

CLAIMS

1. A stable amorphous solid dispersion comprising Compound 1 and a stabilizing polymer, wherein Compound 1 is molecularly dispersed within a polymer matrix formed by the stabilizing polymer in its solid state, wherein the stabilizing polymer is any one of HPMCAS-LF, HPMCAS-MF, or HPMCAS-HF, or a mixture of two or more of the above substances, and the weight ratio of Compound 1 in the form of freebase and the polymer is between 1:9 and 9:1, wherein Compound 1 is 1-((1S, 1aS, 6bS)-5-((7-oxo-5, 6, 7, 8-tetrahydro-1, 8-naphthyridin-4-yl)oxy)-1a, 6b-dihydro-1H-cyclopropa[b]benzofuran-1-yl)-3-(2, 4, 5-trifluorophenyl)urea, and wherein HPMCAS-LF has 5.0-9.0% of acetyl group and 14.0-18.0% of succinoyl group; HPMCAS-MF has 7.0-11.0% of acetyl group and 10.0-14.0% of succinoyl group; and HPMCAS-HF has 10.0-14.0% of acetyl group and 4.0-8.0% of succinoyl group.
2. The amorphous solid dispersion according to Claim 1, wherein the weight ratio of Compound 1 in the form of freebase and the polymer is between 1:4 to 2:3; or 3:7 or 1:4.
3. The amorphous solid dispersion according to Claim 1, wherein the weight ratio of Compound 1 in the form of freebase and the polymer is 1:4.
4. The amorphous solid dispersion according to Claim 1, wherein the stable amorphous solid dispersion has a drug-loading content of 10% to 40%.
5. The amorphous solid dispersion according to Claim 1, wherein the stable amorphous solid dispersion comprises Compound 1 in the form of freebase and HPMCAS-MF in a weight ratio of 3:7; or Compound 1 in the form of freebase and HPMCAS-MF in a weight ratio of 2:3; Compound 1 in the form of freebase and HPMCAS-MF in a weight ratio of 1:4; Compound 1 in the form of freebase and HPMCAS-LF in a weight ratio of 1:9; Compound 1 in the form of freebase and HPMCAS-LF in a weight ratio of 1:4; Compound 1 in the form of freebase and HPMCAS-LF in weight ratio of 3:7; Compound 1 in the form of freebase and HPMCAS-LF in a weight ratio of 2:3; or Compound 1 in the form of freebase and HPMCAS-HF in a weight ratio of 1:4.
6. The amorphous solid dispersion according to Claim 1, wherein the stable amorphous solid dispersion is prepared by microprecipitated bulk powder (MBP) technology.

7. The amorphous solid dispersion according to Claim 1, wherein the stable amorphous solid dispersion has a glass transition temperature of 110-115°C.

8. The amorphous solid dispersion according to Claim 1, wherein the stable amorphous solid dispersion is formulated into an orally administrated formulation.

9. A method for preparing the stable amorphous solid dispersion, comprising the step of co-precipitating Compound 1 and HPMCAS,

wherein the stable amorphous solid dispersion comprises Compound 1 and HPMCAS, wherein Compound 1 is molecularly dispersed within a polymer matrix formed by HPMCAS in its solid state,

wherein HPMCAS is any one of HPMCAS-LF, HPMCAS-MF, or HPMCAS-HF, or a mixture of two or more of the above substances, and the weight ratio of Compound 1 in the form of freebase and HPMCAS is between 1:9 and 9:1,

wherein HPMCAS-LF has 5.0-9.0% of acetyl group and 14.0-18.0% of succinoyl group;

HPMCAS-MF has 7.0-11.0% of acetyl group and 10.0-14.0% of succinoyl group; and

HPMCAS-HF has 10.0-14.0% of acetyl group and 4.0-8.0% of succinoyl group, and

wherein Compound 1 is 1-((1S, 1aS, 6bS)-5-((7-oxo-5, 6, 7, 8-tetrahydro-1, 8-naphthyridin-4-yl)oxy)-1a, 6b-dihydro-1H-cyclopropa[b]benzofuran-1-yl)-3-(2, 4, 5-trifluorophenyl)urea.

10. The method according to Claim 9, wherein Compound 1 and HPMCAS simultaneously precipitate out to form a molecular dispersion of Compound 1 in the matrix formed by HPMCAS.

