dissolution properties even after storage at high humidity, for example, at 90% RH, for example, for 2 weeks. Furthermore, oral solid preparations of the present disclosure comprising a high content (for example, 50% by weight or more) of a DAAO inhibitor may exhibit excellent dissolution properties post-storage. The high DAAO inhibitor content may enable miniaturization of the oral solid preparation, potentially improving patient compliance.

[0007] Non-limiting examples of DAAO inhibitors that are pyridazinone derivatives used in the present disclosure include the compounds described in WO 2013/027000, WO 2015/132608, WO 2013/073577, WO 2014/096757, WO 2019/076329, and the like.

Summary

[0007a] In an aspect, there is provided an oral solid preparation comprising a D-amino acid oxidase (DAAO) inhibitor, a low substituted hydroxypropyl cellulose (L-HPC), and an additive, wherein the DAAO inhibitor is a pyridazinone derivative.

[0007b] In another aspect, there is provided an oral solid preparation comprising:

3% to 60% by weight of 4-hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazine-3(2H)-one;

3% to 15% by weight of a L-HPC;

15% to 85% by weight of a filler;

1% to 10% by weight of a binder; and

0.2% to 3% by weight of a lubricant.

[0007c] In another aspect, there is provided an oral solid preparation comprising:

3% to 60% by weight of 4-hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazine-3(2H)-one;

3% to 15% by weight of a L-HPC;

10% to 75% by weight of mannitol;

5% to 15% by weight of microcrystalline cellulose;

1% to 10% by weight of hydroxypropyl cellulose; and

0.2% to 3% by weight of magnesium stearate.

[0007d] In another aspect, there is provided a method for producing an oral solid preparation as defined above, comprising:

mixing a D-amino acid oxidase inhibitor and an additive to obtain a mixture;

granulating the mixture to obtain at least one granule;

mixing the at least one granule and a L-HPC to obtain at least one mixed granule; and

compressing the at least one mixed granule.

[0007e] In another aspect, there is provided an oral solid preparation as defined above for use as a medicament.

[0007f] In another aspect, there is provided a use of an oral solid preparation as defined above in the manufacture of a medicament for preventing or treating a disease preventable or treatable by a D-amino acid oxidase inhibitor.

[0008] Disclosed herein is an oral solid preparation comprising a D-amino acid oxidase (DAAO) inhibitor, a low-substituted hydroxypropyl cellulose (L-HPC), and an additive, wherein the DAAO inhibitor is a pyridazinone derivative.

[0009] In some examples, the oral solid preparation is a tablet. In some examples, the oral solid preparation is a sugar-coated tablet. In some examples, the oral solid preparation is a film-coated tablet.

[00010] In some examples, the total weight of the oral solid preparation per preparation unit is in the range of 100 mg to 2000 mg.

[00011] In some examples, the oral solid preparation comprises 10 mg to 1000 mg of the DAAO inhibitor per preparation unit. In some examples, the oral solid preparation comprises 50 mg to 600 mg of the DAAO inhibitor per preparation unit. In some examples, the oral solid preparation comprises 10 mg of the DAAO inhibitor per preparation unit. In some examples, the oral solid preparation comprises 25 mg of the DAAO inhibitor per preparation unit. In some examples, the oral solid preparation comprises 50 mg of the DAAO inhibitor per preparation unit. In some examples, the oral solid preparation comprises 100 mg of the DAAO inhibitor per preparation unit. In some examples, the oral solid preparation comprises 125 mg of the DAAO inhibitor per preparation unit. In some examples, the oral solid preparation comprises 250 mg of the DAAO inhibitor per preparation unit.

[00012] In some examples, the DAAO inhibitor is chosen from compounds of Formula (I) as disclosed herein and pharmaceutically acceptable salts thereof.

