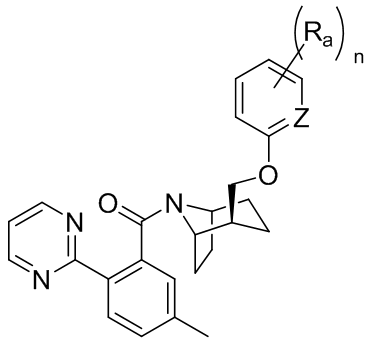
insomnia clearly has adverse effects, such as a residual effect on the second day, resulting in adverse consequences for the patients. Therefore, it is necessary to develop it into a solid pharmaceutical dosage form with higher dissolution rate and dissolution level, as well as higher bioavailability and lower half-life, in order to meet wider clinical administration requirements.

SUMMARY OF THE INVENTION

The object of the present invention is to provide a solid pharmaceutical formulation comprising the compound of formula I with a good stability, a good dissolution effect and a good bioavailability.

The first aspect of the present invention provides a solid pharmaceutical formulation, wherein the solid pharmaceutical formulation comprises an active ingredient, and the active ingredient is a compound represented by formula (I) or a pharmaceutically acceptable salt thereof, or a mixture of both;



(I)

wherein R_a is hydrogen, fluorine, chlorine, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

Z is N or CR_0; R_0 is hydrogen, halogen or C_{1-3} alkyl;

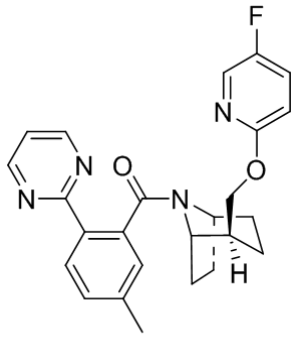
n is 0, 1 or 2;

and the particle size of the active ingredient is D90 ≤ 50 μm.

In another preferred example, the particle size of the active ingredient is D90 ≤ 35 μm. In another preferred example, the particle size of the active ingredient is D90 ≤ 30 μm. In another preferred example, the particle size of the active ingredient is D90 ⩽ 20μm ~~ze~~. In another preferred example, the particle size of the active ingredient is ~~D90opropoxycleient is D90ve ingredient is~~ D90~~hoxy, p~~ ⩽ 10μm ~~ze~~. In another preferred example, ~~of the active eferred example,~~ the particle size of the active ingredient is D90 = 1–μm~~z~~ to 30μm ~~ze~~. In another preferred example, ~~of the active eferred example,~~ the particle size of the active ingredient is D90 =1μm ~~ze~~ to 20μm ~~ze~~. In another preferred example, ~~of the active~~

~~eferred example,~~ the particle size of the active ingredient is D90 = 1 μm to 10 μm or D90 = 10 μm to 20 μm.

In another preferred example, the compound represented by formula (I) is a compound of formula (II):



(II)

((1S,2R,5S)-2-(((5-fluoropyridin-2-yl)oxy)methyl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-2-(pyrimidin-2-yl)phenyl)methanone. As described in patent CN106414439A, the intracellular calcium signal change is detected by FLIPR and indicated by the IC_{50} value of the compound to evaluate the inhibitory effect of the compound of formula (II) on OX1 and OX2 GPCR receptors, and the activities thereof are 20 nM (hOX1R) and 36 nM (hOX2R), respectively.

The pharmaceutically acceptable salt of the present invention includes pharmaceutically acceptable acid addition salt and pharmaceutically acceptable base addition salt. The pharmaceutically acceptable acid addition salt refers to a salt formed by an inorganic or organic acid which can retain the biological effectiveness of the free base without other side effects. The inorganic acid salt includes but is not limited to hydrochloride, hydrobromide, sulfate, phosphate and the like. The organic acid salt includes but is not limited to formate, acetate, propionate, glycolate, gluconate, lactate, oxalate, maleate, succinate, fumarate, tartrate, citrate, glutamate, aspartate, benzoate, mesylate, p-toluenesulfonate, salicylate and the like. These salts can be prepared by methods known in the art. The pharmaceutically acceptable base addition salt includes but is not limited to a salt of an inorganic base such as sodium salt, potassium salt, calcium salt, magnesium salt and the like, and includes but is not limited to a salt of an organic base such as ammonium salt, triethylamine salt, lysine salt, arginine salt and the like. These salts can be prepared by methods known in the art.

The compound represented by formula (I) and formula (II) of the present invention or the

In another preferred example, the solid pharmaceutical formulation further comprises a filler selected from the group consisting of microcrystalline cellulose, lactose, cellulose-lactose complex, pre-gelatinized starch, calcium hydrogen phosphate, calcium carbonate and a combination thereof. The content of the filler is 60%-90%, more preferably 73%-85%, more preferably 73%-82.5% based on the total dry weight of the solid pharmaceutical formulation.

In another preferred example, the filler is microcrystalline cellulose ~~or~~ and lactose.

