.49
	Polyethylene oxide (Polyox™ WSR 303)	220
	Mannitol	43.81
	Magnesium stearate	2.7
	Subtotal (outer shell)	270
Total		400

[0096]

Example 26

Compound X hydrochloride (0.582 g), polyethylene oxide (Polyox™ WSR 303, 1.45 g), mannitol (7.178 g), and magnesium stearate (0.09 g) were blended and tableted with a 6 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce core tablets (93 mg per tablet).

Compound X hydrochloride (0.582 g), polyethylene oxide (Polyox™ WSR 303, 13 g), mannitol (5.918 g), and magnesium stearate (0.2 g) were blended to produce an outer shell blended powder. The core tablet and 197 mg of the outer shell blended powder were tableted with a 9 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce dry coated tablets (290 mg per tablet) containing compound X hydrochloride (10 mg as compound X) shown in Table 26.

[0097]

[Table 26]

Table 26 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	5.82
	Polyethylene oxide (Polyox™ WSR 303)	14.5
	Mannitol	71.78
	Magnesium stearate	0.9
	Subtotal (core tablet)	93
Outer shell	Compound X hydrochloride	5.82
	Polyethylene oxide (Polyox™ WSR 303)	130
	Mannitol	59.18
	Magnesium stearate	2
	Subtotal (outer shell)	197
Total		290

[0098]

Example 27

Compound X hydrochloride (1.164 g), polyethylene oxide (Polyox™ WSR 303, 14.5 g), mannitol (13.046 g), and magnesium stearate (0.29 g) were blended to produce a powder mixture. 290 mg of the powder mixture was tableted with a 9 mmϕ punch by using a manual tablet press (HANDTAB, manufactured by Ichihashi Seiki) to produce single-layered tablets (290 mg per tablet) containing compound X hydrochloride (10 mg as compound X) shown in Table 27.

[0099]

[Table 27]

Table 27 Composition of one single-layered tablet

Additive	Dosage (mg/tablet)
Compound X hydrochloride	11.64
Polyethylene oxide (Polyox™ WSR 303)	145
Mannitol	130.46
Magnesium stearate	2.9
Total	290

[0100]

Example 28

Compound X hydrochloride (125.82 g) and mannitol (125.82 g) were blended in a pouch and passed through a 16 mesh sieve. The blended and sieved powder was additionally blended with spray-dried mannitol (297.45 g), polyethylene oxide (PEO-20NF, 113.22 g) and magnesium stearate (6.69 g) in the pouch and tableted with a 5.5 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to give core tablets (92.86 mg per tablet).

Compound X hydrochloride (69.84 g) and mannitol (69.84 g) were blended in a pouch and passed through a 16 mesh sieve. The blended and sieved powder was additionally blended with spray-dried mannitol (297.45 g), polyethylene oxide (PEO-20NF, 113.22 g) and magnesium stearate (6.69 g) in the pouch to obtain an outer shell blended powder. The core tablet and 197.14 mg of the outer shell blended powder were tableted with a 9 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to produce dry coated tablets (290 mg per tablet) containing compound X hydrochloride (30 mg as compound X). The dry coated tablets were charged in a coating pan (HICOATER LABO, Freund Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methylcellulose (TC-5E) in purified water and dispersing talc and yellow ferric oxide therein, and dried to produce film-coated dry coated tablets shown in Table 28.

[0101]

[Table 28]

Table 28 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	17.46
	Polyethylene oxide (PEO-20NF)	15.71
	Mannitol	17.46
	Spray-dried mannitol	41.3
	Magnesium stearate	0.93
	Subtotal (core tablet)	92.86
Outer shell	Compound X hydrochloride	17.46
	Polyethylene oxide (PEO-20NF)	130
	Mannitol	17.46
	Spray-dried mannitol	30.25
	Magnesium stearate	1.97
	Subtotal (outer shell)	197.14
Film	Hydroxypropyl methylcellulose	9.57
	Talc	1.74
	Yellow ferric oxide	0.29
	Subtotal (film)	11.6
Total		301.6

[0102]

Example 29

Compound X hydrochloride (125.82 g) and mannitol (125.82 g) were blended in a pouch and passed through a 16 mesh sieve. The blended and sieved powder was additionally blended with spray-dried mannitol (297.45 g), polyethylene oxide (PEO-20NF, 113.22 g) and magnesium stearate (6.69 g) in the pouch and tableted with a 6.5 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to give core tablets (130 mg per tablet).

Compound X hydrochloride (41.88 g) and mannitol (41.88 g) were blended in a pouch and passed through a 16 mesh sieve. The blended and sieved powder was additionally blended with spray-dried mannitol (105.44 g), polyethylene oxide (PEO-20NF, 880 g) and magnesium stearate (10.8 g) in the pouch to obtain an outer shell blended powder. The core tablet and 270 mg of

the outer shell blended powder were tableted with a 10 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to produce dry coated tablets (400 mg per tablet) containing compound X hydrochloride (30 mg as compound X). The dry coated tablets were charged in a coating pan (HICOATER LABO, Freund Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methylcellulose (TC-5E) in purified water and dispersing talc and yellow ferric oxide therein, and dried to produce film-coated dry coated tablets shown in Table 29.

[0103]

[Table 29]

Table 29 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	24.44
	Polyethylene oxide (PEO-20NF)	22
	Mannitol	24.44
	Spray-dried mannitol	57.82
	Magnesium stearate	1.3
	Subtotal (core tablet)	130
Outer shell	Compound X hydrochloride	10.48
	Polyethylene oxide (PEO-20NF)	220
	Mannitol	10.48
	Spray-dried mannitol	26.34
	Magnesium stearate	2.7
	Subtotal (outer shell)	270
Film	Hydroxypropyl methylcellulose	13.2
	Talc	2.4
	Yellow ferric oxide	0.4
	Subtotal (film)	16
Total		416

[0104]

Example 30

Compound X hydrochloride (104.76 g) and mannitol (104.76 g) were blended in a pouch and passed through a 16 mesh sieve. The blended and sieved powder was additionally blended with

spray-dried mannitol (179.58 g) polyethylene oxide (PEO-20NF, 472.20 g) and magnesium stearate (8.7 g) in the pouch and tableted with a 9 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to give uncoated tablets (290 mg per tablet) containing compound X hydrochloride (30 mg as compound X). The uncoated tablets were charged in a coating pan (HICOATER LABO, Freund Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methylcellulose (TC-5E) in purified water and dispersing talc and yellow ferric oxide therein, and dried to produce film-coated single-layered tablets shown in Table 30.

[0105]

[Table 30]

Table 30 Composition of one single-layered tablet

Additive		Dosage (mg/tablet)
Uncoated tablet	Compound X hydrochloride	34.92
	Polyethylene oxide (PEO-20NF)	157.4
	Mannitol	34.92
	Spray-dried mannitol	59.86
	Magnesium stearate	2.9
	Subtotal (uncoated tablet)	290
Film	Hydroxypropyl methylcellulose	9.57
	Talc	1.74
	Yellow ferric oxide	0.29
	Subtotal (film)	11.6
Total		301.6

[0106]

Example 31

Compound X hydrochloride (44.83 g) and mannitol (44.83 g) were blended in a pouch and passed through a 16 mesh sieve. The blended and sieved powder was additionally blended with spray-dried mannitol (497.2 g), polyethylene oxide (PEO-20NF, 121 g) and magnesium stearate (7.15 g) in the pouch and tableted with a 5.5 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to give core tablets (92.86 mg per tablet).