[00013] In some examples, the DAAO inhibitor is chosen from 4-hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazine-3(2H)-one (“Compound (A)”) and pharmaceutically

acceptable salts thereof. In some examples, the DAAO inhibitor is Compound (A). In some

examples, Compound (A) is in the form of a solvate. In some examples, Compound (A) is in the form of a non-solvate. In some examples, Compound (A) is in the form of a crystalline form of Compound (A). In some examples, Compound (A) is in the form of an amorphous form of Compound (A).

[00014] In some examples, the oral solid preparation comprises 10 mg to 1000 mg of at least one compound chosen from Compound (A) and pharmaceutically acceptable salts thereof per preparation unit. In some examples, the oral solid preparation comprises 50 mg to 600 mg of at least one compound chosen from Compound (A) and pharmaceutically acceptable salts thereof per preparation unit. In some examples, the oral solid preparation comprises 10 mg of at least one compound chosen from Compound (A) and pharmaceutically acceptable salts thereof per preparation unit. In some examples, the oral solid preparation comprises 25 mg of at least one compound chosen from Compound (A) and pharmaceutically acceptable salts thereof per preparation unit. In some examples, the oral solid preparation comprises 50 mg of at least one compound chosen from Compound (A) and pharmaceutically acceptable salts thereof per preparation unit. In some examples, the oral solid preparation comprises 100 mg of at least one compound chosen from Compound (A) and pharmaceutically acceptable salts thereof per preparation unit. In some examples, the oral solid preparation comprises 125 mg of at least one compound chosen from Compound (A) and pharmaceutically acceptable salts thereof per preparation unit. In some examples, the oral solid preparation comprises 250 mg of at least one compound chosen from Compound (A) and pharmaceutically acceptable salts thereof per preparation unit.

[00015] In some examples, the DAAO inhibitor is chosen from compounds of Formula (I)-a as disclosed herein and pharmaceutically acceptable salts thereof.

[00016] In some examples, the solid oral preparation comprises one type of L-HPC. In some examples, the solid oral preparation comprises two or more types of L-HPC.

[00017] In some examples, the L-HPC comprises 5.0% to 16.0% of a hydroxypropoxy group by dry weight.

[00018] In some examples, the L-HPC is chosen from L-HPC LH-11, L-HPC LH-21, LH-31, L-HPC LH-22, L-HPC LH-32, and combinations of any of the foregoing. In some examples, the L-HPC is L-HPC LH-21.

[00019] In some examples, the content of L-HPC in the oral solid preparation is 1% to 20% by weight.

[00020] In some examples, the additive is chosen from fillers, binders, disintegrants, lubricants, glidants, colorants, pH adjusters, surfactants, stabilizers, acidulants, sweeteners, flavors, coating agents, coating additives, and combinations of any of the foregoing. In some examples, the additive is chosen from fillers, binders, disintegrants, lubricants, and combinations of any of the foregoing.

[00021] In some examples, the additive comprises a filler. In some examples, the filler is D-mannitol. In some examples, the filler is microcrystalline cellulose. In some examples, the content of the filler is 10% to 65% by weight. In some examples, the content of the filler is 10% to 85% by weight. In some examples, the content of the filler is 25% to 65% by weight. In some examples, the content of the filler is 25% to 85% by weight.

[00022] In some examples, the additive comprises a binder. In some examples, the binder is hydroxypropyl cellulose. In some examples, the content of the binder is 0.5% to 20% by weight.

[00023] In some examples, the additive comprises a coating agent. In some examples, the coating agent is chosen from water-soluble film coating agents. In some examples, the additive further comprises a coating additive. In some examples, the coating additive is chosen from light-shielding agents, colorants, plasticizers, organic acids, and combinations of any of the foregoing.

[00024] In some examples, the oral solid preparation comprises:

30% to 60% by weight of Compound (A);

3% to 15% by weight of a L-HPC;

15% to 65% by weight of a filler;

1% to 10% by weight of a binder; and

0.2% to 3% by weight of a lubricant.

[00025] In some examples, the oral solid preparation comprises:

3% to 60% by weight of Compound (A);

3% to 15% by weight of a L-HPC;

25% to 85% by weight of a filler;

1% to 10% by weight of a binder; and

0.2% to 3% by weight of a lubricant.