In another preferred example, the solid pharmaceutical formulation further comprises a disintegrant selected from the group consisting of croscarmellose sodium, hypromellose-K4M, crospovidone, sodium carboxymethyl starch and a combination thereof. The content of the disintegrant is 5%-15% based on the total dry weight of the solid pharmaceutical formulation.

In another preferred example, the disintegrant is croscarmellose sodium or hypromellose-K4M.

In another preferred example, the solid pharmaceutical formulation further comprises a lubricant selected from the group consisting of magnesium stearate, talcum powder, glycerol monostearate, sodium stearyl fumarate and a combination thereof. The content of the lubricant is 0.1%-1%, more preferably 0.4%-0.5%, more preferably 0.48%-0.5% based on the total dry weight of the solid pharmaceutical formulation.

In another preferred example, the solid pharmaceutical formulation is a tablet, a capsule, a powder, a granule, a drop pill or a film, preferably a tablet.

In another preferred example, the solid pharmaceutical formulation comprises the following components based on the total dry weight of the solid pharmaceutical formulation: a) the active ingredient: ((1S,2R,5S)-2-(((5-fluoropyridin-2-yl)oxy)methyl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-2-(pyrimidin-2-yl)phenyl)methanone, or a pharmaceutically acceptable salt thereof, or a mixture of both, wherein the content of the active ingredient is 1%-15%, more preferably 4%-10%, more preferably 9.5%-10%;

b) the filler selected from the group consisting of microcrystalline cellulose, lactose, cellulose-lactose complex, pre-gelatinized starch, calcium hydrogen phosphate, calcium carbonate and a combination thereof, wherein the content of the filler is 60%-90%, more preferably 73%-85%, more preferably 73%-82.5%;

c) the binder selected from the group consisting of hypromellose, hydroxypropyl cellulose, povidone, sodium alginate, carbopol, polyvinyl alcohol and a combination thereof, wherein the content of the binder is 0.5%-10%, more preferably 1.5%-3%;

d) the disintegrant selected from the group consisting of croscarmellose sodium, hypromellose-K4M, crospovidone, sodium carboxymethyl starch and a combination thereof, wherein the content of the disintegrant is 5%-15%; and

e) the lubricant selected from the group consisting of magnesium stearate, talcum powder, glycerol monostearate, sodium stearyl fumarate and a combination thereof, wherein the content of the lubricant is 0.1%-1%, more preferably 0.4%-0.5%, more preferably 0.48%-0.5%;

wherein the particle size of the active ingredient is D90 ⩽ 35~~0~~μm.~~re~~

In another preferred example, the particle size of the active ingredient is D90 ≤ 30 μm. In another preferred example, the particle size of the active ingredient is D90 ≤ 20 μm. In another preferred example, the particle size of the active ingredient is D90 ⩽ 10μm. In another preferred example, the particle size of the active ingredient is D90 ~~lycerol monostearate, sodium stearyl fumarate, and a combination thereof, the conte~~ = 1μm ~~l~~ to 30μm. ~~lyce~~In another preferred example, the particle size of the active ingredient is D90 = 1 μm to 20 μm. In another preferred example, the particle size of the active ingredient is D90 = 1 μm to 10 μm or D90 = 10 μm to 20 μm.

In another preferred example, the solid pharmaceutical ~~-~~formulation is a tablet.

In another preferred example, the content of the active ingredient is 5 mg - 100 mg. In another preferred example, the content of the active ingredient is 10 mg - 50 mg. In another preferred example, the content of the active ingredient is 10 mg, 20 mg or 40 mg.

In another preferred example, the binder is selected from the group consisting of hypromellose-E5, hypromellose-K4M, hypromellose-E50, carbopol, polyvinyl alcohol and a combination thereof.

In another preferred example, the binder is hypromellose-E5.

In another preferred example, the filler is microcrystalline cellulose ~~or~~ and lactose.

In another preferred example, the disintegrant is croscarmellose sodium or hypromellose-K4M.

In another preferred example, the solid pharmaceutical formulation comprises the following components based on the total dry weight of the solid pharmaceutical formulation: a) the active ingredient: ((1S,2R,5S)-2-(((5-fluoropyridin-2-yl)oxy)methyl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-2-(pyrimidin-2-yl)phenyl)methanone, or a pharmaceutically acceptable salt thereof, or a mixture of both, wherein the content of the active ingredient is 4%-10%;

b) the microcrystalline cellulose with a content of 24%-27.5%;

c) the lactose with a content of 48.5%-56.5%;

d) the hypromellose-E5 with a content of 1.5%-3%;

e) the croscarmellose sodium or hypromellose-K4M with a content of 5%-15%; and

f) the magnesium stearate with a content of 0.4%-0.5%;

wherein the particle size of the active ingredient is D90 ⩽ 35 μm, or D90 ≤ 30 μm, or D90 ≤ 20 μm, or D90 ≤ 10 μm, or D90 = 1 μm to 30 μm, or D90 = 1 μm to 20 μm, or D90 =1 μm to 10 μm, or D90 = 10 μm to 20 μm.