Compound X hydrochloride (23.28 g) and mannitol (23.28 g) were blended in a pouch and passed through a 16 mesh sieve. The blended and sieved powder was additionally blended with spray-dried mannitol (214.12 g), polyethylene oxide (PEO-20NF, 520 g) and magnesium stearate (7.88 g) in the pouch to obtain an outer shell blended powder. The core tablet and 197.14 mg of the outer shell blended powder were tableted with a 9 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to produce dry coated tablets (290 mg per tablet) containing compound X hydrochloride (10 mg as compound X). The dry coated tablets were charged in a coating pan (HICOATER LABO, Freund Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methyl cellulose (TC-5E) in purified water and dispersing talc and yellow ferric oxide therein, and dried to produce film-coated dry coated tablets shown in Table 31.

[0107]

[Table 31]

Table 31 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	5.82
	Polyethylene oxide (PEO-20NF)	15.71
	Mannitol	5.82
	Spray-dried mannitol	64.57
	Magnesium stearate	0.93
	Subtotal (core tablet)	92.86
Outer shell	Compound X hydrochloride	5.82
	Polyethylene oxide (PEO-20NF)	130
	Mannitol	5.82
	Spray-dried mannitol	53.53
	Magnesium stearate	1.97
	Subtotal (outer shell)	197.14
Film	Hydroxypropyl methylcellulose	9.57
	Talc	1.74
	Yellow ferric oxide	0.29
	Subtotal (film)	11.6
Total		301.6

[0108]

Example 32

Compound X hydrochloride (44.83 g) and mannitol (44.83 g) were blended in a pouch and passed through a 16 mesh sieve. The blended and sieved powder was additionally blended with spray-dried mannitol (497.2 g), polyethylene oxide (PEO-20NF, 121 g) and magnesium stearate (7.15 g) in the pouch and tableted with a 6.5 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to give core tablets (130 mg per tablet).

Compound X hydrochloride (13.96 g) and mannitol (13.96 g) were blended in a pouch and passed through a 16 mesh sieve. The blended and sieved powder was additionally blended with spray-dried mannitol (161.28 g), polyethylene oxide (PEO-20NF, 880 g) and magnesium stearate (10.8 g) in the pouch to obtain an outer shell blended powder. The core tablet and 270 mg of the outer shell blended powder were tableted with a 10 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to produce dry coated tablets (400 mg per tablet) containing compound X hydrochloride (10 mg as compound X). The dry coated tablets were charged in a coating pan (HICOATER LABO, Freund Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methylcellulose (TC-5E) in purified water and dispersing talc and yellow ferric oxide therein, and dried to produce film-coated dry coated tablets shown in Table 32.

[0109]

[Table 32]

Table 32 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	8.15
	Polyethylene oxide (PEO-20NF)	22
	Mannitol	8.15
	Spray-dried mannitol	90.4
	Magnesium stearate	1.3
	Subtotal (core tablet)	130
Outer shell	Compound X hydrochloride	3.49
	Polyethylene oxide (PEO-20NF)	220
	Mannitol	3.49
	Spray-dried mannitol	40.32
	Magnesium stearate	2.7
	Subtotal (outer shell)	270
Film	Hydroxypropyl methylcellulose	13.2
	Talc	2.4
	Yellow ferric oxide	0.4
	Subtotal (film)	16
Total		416

[0110]

Example 33

Compound X hydrochloride (34.92 g) and mannitol (34.92 g) were blended in a pouch and passed through a 16 mesh sieve. The blended and sieved powder was additionally blended with spray-dried mannitol (319.26 g) polyethylene oxide (PEO-20NF, 472.20 g) and magnesium stearate (8.7 g) in the pouch and tableted with a 9 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to give uncoated tablets (290 mg per tablet) containing compound X hydrochloride (10 mg as compound X). The uncoated tablets were charged in a coating pan (HICOATER LABO, Freund Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methylcellulose (TC-5E) in purified water and dispersing talc and yellow ferric oxide therein, and dried to produce film-coated single-layered tablets shown in Table 33.

[0111]

[Table 33]

Table 33 Composition of one single-layered tablet

Additive		Dosage (mg/tablet)
Uncoated tablet	Compound X hydrochloride	11.64
	Polyethylene oxide (PEO-20NF)	157.4
	Mannitol	11.64
	Spray-dried mannitol	106.42
	Magnesium stearate	2.9
	Subtotal (uncoated tablet)	290
Film	Hydroxypropyl methylcellulose	9.57
	Talc	1.74
	Yellow ferric oxide	0.29
	Subtotal (film)	11.6
Total		301.6

[0112]

Example 34

Compound X hydrochloride (3422 g), mannitol (11520 g), and polyethylene oxide (PEO-20NF, 1540 g) were charged in a fluid bed granulator (FD-WSG-30, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The granulation operation was repeated twice and obtained granulated powder (32960 g) was blended with polyethylene oxide (PEO-20NF, 3080 g) and magnesium stearate (364 g) and tableted with a 6.5 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to give core tablets (130 mg per tablet).

Compound X hydrochloride (1153 g), mannitol (4050 g), and polyethylene oxide (PEO-20NF, 12100 g) were charged in a fluid bed granulator (FD-WSG-30, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The granulation operation was repeated twice and obtained granulated powder (34600 g) was blended with polyethylene oxide (PEO-20NF, 24200 g) and magnesium stearate (594 g) to produce an outer shell blended powder. The core tablet and 270 mg of the outer shell blended powder were tableted with a 10 mmϕ

punch by using a rotary tablet press (HATA TEKKOSHO CO.,LTD.) to produce dry coated tablets (400 mg per tablet) containing compound X (30 mg). The dry coated tablets were charged in a coating pan (DRC-900DS, Powrex Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methylcellulose (TC-5E) in purified water and dispersing sterile talc and yellow ferric oxide therein, and dried to produce film-coated dry coated tablets shown in Table 34.

[0113]

[Table 34]

Table 34 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	24.44
	Polyethylene oxide (PEO-20NF)	22
	Mannitol	82.26
	Magnesium stearate	1.3
	Subtotal (core tablet)	130
Outer shell	Compound X hydrochloride	10.48
	Polyethylene oxide (PEO-20NF)	220
	Mannitol	36.82
	Magnesium stearate	2.7
	Subtotal (outer shell)	270
Film	Hydroxypropyl methylcellulose	13.2
	Sterile talc	2.4
	yellow ferric oxide	0.4
	Subtotal (film)	16
Total		416

[0114]

Example 35

Compound X hydrochloride (3754 g), mannitol (12630 g), and polyethylene oxide (PEO-20NF, 1689 g) were charged in a fluid bed granulator (FD-WSG-30, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The obtained granulated powder (18070 g) was blended with polyethylene oxide (PEO-20NF, 1689 g) and magnesium stearate (200 g) and tableted with a 5.5 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to give core tablets

(92.86 mg per tablet).

Compound X hydrochloride (2270 g), mannitol (6202 g), and polyethylene oxide (PEO-20NF, 8450 g) were charged in a fluid bed granulator (FD-WSG-30, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The granulation operation was repeated twice and obtained granulated powder (33840 g) was blended with polyethylene oxide (PEO-20NF, 16900 g) and magnesium stearate (512.2 g) to produce an outer shell blended powder. The core tablet and 197.14 mg of the outer shell blended powder were tableted with a 9 mmϕ punch by using a rotary tablet press (HATA TEKKOSHO CO.,LTD.) to produce dry coated tablets (290 mg per tablet) containing compound X (30 mg). The dry coated tablets were charged in a coating pan (DRC-900DS, Powrex Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methyl cellulose (TC-5E) in purified water and dispersing sterile talc and yellow ferric oxide therein, and dried to produce film-coated dry coated tablets shown in Table 35.