[00026] In some examples, the filler is mannitol and microcrystalline cellulose.

[00027] In some examples, the binder is hydroxypropyl cellulose.

[00028] In some examples, the lubricant is magnesium stearate.

[00029] In some examples, the oral solid preparation further comprises a film coating.

[00030] In some examples, the film coating comprises a coating agent and a coating additive. In some examples, the film coating comprises a coating agent and a light-shielding agent. In some examples, the film coating comprises a coating agent, a light-shielding agent, and a colorant.

[00031] In some examples, the coating agent is chosen from cellulose-based polymers. In some examples, the coating agent is hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and combinations thereof. In some examples, the coating agent is hydroxypropyl cellulose and hydroxypropylmethyl cellulose. In some examples, the coating agent is hydroxypropylmethyl cellulose.

[00032] In some examples, the film coating comprises hydroxypropylmethyl cellulose, titanium dioxide, and hydroxypropyl cellulose.

[00033] In some examples, when performing a dissolution test for an oral solid preparation of the present disclosure using a paddle method (75 rpm, using 900 mL of a 0.05 mol/L phosphate buffer solution (pH 6.8) comprising 0.5% of sodium dodecyl sulfate (SDS)), 70% or more of the DAAO inhibitor dissolves within 30 minutes.

[00034] In some examples, when performing a dissolution test for an oral solid preparation of the present disclosure using a paddle method (50 rpm, using 900 mL of a 0.05 mol/L phosphate buffer solution (pH 6.8) comprising 0.1% of sodium dodecyl sulfate (SDS)) after storing for two weeks at 40°C/90% relative humidity, 70% or more of the DAAO inhibitor dissolves within 30 minutes. In some examples, the oral solid preparation is placed into a glass bottle and stored without a cap for 2 weeks at 40°C/90% relative humidity before performing the dissolution test.

[00035] In some examples, when performing a dissolution test for an oral solid preparation of the present disclosure using a paddle method (50 rpm, using 900 mL of a 0.05 mol/L phosphate buffer solution (pH 6.8)) after storing for two weeks at 40°C/90% relative humidity, 70% or more of the DAAO inhibitor dissolves within 30 minutes. In some

examples, the oral solid preparation is placed into a glass bottle and stored without a cap for 2 weeks at 40°C/90% relative humidity before performing the dissolution test.

[00036] In some examples, when performing a dissolution test for an oral solid preparation of the present disclosure using a paddle method (50 rpm, using 900 mL of a 0.05 mol/L phosphate buffer (pH 6.8) comprising 0.2% of cetyltrimethylammonium bromide (CTAB)) after storing for two weeks at 40°C/90% relative humidity, 70% or more of the DAAO inhibitor dissolves within 30 minutes. In some examples, the oral solid preparation is placed into a glass bottle and stored without a cap for 2 weeks at 40°C/90% relative humidity before performing the dissolution test.

[00037] In some examples, the oral solid preparation is a specific preparation described herein, for example, in the examples of the present disclosure. In some examples, the oral solid preparation has the composition described in Table 2. In some examples, the oral solid preparation has the composition described in Table 3. In some examples, the oral solid preparation has the composition described in Table 4. In some examples, the oral solid preparation has the composition described in Table 5. In some examples, the oral solid preparation has the composition described in Table 6. In some examples, the oral solid preparation has the composition described in Table 7. In some examples, the oral solid preparation has the composition described in Table 8. In some examples, the oral solid preparation has the composition described in Table 9. In some examples, the oral solid preparation has the composition described in Table 10. In some examples, the oral solid preparation has the composition described in Table 11. In some examples, the oral solid preparation has the composition described in Table 12. In some examples, the oral solid preparation has the composition described in Table 13.

[00038] In some examples, an oral solid preparation of the present disclosure can be used in combination with one or more other types of drugs.