In another preferred example, the solid pharmaceutical formulation comprises the following components based on the total dry weight of the solid pharmaceutical formulation:

a) the active ingredient: ((1S,2R,5S)-2-(((5-fluoropyridin-2-yl)oxy)methyl)-8-azabicyclo[3.2.1]octan-8-yl)(5-methyl-2-(pyrimidin-2-yl)phenyl)methanone, or a pharmaceutically acceptable salt thereof, or a mixture of both, wherein the content of the active ingredient is 9.5%-10%;

b) the microcrystalline cellulose with a content of 24%-27.5%;

c) the lactose with a content of 48.5%-56.5%;

d) the hypromellose-E5 with a content of 1.5% to 3%;

e) the croscarmellose sodium or hypromellose-K4M with a content of 5% to 15%; and

f) the magnesium stearate with a content of 0.48% to 0.5%;

wherein the particle size of the active ingredient is D90 = 1 μm to 30 μm, or D90 = 1 μm to 20 μm, or D90 = 1 μm to 10 μm, or D90 = 10 μm to 20 μm, and the solid pharmaceutical formulation is a tablet.

In another preferred example, the lactose is 200 mesh, 100 mesh, 50 mesh and the like. More preferably, the lactose is 200 mesh.

In another preferred example, the filler is microcrystalline cellulose ~~or~~ and lactose. The weight ratio of microcrystalline cellulose to lactose is (24-27.5):(48.5-56.5).

In another preferred example, the solid pharmaceutical formulation comprises any one of tablets in the preparation example.

In another aspect, the present invention provides a unit dosage form, based on a total weight of the unit dosage form, the unit dosage form comprises: about 10 mg, about 20 mg, or about 40 mg of an active ingredient, wherein the active ingredient is a compound of formula (II); about 25 mg to about 150 mg of microcrystalline cellulose (for example, microcrystalline cellulose PH101); about 50 mg to about 300 mg of lactose (for example, Granulac 200); about 1 mg to about 15 mg of hypromellose (for example, hypromellose E5); about 10 mg to about 50

FIG. 8 is a graph showing the in vitro dissolution curves of the formulations of Preparation Examples 2-8 and Preparation Example 6, using phosphate buffer at pH 6.8 as the dissolution medium.

FIG. 9 is a graph showing the in vitro dissolution curves of the formulations of Preparation Examples 2-8 and Preparation Example 6, using 0.1 N HCl as the dissolution medium.

FIG. 10 is a three-dimensional ellipsoid structure of the single crystal of the compound of formula (II).

Preparation method

The solid pharmaceutical formulation of the present invention can be prepared by methods well known in the art. For example, in the case of granule, the compound represented by formula (I) or formula (II) or a pharmaceutically acceptable salt thereof and an excipient, a binder, a disintegrant, a wetting agent and the like can be mixed, and subjected to stirring granulation, extrusion granulation, rotary granulation, one-step spray granulation and the like, or direct dry granulation as required to prepare the granule. In addition, the granule can also be prepared by applying medicine to pellets. In addition, granulation and grinding can also be carried out as required. Furthermore, excipients, disintegrants, binders, antioxidants, colorants and the like can be further added to the above granule for tableting.

For further illustration, the uncoated tablet (plain tablet) or the coated tablet of the present invention can be prepared by the following preparation process by changing the added amount or the corresponding component according to different prescriptions. The preparation process includes: grinding the active pharmaceutical ingredient, sieving the auxiliary material, weighing, mixing and granulating, wet granule sizing, drying, dry granule sizing, final mixing, tableting, and coating (required when preparing a coated tablet).

Grinding the active pharmaceutical ingredient: the particle size of qualified active pharmaceutical ingredient (the compound of formula (I) or formula (II), the pharmaceutically acceptable salt thereof, or the mixture thereof) should be 120-150 μm, which can be achieved by adjusting different parameters of grinding equipment. (1) Particle size control D90 ⩽ 10 μm, D90 ⩽ 20, u μm or D90 or ⩽ 30μm: pass the qualified active

pharmaceutical ingredient (the compound of formula (I) or formula (II), the pharmaceutically acceptable salt thereof, or the mixture thereof) through a sieve, then add into a jet mill for grinding, control the particle size of the ground active pharmaceutical ingredient by controlling the rotary speed of the feeder at 100 to 500 rpm, adjusting the feed pressure to 3 to 7 bar and the grinding pressure to 2 to 7 bar, and then measure the particle size distribution by a laser particle size distribution analyzer, in which the particle size distribution should meet the particle size D90≤10str μm, D90≤20r μm, or D90≤30r μm; or (2) particle size control D90 ≤50pa μm: taking the qualified active pharmaceutical ingredient (of formula (I) or formula (II)), grinding by a laboratory shear pulverizer, grinding 3 minutes with an interval of 5 minutes, after grinding for a certain period of time, measuring the particle size of the active pharmaceutical ingredient, in which the particle size distribution measured by a laser particle size distribution analyzer should meet D90≤50tsf μm.