[0115]

[Table 35]

Table 35 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	17.46
	Polyethylene oxide (PEO-20NF)	15.71
	Mannitol	58.76
	Magnesium stearate	0.93
	Subtotal (core tablet)	92.86
Outer shell	Compound X hydrochloride	17.46
	Polyethylene oxide (PEO-20NF)	130
	Mannitol	47.71
	Magnesium stearate	1.97
	Subtotal (outer shell)	197.14
Film	Hydroxypropyl methylcellulose	9.57
	Sterile talc	1.74
	yellow ferric oxide	0.29
	Subtotal (film)	11.6
Total		301.6

[0116]

Example 36

Compound X hydrochloride (3492 g), mannitol (9478 g), and polyethylene oxide (PEO-20NF, 7870 g) were charged in a fluid bed granulator (FD-WSG-30, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The granulation operation was repeated twice and obtained granulated powder (41680 g) was blended with polyethylene oxide (PEO-20NF, 15740 g) and magnesium stearate (580 g) and tableted with a 9 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to produce uncoated tablets (290 mg per tablet) containing compound X (30 mg). The uncoated tablets were charged in a coating pan (DRC-900DS, Powrex Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methyl cellulose (TC-5E) in purified water and dispersing sterile talc and yellow ferric oxide therein, and dried to produce film-coated single-layered tablets shown in Table 36.

[0117]

[Table 36]

Table 36 Composition of one single-layered tablet

Additive		Dosage (mg/tablet)
Uncoated tablet	Compound X hydrochloride	34.92
	Polyethylene oxide (PEO-20NF)	157.4
	Mannitol	94.78
	Magnesium stearate	2.9
	Subtotal (uncoated tablet)	290
Film	Hydroxypropyl methylcellulose	9.57
	Sterile talc	1.74
	Yellow ferric oxide	0.29
	Subtotal (film)	11.6
Total		301.6

[0118]

Example 37

Compound X hydrochloride (11410 g), mannitol (564.5 g), and polyethylene oxide (PEO-20NF, 5132 g) were charged in a fluid bed granulator (FD-WSG-30, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The obtained granulated powder (17110 g) was blended with mannitol (723.5 g), polyethylene oxide (PEO-20NF, 188 g), and magnesium stearate (182 g) and tableted with a 6.5 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to give core tablets (130 mg per tablet).

Compound X hydrochloride (10820 g), mannitol (535.4 g), and polyethylene oxide (PEO-20NF, 4866 g) were charged in a fluid bed granulator (FD-WSG-30, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The obtained granulated powder (7849 g) was blended with mannitol (1601 g), polyethylene oxide (PEO-20NF, 30650 g), and magnesium stearate (405 g) to produce an outer shell blended powder. The core tablet and 270 mg of the outer shell blended powder were tableted with a 10 mmϕ punch by using a rotary tablet press (HATA TEKKOSHO CO.,LTD.) to produce dry coated tablets (400 mg per tablet) containing compound X (100 mg). The dry coated tablets were charged in a coating pan (DRC-900DS, Powrex Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methylcellulose (TC-5E) in purified water and dispersing sterile talc and yellow ferric oxide therein, and dried to produce film-coated dry coated tablets shown in Table 37.

[0119]

[Table 37]

Table 37 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	81.5
	Polyethylene oxide (PEO-20NF)	38
	Mannitol	9.2
	Magnesium stearate	1.3
	Subtotal (core tablet)	130
Outer shell	Compound X hydrochloride	34.9
	Polyethylene oxide (PEO-20NF)	220
	Mannitol	12.4
	Magnesium stearate	2.7
	Subtotal (outer shell)	270
Film	Hydroxypropyl methylcellulose	13.2
	Sterile talc	2.4
	Yellow ferric oxide	0.4
	Subtotal (film)	16
Total		416

[0120]

Example 38

Compound X hydrochloride (11060 g), mannitol (547 g), and polyethylene oxide (PEO-20NF, 4974 g) were charged in a fluid bed granulator (FD-WSG-30, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The obtained granulated powder (16580 g) was blended with mannitol (682.3 g), polyethylene oxide (PEO-20NF, 232.4 g), and magnesium stearate (176.7 g) and tableted with a 6 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to give core tablets (93 mg per tablet).

Compound X hydrochloride (11060 g), mannitol (547 g), and polyethylene oxide (PEO-20NF, 4974 g) were charged in a fluid bed granulator (FD-WSG-30, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated powder. The obtained granulated powder (16580 g) was blended with mannitol (750.7 g), polyethylene oxide (PEO-20NF, 19730 g), and

magnesium stearate (374.3 g) to produce an outer shell blended powder. The core tablet and 197 mg of the outer shell blended powder were tableted with a 9 mmϕ punch by using a rotary tablet press (HATA TEKKOSHO CO.,LTD.) to produce dry coated tablets (290 mg per tablet) containing compound X (100 mg). The dry coated tablets were charged in a coating pan (DRC-900DS, Powrex Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methylcellulose (TC-5E) in purified water and dispersing sterile talc and yellow ferric oxide therein, and dried to produce film-coated dry coated tablets shown in Table 38.

[0121]

[Table 38]

Table 38 Composition of one dry coated tablet

Additive		Dosage (mg/tablet)
Core tablet	Compound X hydrochloride	58.2
	Polyethylene oxide (PEO-20NF)	27.4
	Mannitol	6.47
	Magnesium stearate	0.93
	Subtotal (core tablet)	93
Outer shell	Compound X hydrochloride	58.2
	Polyethylene oxide (PEO-20NF)	130
	Mannitol	6.83
	Magnesium stearate	1.97
	Subtotal (outer shell)	197
Film	Hydroxypropyl methylcellulose	9.57
	Sterile talc	1.74
	Yellow ferric oxide	0.29
	Subtotal (film)	11.6
Total		301.6

[0122]

Example 39

Compound X hydrochloride (13970 g), mannitol (691.1 g), and polyethylene oxide (PEO-20NF, 6282 g) were charged in a fluid bed granulator (FD-WSG-30, Powrex Corp.), granulated while spraying purified water, and dried to give a granulated

powder. The obtained granulated powder (20940 g) was blended with mannitol (904.9 g), polyethylene oxide (PEO-20NF, 12610 g), and magnesium stearate (348 g) and tableted with a 9 mmϕ punch by using a rotary tablet press (Kikusui Seisakusho) to produce uncoated tablets (290 mg per tablet) containing compound X (100 mg). The uncoated tablets were charged in a coating pan (DRC-900DS, Powrex Corp.), and coated by spraying a coating suspension produced by dissolving hydroxypropyl methylcellulose (TC-5E) in purified water and dispersing sterile talc and yellow ferric oxide therein, and dried to produce film-coated single-layered tablets shown in Table 39.

[0123]

[Table 39]

Table 39 Composition of one single-layered tablet

Additive		Dosage (mg/tablet)
Uncoated tablet	Compound X hydrochloride	116.4
	Polyethylene oxide (PEO-20NF)	157.4
	Mannitol	13.3
	Magnesium stearate	2.9
	Subtotal (uncoated tablet)	290
Film	Hydroxypropyl methylcellulose	9.57
	Sterile talc	1.74
	Yellow ferric oxide	0.29
	Subtotal (film)	11.6
Total		301.6

[0124]

Experimental Example 1

The dissolution property of the preparations obtained in Examples 1, 2, 4, and 5 was evaluated by the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 50 rpm, 900 mL). The results are shown in Table 1.

[0125]

Experimental Example 2

The dissolution property of the preparations obtained in Examples 2, 3, 6, 9, 10, and 11 was evaluated by the Paddle

Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 50 rpm, 900 mL). The results are shown in Table 2.

[0126]

Experimental Example 3

The dissolution property of the preparations obtained in Examples 7, 8, and 9 was evaluated by the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 50 rpm, 900 mL). The results are shown in Table 3.

[0127]

Experimental Example 4

The dissolution property of the preparations obtained in Examples 9 and 12 was evaluated by the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 50 rpm, 900 mL). The results are shown in Table 4.

[0128]

Experimental Example 5

The dissolution property of the preparation obtained in Example 13 was evaluated by the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 50 rpm, 900 mL). The results are shown in Table 5.

[0129]

Experimental Example 6

The dissolution property of the preparations obtained in Examples 14, 15, 16, 17, 18, and 19 was evaluated by the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 50 rpm, 900 mL). The results are shown in Table 6.

