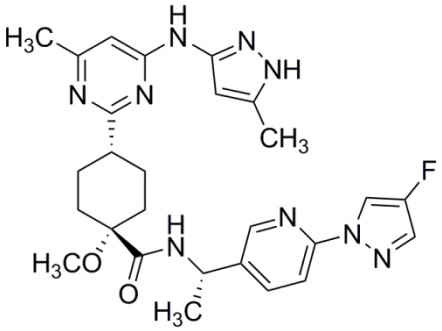
PRALSETINIB PHARMACEUTICAL COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 63/032,030, filed May 29, 2020, the disclosure of which is hereby incorporated by reference in its entirety for all purposes.

Background

[0002] Pralsetinib is disclosed as one of many RET inhibitor compounds in patent publication WO2017/079140. A clinical trial (NCT03037385), entitled "Phase 1/2 Study of the Highly-selective RET Inhibitor, Pralsetinib (BLU-667), in Patients with Thyroid Cancer, Non-Small Cell Lung Cancer, and Other Advanced Solid Tumors (ARROW)" in underway. Pralsetinib is a potent and selective RET inhibitor provided in an oral dosage form to selectively target oncogenic RET alterations in certain cancer patients, including patients having a cancer harboring the most prevalent RET fusions and certain RET activating mutations. Pralsetinib can also be referred to as: (cis)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4 methyl-6-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-yl)cyclohexanecarboxamide, and has the following chemical structure:



(I).

[0003] However, pralsetinib has a low aqueous solubility and as such, there remains a need for pharmaceutical compositions of pralsetinib that not only enhance its aqueous solubility but also to provide immediate release upon administration.

Summary

[0003a] In one aspect of the present disclosure, there is provided a pharmaceutical composition comprising 1) an amorphous solid dispersion comprising pralsetinib or a

pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable hydrophilic polymer; and 2) an effervescent couple.

[0003b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising 1) an amorphous solid dispersion comprising pralsetinib or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable amphiphilic polymer; and 2) an effervescent couple.

[0003c] In a further aspect of the present disclosure, there is provided an oral dosage form comprising a) an amorphous solid dispersion comprising pralsetinib, or a pharmaceutically acceptable salt thereof and hydroxypropyl methylcellulose (HPMC); b) microcrystalline cellulose (MCC); c) pregelatinized starch; d) sodium bicarbonate; e) citric acid; and f) magnesium stearate.

[0003d] In another aspect of the present disclosure, there is provided an immediate release oral dosage form comprising:

a) an amorphous solid dispersion comprising: pralsetinib, or a pharmaceutically acceptable salt thereof, and hydroxypropyl methylcellulose E3, wherein the pralsetinib or an equivalent amount of pharmaceutically acceptable salt thereof and the hydroxypropyl methyl cellulose E3 are in about a 1:1 weight ratio;

b) an effervescent couple comprising about 3 to about 13 w/w% citric acid and about 7 to about 30 w/w% sodium bicarbonate; wherein w/w% is based on the total weight of the oral dosage form;

c) a diluent; and optionally

d) moisture scavenger and/or a lubricant.

[0003e] In a further aspect of the present disclosure, there is provided a method for preparing the amorphous solid dispersion disclosed herein, comprising: mixing the pralsetinib or the pharmaceutically acceptable salt thereof, with the hydrophilic polymer in about a 1:1 ratio; adding a solvent, and removing the solvent by heating.

[0003f] In another aspect of the present disclosure, there is provided a use of the composition disclosed herein or an oral dosage form disclosed herein, in the manufacture of a medicament for treating a RET-altered cancer.

[0003g] In a further aspect of the present disclosure, there is provided a use of the composition disclosed herein or an oral dosage form disclosed herein, in the manufacture of a

medicament for treating a patient with rearranged during transfection (RET)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

[0003h] In another aspect of the present disclosure, there is provided a use of the composition disclosed herein or an oral dosage form disclosed herein, in the manufacture of a medicament for treating a patient with RET-mutation positive locally advanced or metastatic medullary thyroid cancer (MTC).

[0003i] In a further aspect of the present disclosure, there is provided a use of the composition disclosed herein or an oral dosage form disclosed herein, in the manufacture of a medicament for treating a patient with RET-fusion positive locally advanced or metastatic thyroid cancer who require systemic therapy and have no satisfactory alternative treatment options.

[0003j] In another aspect of the present disclosure, there is provided a composition disclosed herein or an oral dosage form disclosed herein, for use in therapy.