Sieving the auxiliary material: obtain a qualified auxiliary material, lactose (Granulac 200 mesh).

Weighing: weigh the active pharmaceutical ingredient (ground), microcrystalline cellulose (PH101), lactose (Granulac 200 mesh) (sieved), hypromellose-E5, croscarmellose sodium or hypromellose-K4M (with a disintegrant added).

Mixing and granulating: pulping, i.e., binder preparation: weigh 300g of purified water, add 30 g of hypromellose-E5 while stirring, keep stirring until dissolved to obtain a 10% hypromellose-E5 aqueous solution, pass through a 60-mesh sieve and reserve. Mixing, i.e.: add the active pharmaceutical ingredient (ground) and lactose (sieved) into a wet mixing granulator successively to start stirring and mixing with a stirring speed of 300-500 rpm (for example, 300 rpm or 400 rpm), a chopping speed of 350-400 rpm or 400-500 rpm (for example, 400 rpm), and a stirring time of 300 seconds; open the pot cover, add croscarmellose sodium or hypromellose-K4M (with a disintegrant added), microcrystalline cellulose (PH101) into the pot successively to start stirring and mixing with a stirring speed of 300-500 rpm (for example, 350 rpm or 400 rpm), a chopping speed of 400-500 rpm (preferably 400 rpm), and a stirring time of 600 seconds. Preparing damp mass, the whole process of which is divided into two stages, a first stage: open the wet mixing granulator with pre-set parameters, set the stirring speed to 350-500 rpm (for example, 350 rpm), and the cutting speed to 1000-1500 rpm (for example, 1000 rpm), run for 10 seconds, then slowly add all of 10% (w/w) hypromellose-E5 aqueous binder into the

wet mixing granulator, after adding the binder solution, homogenize the obtained wet granules with stirring paddle and chopper until no obvious agglomerates exist, in which the granulation time (slurry adding time) is ⩽~~the~~ 300 seconds (for example, 60s); and a second stage: set the stirring speed to 500 rpm or 350 rpm, and the cutting speed to 1500 rpm or 1000 rpm, start stirring and cutting at the same time, and continue stirring and cutting for 60s to prepare suitable wet granules.

Wet granule sizing: subject the resulting wet granules to granule sizing by passing through a 18-mesh stainless steel sieve in a swing granule sizing machine or to manually wet granule sizing by passing through a 20-mesh sieve.

Drying: spread the wet granules after granule sizing evenly in a baking tray, in which the thickness of spread wet granules in the tray should be 1.5 cm ± 0.5 cm, put the baking tray with the spread wet granules into an oven to start drying with a drying temperature of 65.0° C ± 5.0°C. Turn the spread wet granules in the tray over and measure the moisture content of the granules for every 30 minutes of drying until the drying end point when the moisture content of the granules after drying ⩽ 2.0%.

Dry granule sizing: subject the dried granules to granule sizing by passing through a 20-mesh stainless steel sieve in a swing granule sizing machine.

Final mixing: add croscarmellose sodium or hypromellose-K4M (with a disintegrant added), the granules after dry granule sizing and magnesium stearate into a mixer at the same time and mix for 300 seconds with a mixing speed of 16 rpm. After final mixing, the total moisture content of the granules should be ⩽ 3.0%.

Tableting: obtain the final mixed granules of the active pharmaceutical ingredient, and subject to tableting by a rotary tableting machine.

Coating: coat the plain tablets obtained by tableting to obtain a desired coating weight gain of 2% to 3%. The stomach-soluble film coating premix is selected as the coating material, and the concentration of the coating solution is 15%. The specific preparation method comprises: taking 30 g of coating powder, adding into 200 g of purified water, and stirring to disperse evenly to obtain the coating solution (formulated according to 200% of the weight gain at 3%), and then coating the tablets by a high-efficiency coater. Coating can be carried out by using the following process parameters.

Inlet air temperature (°C)	55.0-65.0

croscarmellose sodium is croscarmellose sodium SD711 in the specific formulations in the following preparation examples.

Preparation Example 1-1 Uncoated plain tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	4%
microcrystalline cellulose	26.16%
lactose	56.32%
hypromellose-E5	3.04%
croscarmellose sodium	10%
magnesium stearate	0.48%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 6 –to 7 bar, the inlet pressure of 7 –to 8 bar, the feed pressure of 6 –to 7 bar, and the feed rotary speed of 100 –to 150 rpm. After the grinding was completed, samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 10μm (D90 = 7.461 μm)~~– μ 0and t = 7.461 μ .461.~~ The compound of formula (II) with the particle size of D90 ≤ 10 μm (D90 = 7.461 μm) and lactose were added into a wet mixing granulator, stirred and mixed, and then microcrystalline cellulose and croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%. Then dry granule sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted to prepare uncoated plain tablets having a specification of 500 mg.