[0130]

Experimental Example 7

The dissolution property of the preparation obtained in Example 20 was evaluated by the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 50 rpm, 900 mL). The results are shown in Table 7.

[0131]

Experimental Example 8

The dissolution property of the preparation obtained in

Example 21 was evaluated by the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 50 rpm, 900 mL). The results are shown in Table 8.

[0132]

Experimental Example 9

The dissolution property of the preparations obtained in Examples 22, 23, and 24 was evaluated by the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 50 rpm, 900 mL). The results are shown in Table 9.

[0133]

Experimental Example 10

The dissolution property of the preparations obtained in Examples 25, 26, and 27 was evaluated by the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 50 rpm, 900 mL). The results are shown in Table 10.

[0134]

Experimental Example 11

The dissolution property of the preparations obtained in Examples 34, 35, and 36 was evaluated by the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 100 rpm, 900 mL). The results are shown in Table 11.

[0135]

Experimental Example 12

The dissolution property of the preparations obtained in Examples 37, 38, and 39 was evaluated by the Paddle Method (the Japanese Pharmacopoeia dissolution test, 2nd fluid, 100 rpm, 900 mL). The results are shown in Table 12.

[0136]

This application is based on a patent application No. 2015-252657 filed in Japan, the contents of which are incorporated in full herein.

Claims

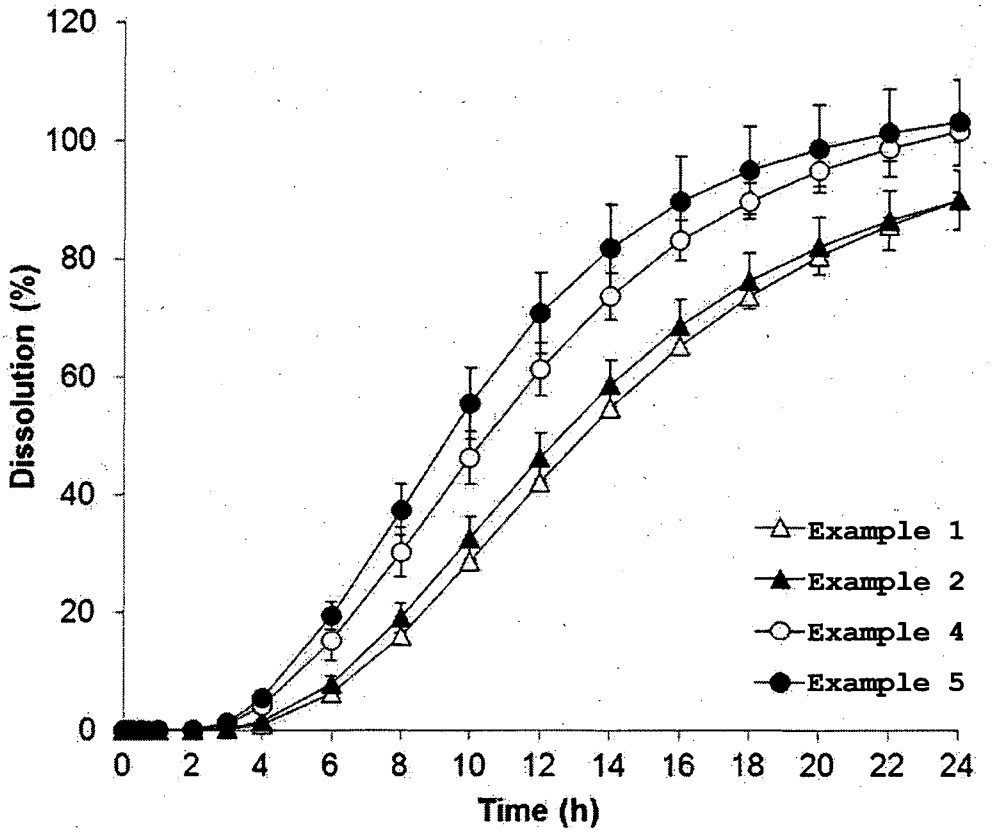
1. A solid preparation comprising N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, and a hydrophilic gel-forming polymer.

2. The solid preparation of claim 1, comprising (1) a core comprising N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, and a first hydrophilic gel-forming polymer; and (2) an outer shell comprising N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof, and a second hydrophilic gel-forming polymer.

3. The solid preparation of claim 2, wherein the first hydrophilic gel-forming polymer and the second hydrophilic gel-forming polymer are the same or different and each is selected from the group consisting of polyethylene oxide, hydroxypropyl methyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, carboxyvinyl polymer, methyl cellulose, and sodium carboxymethyl cellulose.

4. The solid preparation of claim 2, wherein, in the preparation, the content of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in the core is the same as or higher than the content of N-methyl-N-(1-methylethyl)-6,7,8,9-tetrahydropyrazino[2,3-f][1,4]oxazepin-3-amine or a salt thereof in the outer shell.

Fig. 1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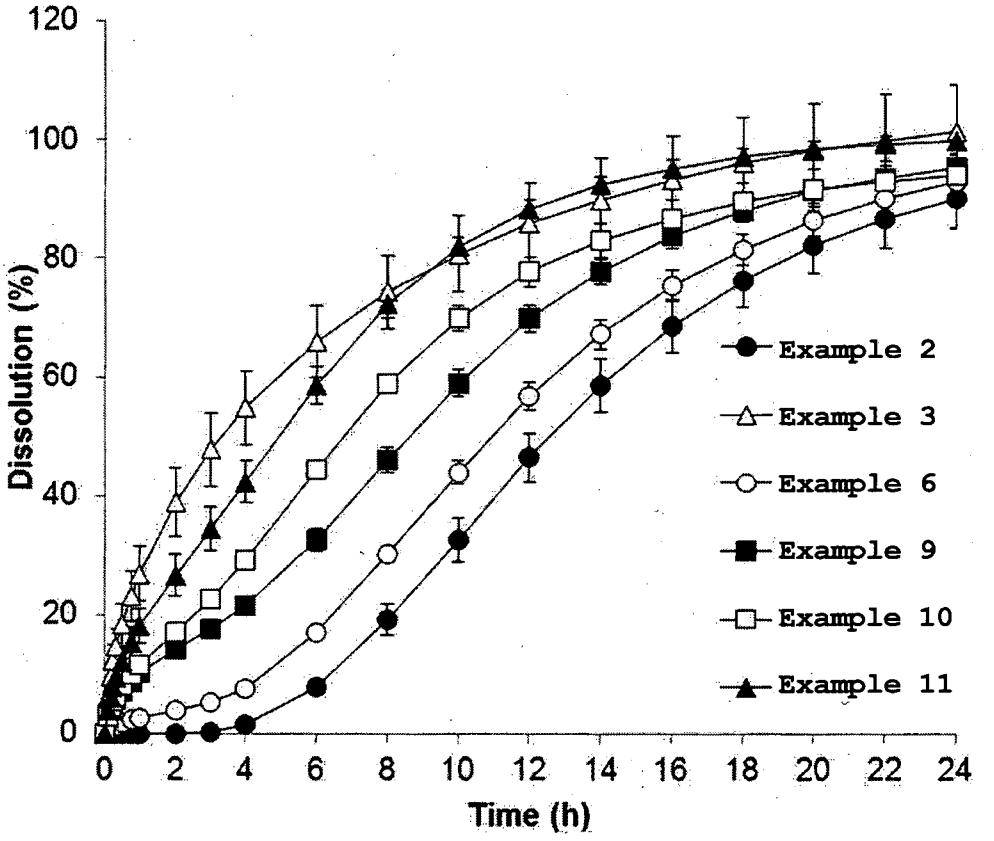
Time (h)
Example 1
Example 2
Example 4
Example 5

