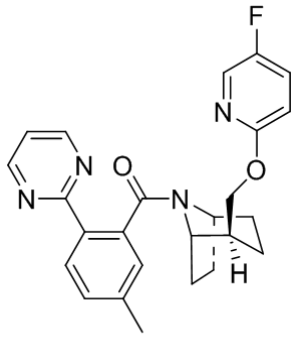
CLAIMS

1. A solid pharmaceutical formulation, wherein the solid pharmaceutical formulation comprises an active ingredient, and the active ingredient is a compound of formula (II) or a pharmaceutically acceptable salt thereof, or a mixture of both;



(II)

and the particle size of the active ingredient is D90 $\leqslant$ 35 μm.

2. The solid pharmaceutical formulation according to claim 1, wherein the particle size of the active ingredient is D90 $\leqslant$ 20 μm.

3. The solid pharmaceutical formulation according to claim 1, wherein the content of the active ingredient is 1%-15% based on the total dry weight of the solid pharmaceutical formulation.

4. The solid pharmaceutical formulation according to claim 1, wherein the solid pharmaceutical formulation further comprises a 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% based on the total dry weight of the solid pharmaceutical formulation.

5. The solid pharmaceutical formulation according to claim 1, wherein 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, wherein the content of the filler is 60%-90% based on the total dry weight of the solid pharmaceutical formulation.

6. The solid pharmaceutical formulation according to claim 1, wherein 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, wherein the content of the disintegrant is 5%-15% based on the total dry weight of the solid pharmaceutical formulation.

7. The solid pharmaceutical formulation according to claim 1, wherein 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, wherein the content of the lubricant is 0.1%-1% based on the total dry weight of the solid pharmaceutical formulation.

8. The solid pharmaceutical formulation according to claim 1, wherein the solid pharmaceutical formulation is a tablet, a capsule, a powder, a granule, a drop pill or a film.

9. The solid pharmaceutical formulation according to claim 1, wherein 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%;

b) 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, wherein the content of the filler is 60%-90%;

c) a 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%;

d) a 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) a 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%;

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.

10. The solid pharmaceutical formulation according to claim 1, wherein 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) microcrystalline cellulose with a content of 24%-27.5%;

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

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

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

f) 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.

11. The solid pharmaceutical formulation according to claim 1, wherein 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) microcrystalline cellulose with a content of 24%-27.5%;

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

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

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

f) magnesium stearate with a content of 0.48%-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.

12. A method for preparing a tablet, wherein the method comprises the following steps:

(a) performing wet granulation after mixing an active ingredient particle, a filler, a binder and a first disintegrant;

(b) drying a resulting product obtained in step (a);

(c) dry-blending a resulting product obtained in step (b), a second disintegrant and a lubricant; and

(d) compressing a resulting product obtained in step (c) into the tablet;

wherein the active ingredient is ((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; and

the particle size of the active ingredient particle is D90 ≤ 35μm.

13. The method according to claim 12, wherein the content of the active ingredient is 4%-10% based on the total dry weight of the mixture obtained in step (c).

14. The method according to claim 12, wherein the content of the filler is 73%-82.5% based on the total dry weight of the mixture obtained in step (c).

15. The method according to claim 12, wherein the content of the binder is 1.5%-3% based on the total dry weight of the mixture obtained in step (c).

16. The method according to claim 12, wherein the content of the first disintegrant is 2%-

10% based on the total dry weight of all components in step (a); and wherein the content of the second disintegrant is 5%-10%, based on the total dry weight of all components in step (c).

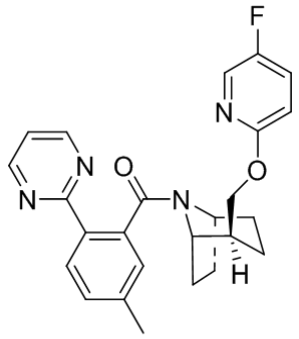
17. The method according to claim 12, wherein the content of the lubricant is 0.1%-1% based on the total dry weight of all components in step (c).