[00039] Also disclosed herein is a method of preparing an oral solid preparation described herein.

[00040] In some examples, the method comprises:

mixing a DAAO inhibitor and an additive to obtain a mixture;

granulating the mixture to obtain at least one granule;

mixing the at least one granule and a L-HPC to obtain at least one mixed granule; and

compressing the at least one mixed granule.

[00041] Also disclosed herein is a method of treating preventing or treating a disease preventable or treatable by a D-amino acid oxidase inhibitor in a mammal in need thereof, the method comprising administering an oral solid preparation described herein to the mammal.

[00042] In some examples, the disease preventable or treatable by a D-amino acid oxidase inhibitor is chosen from schizophrenia and other mental disorders, dementia and other cognitive disorders, anxiety disorder, mood disorders, sleep disorders, disorders generally first diagnosed in early childhood, childhood or adolescence, pain, neurodegenerative disorders, and ataxic disorders.

[00043] In some examples, the oral solid preparation is administered in combination with another active pharmaceutical ingredient (i.e., a combination drug). In some examples, the oral solid preparation and the combination drug are administered at the same time. In some examples, the oral solid preparation and the combination drug are administered at different times. In some examples, the oral solid preparation and the combination drug are administered in the same preparation. In some examples, the oral solid preparation and the combination drug are administered in different preparations.

Example Embodiments 1:

[00044] Without limitation, some embodiments of the disclosure include:

1. An oral solid preparation comprising a D-amino acid oxidase inhibitor, a low-substituted hydroxypropyl cellulose (L-HPC), and an additive, wherein the D-amino acid oxidase inhibitor is a pyridazinone derivative.

2. The oral solid preparation according to Embodiment 1, wherein the additive is chosen from a filler, a binder, a disintegrant, and a lubricant.

3. The oral solid preparation according to Embodiment 1 or 2, wherein the oral solid preparation is a tablet.

4. The oral solid preparation according to any one of Embodiments 1 to 3, wherein the

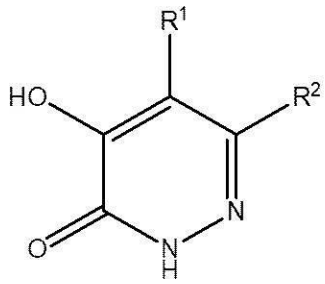
What is claimed is:

1. An oral solid preparation comprising a D-amino acid oxidase (DAAO) inhibitor, a low-substituted hydroxypropyl cellulose (L-HPC), and an additive, wherein the DAAO inhibitor is a pyridazinone derivative.

2. The oral solid preparation according to claim 1, wherein the oral solid preparation is a tablet.

3. The oral solid preparation according to claim 1 or 2, wherein the additive is chosen from fillers, binders, disintegrants, lubricants, and combinations of any of the foregoing.

4. The oral solid preparation according to any one of claims 1 to 3, wherein the DAAO inhibitor is chosen from compounds of Formula (I):



(I), wherein:

R^1 is hydrogen, fluorine, or trifluoromethyl;

R^2 is chosen from $-XYR^3$ groups;

X and Y are independently chosen from a bond, oxygen, -C(O), $-S(O)_n$ groups, $-C(O)NR^4$ groups, $-S(O)_2NR^4$ groups, $-NR^4$ groups,  , and $-CR^4R^5-$ groups, wherein:

X and Y are not both a bond; and

when neither X nor Y is a bond, then at least one of X and Y is chosen from $-CR^4R^5-$ groups;

n is 0, 1, or 2;

each R^4 is independently chosen from hydrogen, C_1-C_6 alkyl groups, and C_1-C_6 haloalkyl groups;

each R^5 is independently chosen from hydrogen, C_1-C_6 alkyl groups, C_1-C_6 haloalkyl groups, and =CH-;