Fig. 2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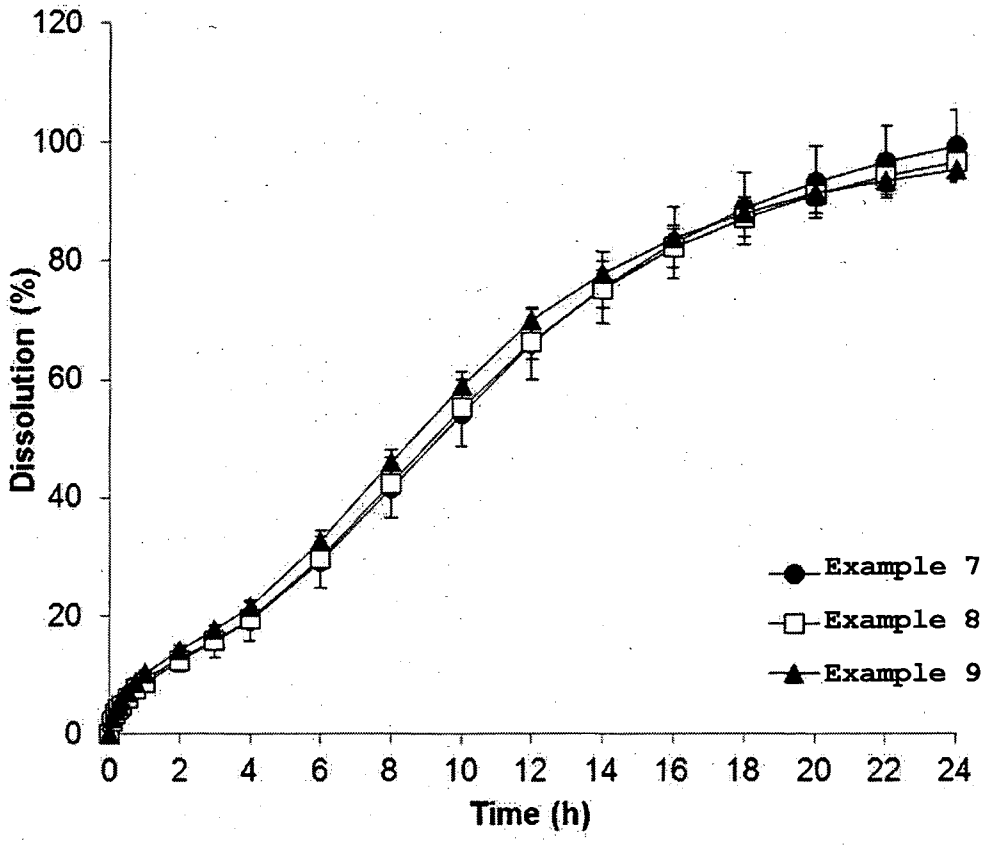
Time (h)
Example 2
Example 3
Example 6
Example 9
Example 10
Example 11

Fig. 3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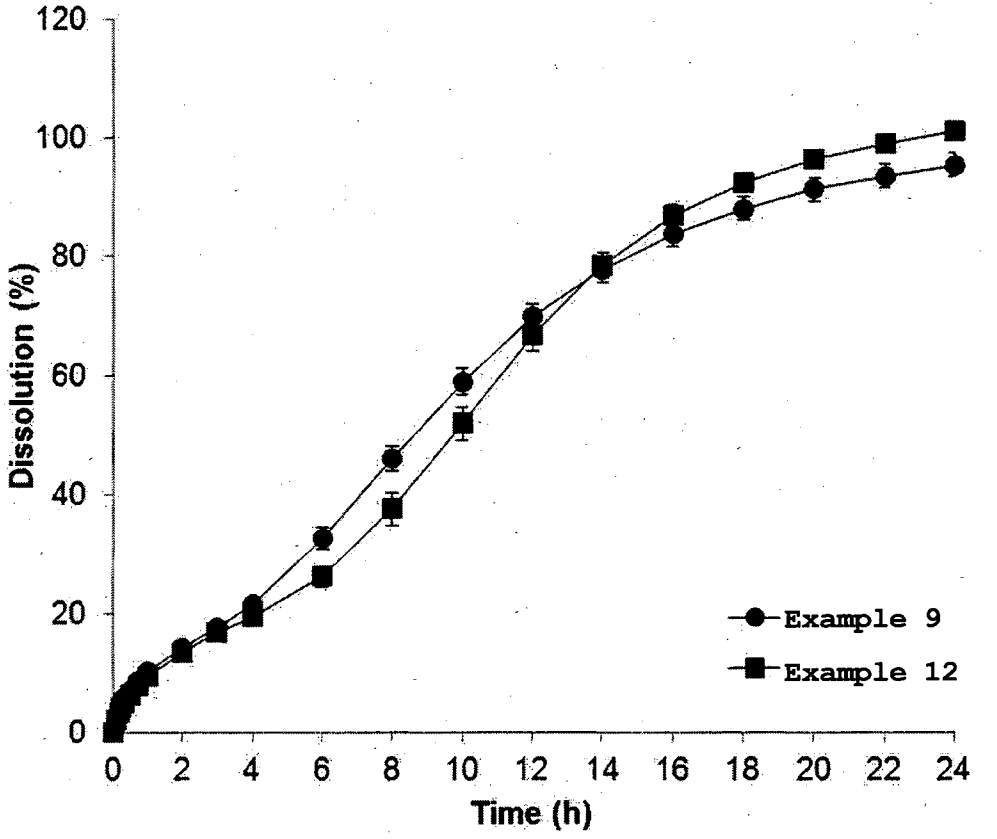
Time (h)
Example 7
Example 8
Example 9

Fig. 4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Dissolution (%)
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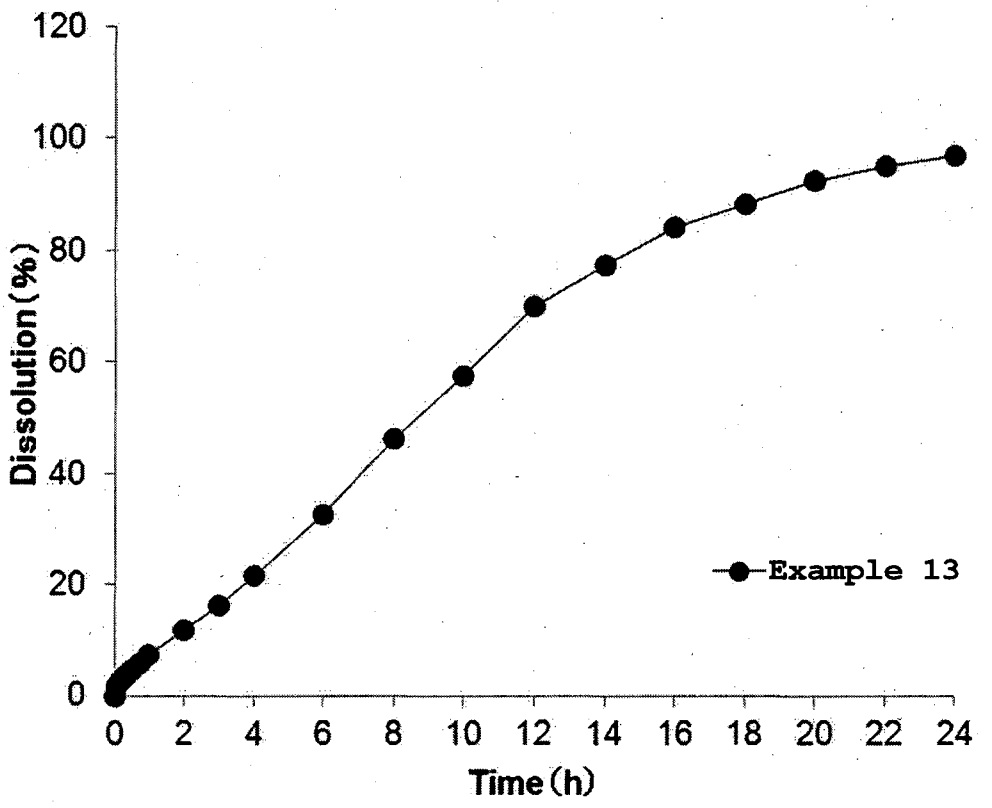
Time (h)
Example 9
Example 12