11. The method according to Claim 9, said method comprises the step of a solvent controlled precipitation.

12. The method according to Claim 9, said method comprises the step of microprecipitated bulk powder (MBP) technology.

13. The method according to any one of Claims 9-12, wherein the weight ratio of Compound 1 in the form of freebase and HPMCAS is between 1:4 to 2:3; or 3:7 or 1:4.

14. The method according to any one of Claims 9-12, wherein Compound 1 in the form of freebase and HPMCAS-MF is in a weight ratio of 3:7; or Compound 1 in the form of freebase and HPMCAS-MF is in a weight ratio of 2:3; or Compound 1 in the form of freebase and

HPMCAS-MF is in a weight ratio of 1:4; or Compound 1 in the form of freebase and HPMCAS-LF is in a weight ratio of 1:9; or Compound 1 in the form of freebase and HPMCAS-LF is in a weight ratio of 1:4; or Compound 1 in the form of freebase and HPMCAS-LF is in a weight ratio of 3:7; or Compound 1 in the form of freebase and HPMCAS-LF is in a weight ratio of 2:3; or Compound 1 in the form of freebase and HPMCAS-HF in a weight ratio of 1:4.

15. The method according to any one of Claims 9-12, said method comprising dissolving Compound 1 and HPMCAS in an organic solvent.

16. The method according to Claim 15, wherein the organic solvent is N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAc), dimethyl sulfoxide (DMSO) or N-methyl-2-pyrrolidone (NMP).

17. The method according to any one of Claims 9-12, wherein the resulting solution of Compound 1 and HPMCAS is added into water or an acidic aqueous solution, whereby Compound 1 and HPMCAS simultaneously precipitate out to form a solid dispersion.

18. The method according to Claim 17, wherein the acidic aqueous solution is aqueous hydrochloric acid (HCl).

19. The method according to Claim 18, wherein water or the acidic aqueous solution is optionally cooled.

20. The method according to Claim 19, wherein water or the acidic aqueous solution is optionally cooled to 2-8 °C.

21. The method according to Claim 17, wherein the resulting solid is dried to give the amorphous solid dispersion as MBP.

22. The method according to Claim 21, wherein the resulting solid is further optionally micronized by, e.g., jet-milling to give a powder with a particle size suitable for drug formulation, e.g., of D₉₀ less than 150µm or 200µm.

23. The method according to Claim 22, wherein the solid dispersion is in an amorphous form.

24. The method according to Claim 22, wherein the solid dispersion has a glass transition temperature of 110-115°C.

25. The method according to Claim 9, said comprising:

- a) dissolving Compound 1 and HPMCAS in an organic solvent;
- b) co-precipitating Compound 1 and HPMCAS by adding the solution of a) into water or an acidic aqueous solution; and
- c) washing the resulting solid with water and/or aqueous hydrochloric acid to remove the organic solvent.

26. A use of Compound 1 in the amorphous solid dispersion according to any one of Claims 1-8 in the manufacture of a medicament for treating or preventing a disease or disorder responsive to inhibition of Raf kinases in a subject, wherein the disease or disorder is a cancer selected from the group consisting of brain cancer, lung cancer, kidney cancer, bone cancer, liver cancer, bladder cancer, breast, head and neck cancer, ovarian cancer, melanoma, skin cancer, adrenal cancer, cervical cancer, lymphoma, or thyroid tumors and their complications, wherein Compound 1 is 1-((1S, 1aS, 6bS)-5-((7-oxo-5, 6, 7, 8-tetrahydro-1, 8-naphthyridin-4-yl)oxy)-1a, 6b-dihydro-1H-cyclopropa[b]benzofuran-1-yl)-3-(2, 4, 5-trifluorophenyl)urea.

27. The use according to Claim 26, wherein the disease is BRAF (V600E or non-V600E) or NRAS or KRAS mutant cancer selected from brain cancer, lung cancer, kidney cancer, bone cancer, liver cancer, bladder cancer, breast, head and neck cancer, ovarian cancer, melanoma, skin cancer, adrenal cancer, cervical cancer, lymphoma, or thyroid tumors and their complications.

28. The use according to Claim 26, wherein the dosage of Compound 1 to be administered is 1-200 mg/day, and the administration frequency is one to three times a day.

29. The use according to Claim 26, wherein the dosage of Compound 1 to be administered is 2.5-100 mg/day, and the administration frequency is one to three times a day.

30. The use according to Claim 26, wherein the dosage of Compound 1 to be administered is 5-50 mg/day, and the administration frequency is one time a day.