R^3 is chosen from saturated or unsaturated carbocyclic or heterocyclic ring systems of 3 to 10 members, wherein the ring system is optionally substituted by at least one substituent chosen from halogen groups, hydroxyl, cyano, oxo, C_1-C_6 alkyl groups, C_2-C_6 alkenyl groups, C_1-C_6 haloalkyl groups, C_1-C_6 hydroxyalkyl groups, C_1-C_6 alkoxy groups, C_1-C_6 haloalkoxy groups, C_1-C_6 alkylthiogroups, C_1-C_6 alkylsulfinyl groups, C_1-C_6 alkylsulfonyl groups, C_1-C_6 alkylcarbonyl groups, C_1-C_6 alkylcarbonyloxy groups, C_1-C_6 alkoxycarbonyl groups, amino, -$CON(R^6)_2$ groups, C_1-C_6 alkyl amino groups, di-(C_1-C_6 alkyl) amino groups, C_3-C_6 cycloalkyl groups, C_3-C_6 cycloalkyloxy groups, C_3-C_6 cycloalkyl methyl groups, -[O]p-(CH_2)q-O-R^7 groups, and saturated or unsaturated heterocyclic rings of 4 to 6 members optionally substituted by at least one substituent chosen from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups;

each R^6 is independently chosen from hydrogen and C_1-C_6 alkyl groups;

p is 0 or 1;

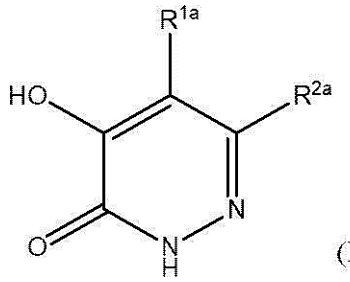
q is 1, 2, 3, or 4; and

R^7 is chosen from C_1-C_6 alkyl groups,

and pharmaceutically acceptable salts thereof.

5. The oral solid preparation according to any one of claims 1 to 4, wherein the DAAO inhibitor is chosen from 4-hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazine-3(2H)-one and pharmaceutically acceptable salts thereof.

6. The oral solid preparation according to any one of claims 1 to 3, wherein the DAAO inhibitor is chosen from compounds of Formula (I)-a:



(I)-a, wherein:

R^{1a} is hydrogen, fluorine, or trifluoromethyl;

R^{2a} is chosen from C_2-C_8 alkyl groups, C_3-C_8 cycloalkyl groups, and tetrahydropyranyl, each of which may be optionally substituted with at least one substituent, or R^{2a} is chosen from -$NR^{3a}R^{4a}$ groups;

R^{3a} and R^{4a} are independently chosen from hydrogen and C_1-C_6 alkyl groups, or R^{3a} and R^{4a} form a saturated or unsaturated heterocyclic ring of 4 to 8 members together with a bonded nitrogen atom, and each alkyl group or heterocyclic ring may be optionally substituted by at least one substituent; and

the optional substituents for R^{2a}, R^{3a}, and R^{4a} are independently chosen from halogen groups, hydroxyl, cyano, carboxyl, C_1-C_6 alkyl groups, difluoromethyl, trifluoromethyl, C_1-C_6 alkoxy groups, difluoromethoxy, and trifluoromethoxy, provided that the compound is not:

2,3-dihydro-4-hydroxy-6-morpholinopyridazine-3-one, or

6-amino-4-hydroxy-pyridazinone,

and pharmaceutically acceptable salts thereof.

7. The oral solid preparation according to any one of claims 1 to 6, wherein the oral solid preparation comprises 10 mg to 1000 mg of the DAAO inhibitor per preparation unit.

8. The oral solid preparation according to any one of claims 1 to 7, wherein one type of L-HPC is used.

9. The oral solid preparation according to any one of claims 1 to 7, wherein two or more types of L-HPC is used.

10. The oral solid preparation according to any one of claims 1 to 9, wherein the content of

L-HPC is 1% to 20% by weight.

11. An oral solid preparation comprising:

3% to 60% by weight of 4-hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazine-3(2H)-one;

3% to 15% by weight of a L-HPC;

15% to 85% by weight of a filler;

1% to 10% by weight of a binder; and

0.2% to 3% by weight of a lubricant.