Fig. 5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Dissolution (%)
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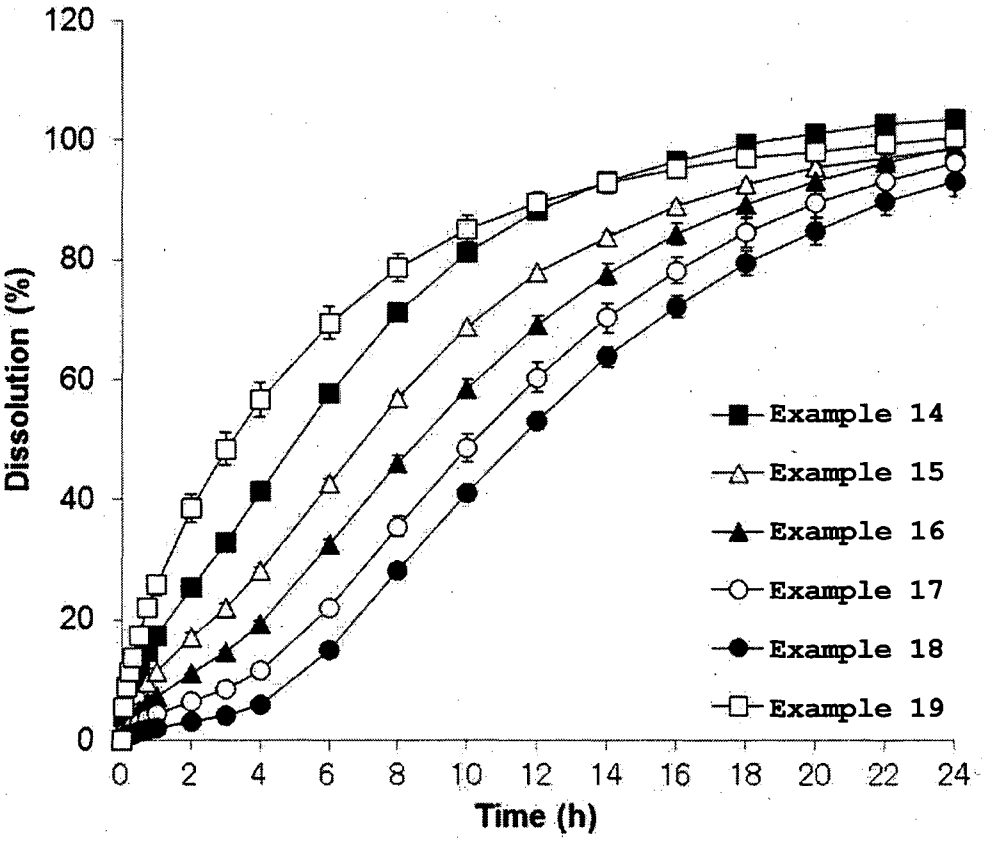
Time (h)
Example 13

Fig. 6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Dissolution (%)
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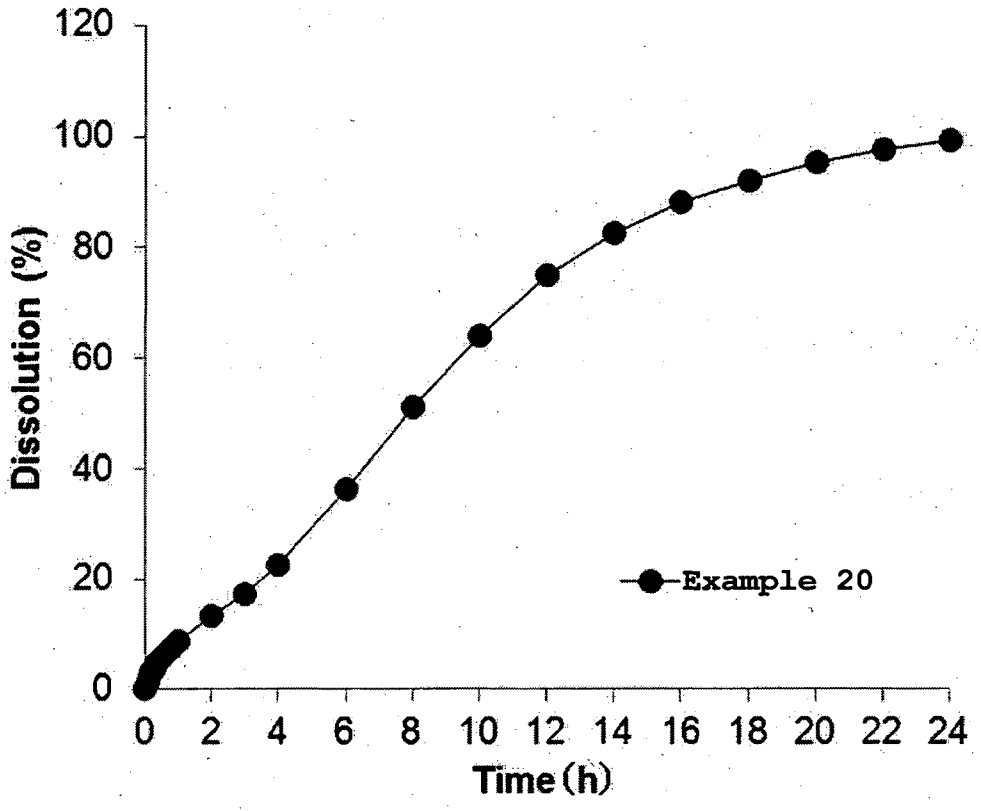
Time (h)
Example 14
Example 15
Example 16
Example 17
Example 18
Example 19

Fig. 7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Dissolution (%)
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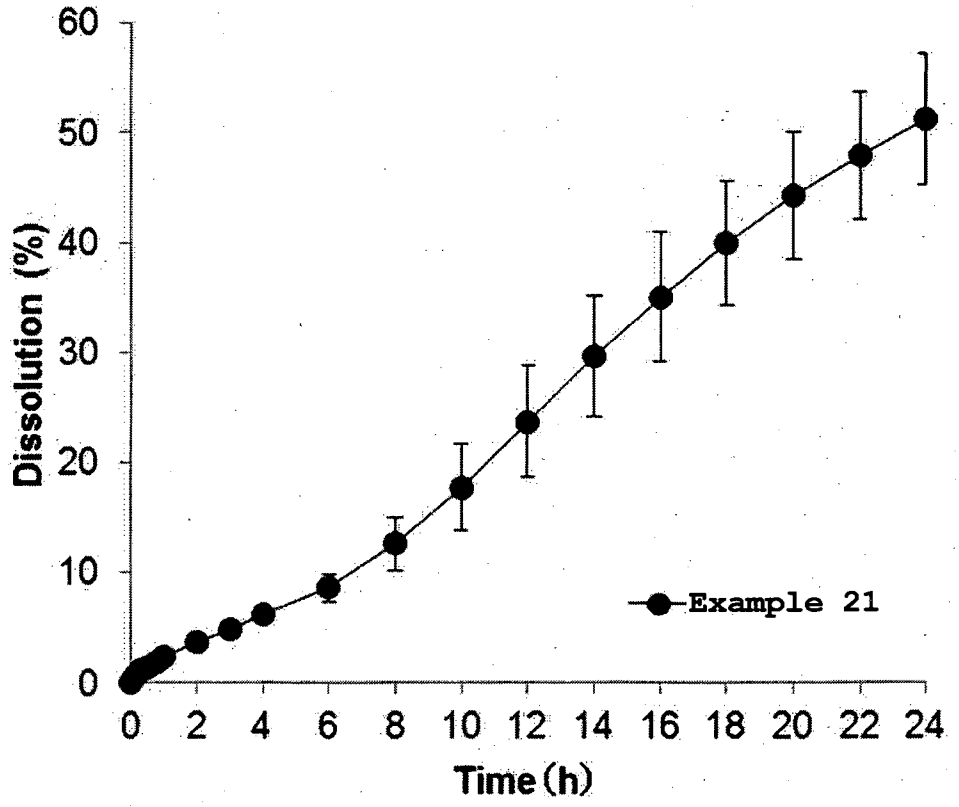
Time (h)
Example 20