Preparation Example 1-2 Uncoated plain tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	4%
microcrystalline cellulose	26.16%
lactose	56.32%
hypromellose-E5	3.04%

croscarmellose sodium	10%
magnesium stearate	0.48%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 4 –to 6 bar, the inlet pressure of 6 –to 7 bar, the feed pressure of 5 –to 6 bar, and the feed rotary speed of 200 –to 300 rpm. Samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 20μm (D90 = 17.89 μm). μ 0and t = 17.89 μ 7.89The compound of formula (II) with D90 ≤ 20 μm (D90 = 17.89 μm) and lactose were added into a wet mixing granulator, stirred and mixed, and then microcrystalline cellulose and croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%. Then dry granule sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted to prepare uncoated plain tablets having a specification of 500 mg.

Preparation Example 1-3 Uncoated plain tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	4%
microcrystalline cellulose	26.16%
lactose	56.32%
hypromellose-E5	3.04%
croscarmellose sodium	10%
magnesium stearate	0.48%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 2 –to 4 bar, the inlet pressure of 4 –to 5 bar, the feed pressure of 3 –to 4 bar, and the feed rotary speed of 300 –to 400 rpm. After the grinding was completed, samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 35μm (D90 = 30.7 μm). μ 5and t = 30.7 μ 0.7dThe compound of formula (II) with D90 ≤ 35 μm (D90 = 30.7 μm) and lactose were added into a wet

mixing granulator, stirred and mixed, and then microcrystalline cellulose and croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ≤ ~~e~~ 2.0%. Then dry granule sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted to prepare uncoated plain tablets having a specification of 500 mg.

Preparation Example 1-4 Uncoated plain tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	4%
microcrystalline cellulose	26.16%
lactose	56.32%
hypromellose-E5	3.04%
croscarmellose sodium	10%
magnesium stearate	0.48%

After the compound of formula (II) was passed through a 20-mesh sieve, the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 150μm ~~μ 5~~ (D90 = 144.5 μm). The compound of formula (II) with the particle size of D90 ≤ 150 μm (D90 = 144.5 μm) and lactose were added into a wet mixing granulator, stirred and mixed, and then microcrystalline cellulose and croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%. Then dry granule sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted to prepare uncoated plain tablets having a specification of 500 mg.

Preparation Example 2-1 Coated tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	9.76%
microcrystalline cellulose	24.88%

lactose	49.76%
hypromellose-E5	2.93%
croscarmellose sodium	9.76%
magnesium stearate	0.49%
film coating premix	2.44%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 4 –to 6 bar, the inlet pressure of 6 –to 7 bar, the feed pressure of 5 –to 6 bar, and the feed rotary speed of 200 –to 300 rpm. Samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 20μm (D90 = 17.89 μm)-. ~~-μ 0and t = 17.89 -μ 7.89~~The compound of formula (II) with the particle size of D90 ≤ 20 μm (D90 = 17.89 μm) and lactose were added into a wet mixing granulator, stirred and mixed, and then microcrystalline cellulose and croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ≤ 2.0%. Then dry granule ~~ellose sodium wergranule~~ sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted and coated with a stomach-soluble film coating premix to prepare tablets having a specification of ~~in a mixer5 aqueous solution was slowly added into the wet mixing granulator for performing wet gratablets having a specification of~~ 205 mg.

Preparation Example 2-2 Coated tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	9.76%
microcrystalline cellulose	24.88%
lactose	49.76%
hypromellose-E5	2.93%
croscarmellose sodium	9.76%
magnesium stearate	0.49%
film coating premix	2.44%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 4 –to 6 bar, the inlet pressure of 6 –to 7 bar, the feed pressure of 5 –to 6 bar, and the feed rotary speed of 200 –to 300 rpm. Samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 20μm (D90 = 17.89 μm). μ 0and t = 17.89 μ 7.89The compound of formula (II) with D90 ≤ 20 μm (D90 = 17.89 μm) and lactose were added into a wet mixing granulator, stirred and mixed, and then microcrystalline cellulose and croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%. Then dry granule sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted and coated with a stomach-soluble film coating premix to prepare tablets having a specification of 410mg.

Preparation Example 2-3 Coated tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	9.76%
microcrystalline cellulose	24.88%
lactose	49.76%
hypromellose-E5	2.93%
croscarmellose sodium	9.76%
magnesium stearate	0.49%
film coating premix	2.44%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 6 –to 7 bar, the inlet pressure of 7 –to 8 bar, the feed pressure of 6 –to 7 bar, and the feed rotary speed of 100 –to 150 rpm. After the grinding was completed, samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 10μm (D90 = 7.461 μm). μ 0and t = 7.461 μ .461The compound of formula (II) with the particle size of D90 ≤ 10 μm (D90 = 7.461 μm) and lactose were added into a wet mixing granulator, stirred and mixed, and then microcrystalline cellulose and

croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%. Then dry granule sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted and coated with a stomach-soluble film coating premix to prepare tablets having a specification of 205 mg.