12. The oral solid preparation according to any one of claims 3 to 11, wherein the filler is chosen from mannitol, microcrystalline cellulose, starches, and combinations of any of the foregoing.

13. The oral solid preparation according to any one of claims 3 to 12, wherein the filler is mannitol and microcrystalline cellulose.

14. The oral solid preparation according to any one of claims 3 to 12, wherein the binder is hydroxypropyl cellulose.

15. The oral solid preparation according to any one of claims 3 to 14, wherein the lubricant is magnesium stearate.

16. The oral solid preparation according to any one of claims 1 to 15, wherein the L-HPC comprises 5.0% to 16.0% of a hydroxypropoxy group by dry weight.

17. The oral solid preparation according to any one of claims 1 to 16, wherein the L-HPC is L-HPC LH-21.

18. An oral solid preparation comprising:

3% to 60% by weight of 4-hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazine-3(2H)-one;

3% to 15% by weight of a L-HPC;

10% to 75% by weight of mannitol;

5% to 15% by weight of microcrystalline cellulose;

1% to 10% by weight of hydroxypropyl cellulose; and

0.2% to 3% by weight of magnesium stearate.

19. The oral solid preparation according to any one of claims 1 to 18, further comprising a film coating.

20. The oral solid preparation according to claim 19, wherein the film coating comprises a coating agent and a coating additive.

21. The oral solid preparation according to claim 19, wherein the film coating comprises a coating agent and a light-shielding agent.

22. The oral solid preparation according to claim 19, wherein the film coating comprises a coating agent, a light-shielding agent, and a colorant.

23. The oral solid preparation according to claim 19, wherein the film coating comprises hydroxypropyl methylcellulose, titanium dioxide, and hydroxypropyl cellulose.

24. The oral solid preparation according to any one of claims 1 to 23, wherein 70% or more of the DAAO inhibitor dissolves within 30 minutes when performing a first dissolution test using a first paddle method.

25. The oral solid preparation according to claim 24, wherein the first paddle method comprises paddling at 75 rpm using 900 mL of a 0.05 mol/L phosphate buffer solution (pH 6.8) comprising 0.05% of cetyltrimethylammonium bromide (CTAB).

26. The oral solid preparation according to any one of claims 1 to 25, wherein 70% or more of the DAAO inhibitor dissolves within 30 minutes when performing a second dissolution test using a second paddle method, wherein the DAAO inhibitor was stored for two weeks at 40°C/90% relative humidity before performing the second dissolution test.

27. The oral solid preparation according to claim 26, wherein the second paddle method comprises paddling at 50 rpm using 900 mL of a 0.05 mol/L phosphate buffer solution (pH 6.8) containing 0.1% of sodium dodecyl sulfate (SDS).

28. A method for producing an oral solid preparation according to any one of claims 1 to 27, comprising:

mixing a D-amino acid oxidase inhibitor and an additive to obtain a mixture;

granulating the mixture to obtain at least one granule;

mixing the at least one granule and a L-HPC to obtain at least one mixed granule; and

compressing the at least one mixed granule.

29. The method according to claim 28, wherein mixing the D-amino acid oxidase inhibitor and the additive further comprises mixing a L-HPC with the D-amino acid oxidase inhibitor and the additive.

30. An oral solid preparation according to any one of claims 1 to 27 for use as a medicament.

31. Use of an oral solid preparation according to any one of claims 1 to 27 in the manufacture of a medicament for preventing or treating a disease preventable or treatable by a D-amino acid oxidase inhibitor.

32. The use according to claim 31, wherein the disease preventable or treatable by a D-amino acid oxidase inhibitor is chosen from schizophrenia and other mental disorders, dementia and other cognitive disorders, anxiety disorder, mood disorders, sleep disorders, disorders generally first diagnosed in early childhood, childhood or adolescence, pain, neurodegenerative disorders,

and ataxic disorders.