Fig. 8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Dissolution (%)
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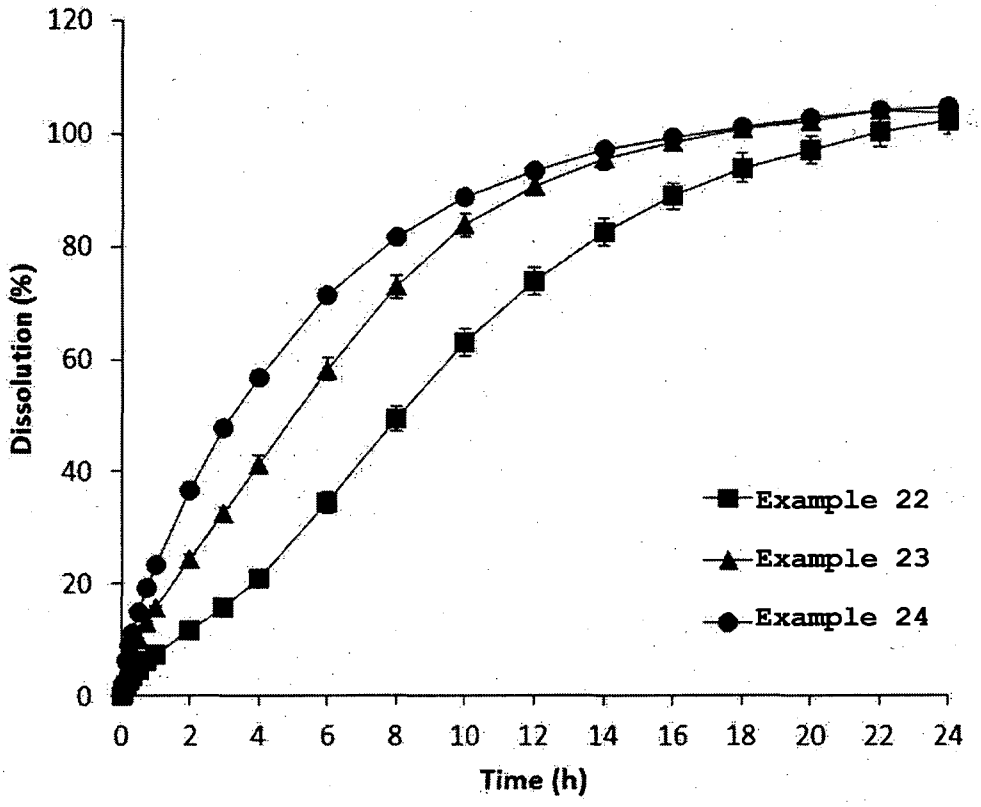
Time (h)
Example 21

Fig. 9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Dissolution (%)
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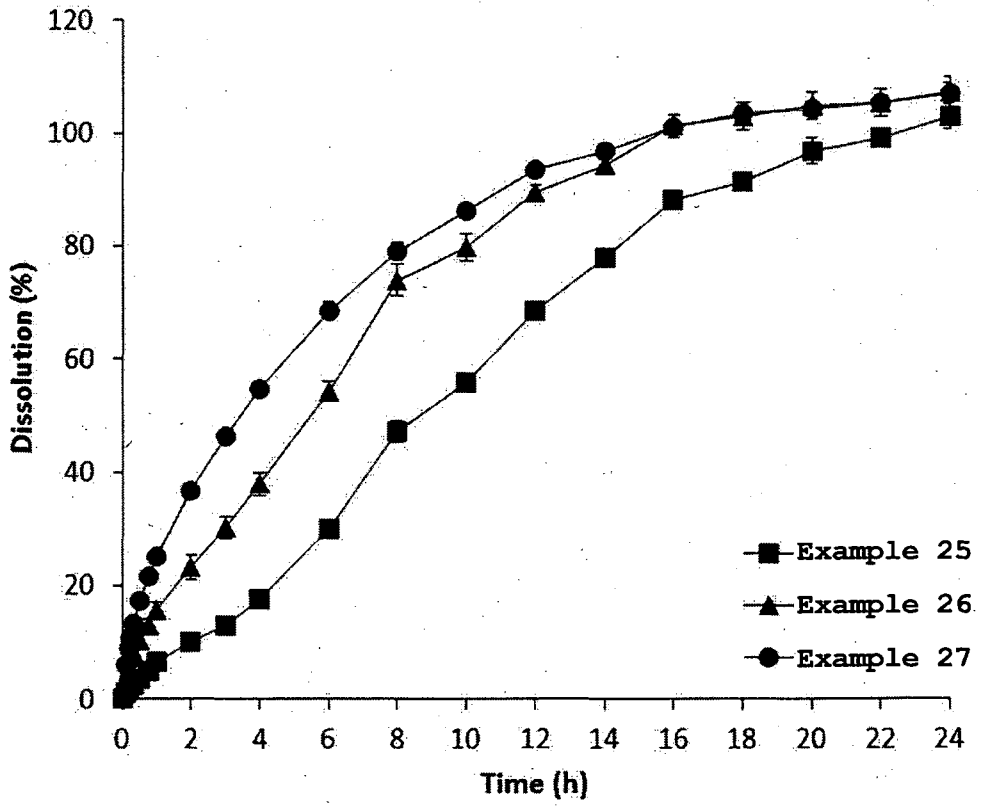
Time (h)
Example 22
Example 23
Example 24

Fig. 10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Dissolution (%)
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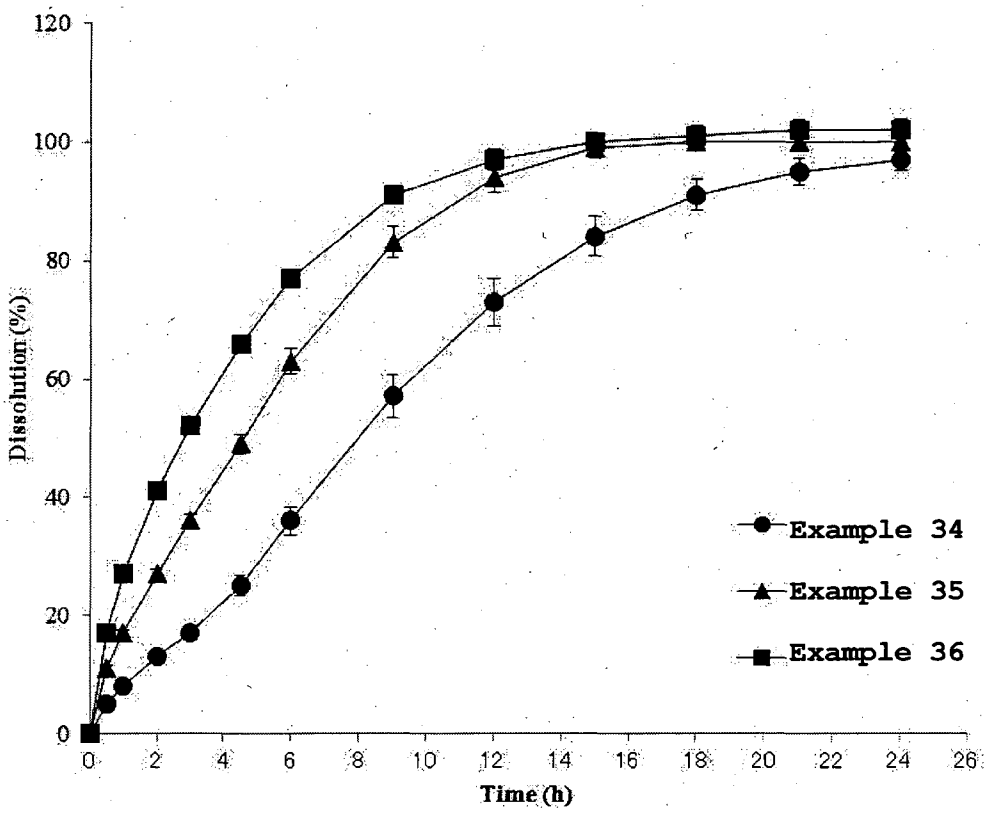
Time (h)
Example 25
Example 26
Example 27