18. The method according to claim 12, wherein the method further comprises:

(e) coating a resulting product obtained in step (d).

19. A unit dosage form, wherein based on a total weight of the unit dosage form, the unit dosage form comprises:

10 mg, 20 mg, or 40 mg of an active ingredient, wherein the active ingredient is a compound of formula (II);



(II)

25 mg to 150 mg of microcrystalline cellulose;

50 mg to 300 mg of lactose;

1 mg to 15 mg of hypromellose;

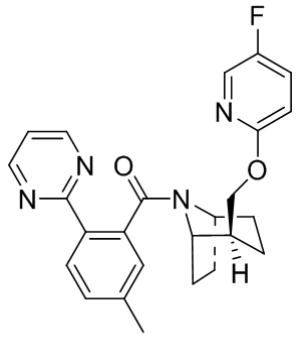
10 mg to 50 mg of croscarmellose sodium; and

0.5 mg to 3 mg of magnesium stearate,

wherein the particle size of the active ingredient is D90 = 1 μm to 20 μm; or

wherein based on a total weight of the unit dosage form, the unit dosage form comprises:

8 mg to 12 mg of an active ingredient, wherein the active ingredient is a compound of formula (II);



(Ⅱ)

20 mg to 30 mg of microcrystalline cellulose;

46 mg to 56 mg of lactose;

2 mg to 4 mg of hypromellose;

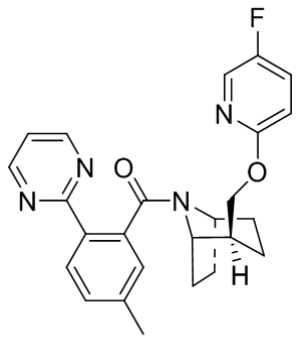
5 mg to 15 mg of croscarmellose sodium; and

0.3 mg to 0.7 mg of magnesium stearate,

wherein the particle size of the active ingredient is D90 = 1 μm to 20 μm; or

wherein based on a total weight of the unit dosage form, the unit dosage form comprises:

18 mg to 22 mg of an active ingredient, wherein the active ingredient is a compound of formula (II);



(Ⅱ)

46 mg to 56 mg of microcrystalline cellulose;

97 mg to 107 mg of lactose;

5 mg to 7 mg of hypromellose;

15 mg to 25 mg of croscarmellose sodium; and

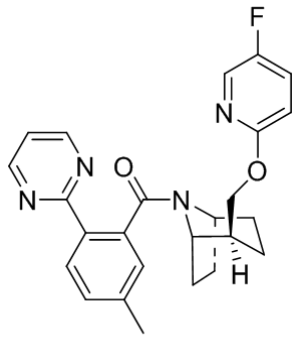
0.8 mg to 1.2 mg of magnesium stearate,

wherein the particle size of the active ingredient is D90 = 1 μm to 20 μm; or

wherein based on a total weight of the unit dosage form, the unit dosage form

comprises:

38 mg to 42 mg of an active ingredient, wherein the active ingredient is a compound of formula (II);



(II)

97 mg to 107 mg of microcrystalline cellulose;

199 mg to 209 mg of lactose;

11 mg to 13 mg of hypromellose;

35 mg to 45 mg of croscarmellose sodium; and

1.8 mg to 2.2 mg of magnesium stearate,

wherein the particle size of the active ingredient is D90 = 1 μm to 20 μm.

20. The solid pharmaceutical formulation according to claim 1 or the unit dosage form according to claim 19, wherein the compound of formula (II) as the active ingredient exists in crystalline form A or crystalline form B.

21. The unit dosage form according to claim 19, wherein the unit dosage form is a tablet or a capsule.

22. Use of the solid pharmaceutical formulation according to any one of claims 1 to 11, or the unit dosage form according to claim 19 in the manufacture of a medicament for treating an orexin-associated disease, wherein the orexin-associated disease include insomnia, chronic obstructive pulmonary disease, obstructive sleep apnea, somnolence, anxiety, obsessive-compulsive disorder, panic, nicotine dependence or eating disorder.