Preparation Example 2-4 Coated tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	9.76%
microcrystalline cellulose	24.88%
lactose	49.76%
hypromellose-E5	2.93%
croscarmellose sodium	9.76%
magnesium stearate	0.49%
film coating premix	2.44%

The compound of formula (II) was passed through a 20-mesh sieve, and ground by a laboratory shear pulverizer, grinding 3 minutes with an interval of 5 minutes. After grinding for 10 minutes, the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 50μm~~μ0~~ (D90 = 45.71 μm). The compound of formula (II) with the particle size of D90 ≤ 50 μm (D90 = 45.71 μm) and lactose were added into a wet mixing granulator, stirred and mixed, and then microcrystalline cellulose and croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%. Then dry granule sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted and coated with a stomach-soluble film coating premix to prepare tablets having a specification of 205 mg.

Preparation Example 2-5 Coated tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	9.76%
microcrystalline cellulose	24.88%
lactose	49.76%
hypromellose-E5	2.93%
croscarmellose sodium	9.76%
magnesium stearate	0.49%
film coating premix	2.44%

After the compound of formula (II) was passed through a 20-mesh sieve, the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 150μm~~-μ 5~~ (D90 = 144.5 μm). The compound of formula (II) with the particle size of D90 ≤ 150 μm (D90 = 144.5 μm) and lactose were added into a wet mixing granulator, stirred and mixed, and then microcrystalline cellulose and croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%. Then dry granule sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted and coated with a stomach-soluble film coating premix to prepare tablets having a specification of 205 mg.

Preparation Example 2-6 Uncoated plain tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	10%
microcrystalline cellulose	25.5%
lactose	51%
hypromellose-E5	3%
croscarmellose sodium	10%
magnesium stearate	0.5%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 4 –to 6 bar, the inlet pressure of 6 –to 7 bar, the feed pressure of 5 –to 6 bar, and

the feed rotary speed of 200 –to 300 rpm. Samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 20μm (D90 = 17.89 μm)-. μ 0and t = 17.89 μ 7.89The compound of formula (II) with the particle size of D90 ≤ 20 μm (D90 = 17.89 μm) and lactose were added into a wet mixing granulator, stirred and mixed, and then microcrystalline cellulose and croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%.d t Then dry granule hee sodium wergranule sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted to prepare uncoated tablets having a specification of 200mg.

Preparation Example 2-7 Uncoated plain tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	10%
microcrystalline cellulose	25.5%
lactose	51%
hypromellose-E5	3%
croscarmellose sodium	10%
magnesium stearate	0.5%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 4 –to 6 bar, the inlet pressure of 6 –to 7 bar, the feed pressure of 5 to– 6 bar, and the feed rotary speed of 200 to– 300 rpm. Samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 20-μm (D90 = 17.89 μm)-. μ 0and t = 17.89 μ 7.89The compound of formula (II) with the particle size of D90 ⩽ 20 μm (D90 = 17.89 μm) μ 00red = 17.89 μm) and lactose were added, stirred and mixed, and then microcrystalline cellulose and croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%.d Then dry granulethee sodium wergranule sizing was performed. The resulting granules after dry granule sizing,

croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ≤ 3.0%. in a mixerd and mixed. The granules were tableted to prepare uncoated plain tablets having a specification of 400 mg.

Then 10% (mass percentuncoated tablets having a specification of 400mg.

Preparation Example 2-8 Coated tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	9.76%
microcrystalline cellulose	24.88%
lactose	49.76%
hypromellose-E5	2.93%
croscarmellose sodium	9.76%
magnesium stearate	0.49%
film coating premix	2.44%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 6 –to 7 bar, the inlet pressure of 7 to– 8 bar, the feed pressure of 6 to– 7 bar, and the feed rotary speed of 100 to– 150 rpm. After the grinding was completed, samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ≤ 10μm (D90 = 8.93 μm) μ 0and t = 8.93d m). The compound of formula (II) with the particle size of D90 ≤ 10 μm (D90 = 8.93 μm) and lactose were added into a wet mixing granulator, stirred and mixed, and then microcrystalline cellulose and croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ≤ 2.0%. Then dry granule d themass percentgranule sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ≤ 3.0%. The granules were tableted and coated with a stomach-soluble film coating premix to prepare tablets having a specification of 205 mg.in a mixerE5 aqueous solution was slowly added into the wet mixing granulator for performing wet grtablets having a specification of 205 mg.