Fig. 11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Dissolution (%)
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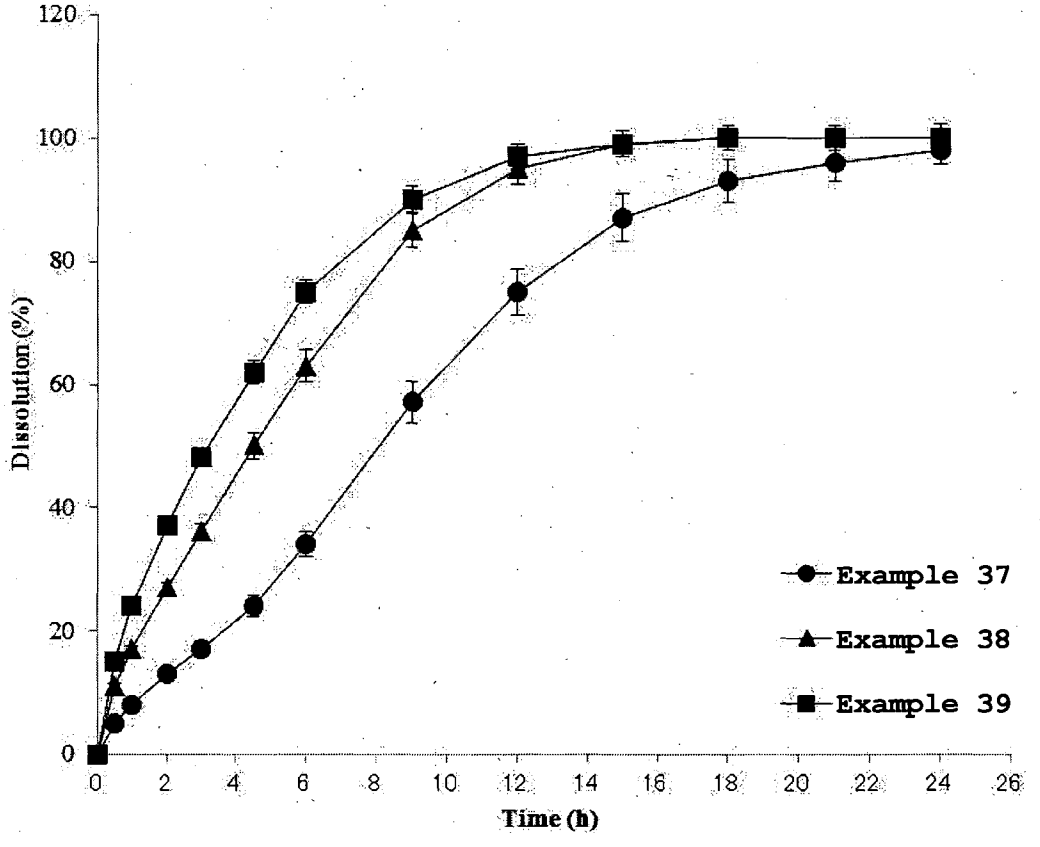
Time (h)
Example 34
Example 35
Example 36

Fig. 12


120
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20
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Dissolution (%)
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Time (h)
Example 37
Example 38
Example 39

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2016/089222

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/24 A61K31/00
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, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/317651 A1 (HIRONOBU M; IZUMI N; KUSUMOTO T; MAEZAKI H; NOMURA I; SASAKI S; SHIGEK) 16 December 2010 (2010-12-16) cited in the application paragraphs [0103], [0425] - [0430] claims; examples	1-4
A	EP 1 591 120 A1 (TAKEDA CHEMICAL INDUSTRIES LTD [JP]) 2 November 2005 (2005-11-02) the whole document	1-4
A	EP 1 337 518 A1 (BIOVITRUM AB [SE]) 27 August 2003 (2003-08-27) the whole document	1-4

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☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 April 2017	21/04/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ceyte, Mathilde

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2016/089222

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010317651 A1	16-12-2010	AR 077094 A1	03-08-2011
		AU 2010260847 A1	19-01-2012
		BR PI1011502 A2	22-03-2016
		CA 2765239 A1	23-12-2010
		CN 102458579 A	16-05-2012
		CO 6491037 A2	31-07-2012
		CR 20120021 A	06-03-2012
		DK 2442870 T3	30-06-2014
		DO P2011000393 A	15-02-2012
		EA 201270017 A1	30-07-2012
		EC SP12011603 A	30-03-2012
		EP 2442870 A1	25-04-2012
		ES 2480275 T3	25-07-2014
		HK 1169623 A1	14-11-2014
		HR P20140589 T1	01-08-2014
		IL 216761 A	31-03-2016
		JP 5579203 B2	27-08-2014
		JP 5579262 B2	27-08-2014
		JP 2012107032 A	07-06-2012
		JP 2012530051 A	29-11-2012
		KR 20120034734 A	12-04-2012
		MA 33430 B1	03-07-2012
		MY 157497 A	15-06-2016
		NZ 597507 A	27-09-2013
		PE 10492012 A1	22-08-2012
		PT 2442870 E	16-07-2014
		RS 53414 B	31-12-2014
		SG 176696 A1	30-01-2012
		SI 2442870 T1	31-07-2014
		SM T201400080 B	08-09-2014
		TW 201109338 A	16-03-2011
		TW 201529584 A	01-08-2015
		UA 108357 C2	27-04-2015
		US 2010317651 A1	16-12-2010
		US 2011282054 A1	17-11-2011
		US 2011288291 A1	24-11-2011
		US 2012135979 A1	31-05-2012
		UY 32707 A	31-01-2011
		WO 2010147226 A1	23-12-2010
		ZA 201109370 B	31-10-2012
EP 1591120 A1	02-11-2005	CA 2514547 A1	12-08-2004
		EP 1591120 A1	02-11-2005
		US 2006199795 A1	07-09-2006
		WO 2004067008 A1	12-08-2004
EP 1337518 A1	27-08-2003	AT 433962 T	15-07-2009
		AU 1529402 A	27-05-2002
		BR 0115436 A	06-01-2004
		CA 2428905 A1	23-05-2002
		CA 2449899 A1	23-05-2002
		CN 1520404 A	11-08-2004
		DK 1337518 T3	19-10-2009
		EA 200300595 A1	30-10-2003
		EP 1337518 A1	27-08-2003
		ES 2328671 T3	17-11-2009
		HK 1066810 A1	14-07-2006
		IL 155875 A	17-06-2007

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2016/089222

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		JP 4204315 B2	07-01-2009
		JP 2004531465 A	14-10-2004
		KR 20030060946 A	16-07-2003
		MX PA03004391 A	31-05-2004
		NO 20032253 A	18-07-2003
		NZ 525699 A	24-03-2005
		PL 360982 A1	20-09-2004
		WO 0240457 A1	23-05-2002