Preparation Example 3 Uncoated plain tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	4%
microcrystalline cellulose	26.2%
lactose	56.3%
hypromellose-E5	3%
croscarmellose sodium	10%
magnesium stearate	0.48%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 6 –to 7 bar, the inlet pressure of 7 to– 8 bar, the feed pressure of 6 to– 7 bar, and the feed rotary speed of 100 to– 150 rpm. After the grinding was completed, samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 10μm (D90 = 7.461 μm). ~~μ 0and t = 7.461 μ .461~~The compound of formula (II) with the particle size of D90 ≤ 10 μm (D90 = 7.461 μm), lactose, and microcrystalline cellulose were added into a wet mixing granulator, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ≤ 2.0%. Then dry granule sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted to prepare tablets having a specification of 500mg.

Preparation Example 4-1 Uncoated plain tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	10%
microcrystalline cellulose	24.3%
lactose	48.7%
hypromellose-E5	1.5%
hypromellose-K4M	15%
magnesium stearate	0.5%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 4 –to 6 bar, the inlet pressure of 6 to– 7 bar, the feed pressure of 5 to– 6 bar, and the feed rotary speed of 200 to– 300 rpm. Samples were taken and tested, and the particle size

distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 20μm (D90 = 17.89 μm). ~~μ 0and t = 17.89 μ 7.89~~The compound of formula (II) with D90 ≤ 20 μm (D90 = 17.89 μm), lactose, microcrystalline cellulose and hypromellose-K4M were added into a wet mixing granulator, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%. Then dry granule sizing was performed. The resulting granules after dry granule sizing, hypromellose-K4M and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted to prepare tablets having a specification of 200mg.

Preparation Example 4-2 Uncoated plain tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	10%
microcrystalline cellulose	27.5%
lactose	55%
hypromellose-E5	2%
hypromellose-K4M	5%
magnesium stearate	0.5%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 4 –to 6 bar, the inlet pressure of 6 to 7 bar, the feed pressure of 5 to 6 bar, and the feed rotary speed of 200 to 300 rpm. Samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 20μm (D90 = 17.89 μm). ~~μ 0and t = 17.89 μ 7.89~~The compound of formula (II) with D90 ≤ 20 μm (D90 = 17.89 μm), lactose, microcrystalline cellulose and hypromellose-K4M were added into a wet mixing granulator, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%. Then dry granule sizing was performed, and the resulting granules after dry granule sizing, hypromellose-K4M and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted to prepare tablets having a specification of 200mg.

Preparation Example 4-3 Uncoated plain tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	10%
microcrystalline cellulose	25.8%
lactose	51.7%
hypromellose-E5	2%
hypromellose-K4M	10%
magnesium stearate	0.5%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 4 –to 6 bar, the inlet pressure of 6 to– 7 bar, the feed pressure of 5 to– 6 bar, and the feed rotary speed of 200 to– 300 rpm. Samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 20μm (D90 = 17.89 μm). ~~μ 0and t = 17.89 μ 7.89~~The compound of formula (II) with D90 ≤ 20 μm (D90 = 17.89 μm), lactose, microcrystalline cellulose and hypromellose-K4M were added into a wet mixing granulator, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%. Then dry granule sizing was performed, and the resulting granules after dry granule sizing, hypromellose-K4M and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted to prepare tablets having a specification of 200mg.

Preparation Example 5 Coated tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	9.8%
microcrystalline cellulose	25%
lactose	50%
hypromellose-E5	2.94%
croscarmellose sodium	9.8%
magnesium stearate	0.49%
film coating premix	1.96%

The compound of formula (II) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 4 –to 6 bar, the inlet pressure of 6 to– 7 bar, the feed pressure of 5 to– 6 bar, and the feed rotary speed of 200 to– 300 rpm. Samples were taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 20μm (D90 = 17.89 μm). μ 0and t = 17.89 μ 7.89The compound of formula (II) with D90 ≤ 20 μm (D90 = 17.89 μm) and lactose were added into a wet mixing granulator, stirred and mixed, and then microcrystalline cellulose and croscarmellose sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ⩽ 2.0%. Then dry granule sizing was performed. The resulting dry granules, croscarmellose sodium and magnesium stearate were finally mixed in a mixer. The total moisture content of the granules after final mixing was ⩽ 3.0%. The granules were tableted and coated with a stomach-soluble film coating premix to prepare tablets having a specification of 102mg.

Preparation Example 6 Coated tablet formulation

Tablet formulation comprising the compound of formula (II) (mass percent):

compound of formula (II)	9.76%
microcrystalline cellulose	24.88%
lactose	49.76%
hypromellose-E5	2.93%
croscarmellose sodium	9.76%
magnesium stearate	0.49%
film coating premix	2.44%

The compound of formula (II) (in crystalline form B) was passed through a 20-mesh sieve, and then the sieved active pharmaceutical ingredient was added into a jet mill and ground under the grinding pressure of 6 –to 7 bar, the inlet pressure of 7 to– 8 bar, the feed pressure of 6 to– 7 bar, and the feed rotary speed of 100 to– 150 rpm. Samples was taken and tested, and the particle size distribution was measured by a laser particle size distribution analyzer, showing the particle size D90 ⩽ 20μm (D90 = 10.09 μm). μ 0and t = 10.09 μ 0.09The compound of formula (II) with the particle size of D90 ≤ 20 μm (D90 = 10.09 μm) and lactose were added into a wet mixing granulator, stirred and mixed, and then microcrystalline cellulose and croscarmellose

sodium were added, stirred and mixed. Then 10% (mass percent) hypromellose-E5 aqueous solution was slowly added into the wet mixing granulator for performing wet granulation. The resultant was subjected to wet granule sizing and dried in an oven. The moisture content of the dried granules was ≤ 2.0%. Then dry granule ~~d thewas slowly agranule~~ sizing was performed. The resulting granules after dry granule sizing, croscarmellose sodium and magnesium stearate were finally mixed in a mixer, the total moisture content of the granules after final mixing was ≤ 3.0%. The granules were tableted and coated with a stomach-soluble film coating premix to prepare tablets having a specification of 205 mg.~~or performing wet granulationution was slowly added for mach soluble film coating premix to prepare tablets having a specification of 205 mg.~~

Test Example 1 In vitro dissolution test

According to the second method of Chinese Pharmacopoeia 2015 4th Edition General Principles 0931, the tablet formulations prepared in the above preparation examples were subjected to an in vitro dissolution test to detect their dissolution levels in a phosphate buffer under pH 6.8, in which the dissolution device used paddle method, the dissolution medium was a pH 6.8 buffer, the water bath temperature was 37.0±0.5°C, the dissolution volume was 900ml, the rotation speed was 50 rpm, the sampling time was 5min, 10min, 15min, 20min, 30min, 45min, 60min, the sampling volume was 5ml, and the filter membrane was polyethersulfone filter. The test results were shown in the following Tables 1-1 to 1-5 and FIGs 1 to 5.

Table 1-1 In vitro dissolution results of Preparation Examples 1-1 to 1-4

T, min	Preparation Example1-4		Preparation Example1-3		Preparation Example1-2		Preparation Example1-1	
	Dissolution Level,%	RSD	Dissolution Level,%	RSD	Dissolution Level,%	RSD	Dissolution Level,%	RSD
0	0	0	0	0	0.0	0	0	0
5	11	10.1	35.6	2.6	29.6	2.1	38.8	6.5
10	30.3	48.3	47.5	4.1	48.0	1.9	52.5	2.1
15	27.9	1.2	54.6	4.5	58.6	1.0	61.5	1.8
20	33.3	3.1	59.3	0.1	65.9	0.4	68.2	0.7
30	41.4	1.3	66.8	1.0	75.4	1.2	75.4	0.6
45	47.1	0.9	75.7	0.9	82.0	0.4	82.4	0.6
60	51.3	3.9	79.5	0.7	86.5	1.0	86.9	0.8

Table 1-2 In vitro dissolution results of Preparation Examples 2-1, 2-2, 2-6 and 2-7

Blood collection: forelimb venous blood collection was used. Blood collection time was each administration day (i.e., Day 1, Day 5, Day 8, Day 12 and Day 15). Blood collection time points were before administration (0h), 5min, 15min, 30min, 1h, 2h, 4h, 6h, 8h and 24h after administration. About 1 mL of blood was collected in EDTA dipotassium anticoagulant vacuum blood collection tube. After blood collection, the blood collection tube was shaken gently to mix blood and anticoagulant thoroughly. Blood was placed in crushed ice after collection, and centrifuged (4°C, 2000 g, 10 min) within 1 hour after collection. After centrifugation, about 400 μL of plasma was collected in a brown plastic tube, and immediately stored in a container of dry ice, then transferred to an ultra-low temperature refrigerator (≤-65° C) and stored in the dark.

Sample analysis: HPLC-MS/MS method was used to detect the concentration of the active ingredients in the sample, and Microsoft Excel 2013 was used for data processing and calculation. After analyzing and measuring the concentration of samples in plasma, the concentration-time curve was plotted by WinNonlin6.3 software, and the pharmacokinetic parameters were calculated according to the non-compartmental model. The results of the pharmacokinetic parameters of the corresponding formulations are shown in the ~~followign~~ following Table 3-1, Table 3-2 and Table 3-3, respectively. The results in the same table are obtained by testing in the same batch, and the results in different tables are obtained by testing in different batches.

Table 3-1 Oral bioavailability of Preparation Examples 1-~~1~~4, 1-~~2~~ 3 and ~~2-4~~1-2

Preparation Example	Preparation Example1-4	Preparation Example1-3	Preparation Example1-2
		2mpk	
AUC_{0-t} (hr*ng/mL)	888	1537	2096
$AUC_{0-\infty}$ (hr*ng/mL)	1069	1804	2169
T_{max}(h)	1.17	0.667	1.33
C_{max}(ng/mL)	288	708	827
F(%)	53.1	89.7	108

Table 3-2 Oral bioavailability of Preparation Examples 2-1, 2-3 and 2-5