[0004] The present disclosure features pharmaceutical compositions comprising 1) an amorphous solid dispersion comprising pralsetinib, or a pharmaceutically acceptable salt

thereof, and a pharmaceutically acceptable hydrophilic polymer; and 2) an effervescent couple.

[0005] In one example, provided herein is a pharmaceutical composition comprising 1) an amorphous solid dispersion comprising pralsetinib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable amphiphilic polymer; and 2) an effervescent couple.

[0006] In one example, provided herein is a pharmaceutical composition

[0007] comprising 1) an amorphous solid dispersion comprising pralsetinib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable hydrophilic and amphiphilic polymer; and 2) an effervescent couple.

[0008] In one example, the disclosure features an oral dosage form comprising (a) an amorphous solid dispersion of pralsetinib, or a pharmaceutically acceptable salt thereof; and hydroxypropyl methylcellulose (HPMC); (b) a diluent; (c) sodium bicarbonate; (d) citric acid; (e) a moisture scavenger; and (f) a lubricant.

[0009] In one example, the disclosure features an oral dosage form comprising (a) an amorphous solid dispersion of pralsetinib, or a pharmaceutically acceptable salt thereof; and hydroxypropyl methylcellulose (HPMC); (b) a diluent; (c) sodium bicarbonate; (d) citric acid; and (e) a lubricant.

[0010] In one example, the disclosure features an oral dosage form comprising (a) an amorphous solid dispersion of pralsetinib, or a pharmaceutically acceptable salt thereof; and hydroxypropyl methylcellulose acetate succinate (HPMCAS); (b) a diluent; (c) sodium bicarbonate; (d) citric acid; (e) a moisture scavenger; and (f) a lubricant.

[0011] In one example, the disclosure features an oral dosage form comprising (a) an amorphous solid dispersion of pralsetinib, or a pharmaceutically acceptable salt thereof; and hydroxypropyl methylcellulose (HPMC); (b) microcrystalline cellulose (MCC); (c) pregelatinized starch; (d) sodium bicarbonate; (e) citric acid; and (f) magnesium stearate.

[0012] In one example, the disclosure features an oral dosage form comprising (a) an amorphous solid dispersion of pralsetinib, or a pharmaceutically acceptable salt thereof; and

hydroxypropyl methylcellulose (HPMC); (b) microcrystalline cellulose (MCC); (c) sodium bicarbonate; (d) citric acid; and (e) magnesium stearate.

[0013] Another example of the disclosure features a method for preparing the amorphous solid dispersion as described herein, comprising: dissolving the pralsetinib or the pharmaceutically acceptable salt thereof, with a hydrophilic polymer, e.g., in a 1:1 ratio, using a suitable manufacturing method so as to achieve an amorphous solid dispersion.

[0014] Also provided herein is a method for preparing the amorphous solid dispersion as described herein, comprising: dissolving the pralsetinib or the pharmaceutically acceptable salt thereof, with an amphiphilic polymer, e.g., in a 1:1 ratio, using a suitable manufacturing method so as to achieve an amorphous solid dispersion.

[0015] The amorphous solid dispersion can be prepared by hot melt extrusion, lyophilization, spray drying, solvent casting, or melt quenching. One example of the disclosure uses a spray drying with a suitable solvent as a method of manufacture (e.g., adding a suitable solvent and removing the solvent by heating).

[0016] Another example of the disclosure features a method of treating a RET-altered cancer comprising administering to a patient in need thereof a therapeutically effective amount of the compositions and oral dosage forms disclosed herein.

[0017] Another example of the disclosure features a method of treating a patient with rearranged during transfection (RET)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) comprising administering to a patient in need thereof a therapeutically effective amount of the compositions and oral dosage forms disclosed herein. In a particular example, the (RET)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) is detected by an FDA approved test.

[0018] Another example of the disclosure features a method of treating a patient with RET-mutation positive locally advanced or metastatic medullary thyroid cancer (MTC) comprising administering to the patient in need thereof a therapeutically effective amount of the compositions and oral dosage forms disclosed herein. In a particular example, the patients are 12 years of age and older.

[0019] Another example of the disclosure features a method of treating a patient with RET-fusion positive locally advanced or metastatic thyroid cancer who require systemic therapy and have no satisfactory alternative treatment options comprising administering to the patient in need thereof a therapeutically effective amount of the compositions and oral dosage forms disclosed herein. In a particular example, the patients are 12 years of age and older.

Brief Description of the Figures

[0020] FIG. 1A is an X-ray powder diffraction pattern (XRPD) pattern of pralsetinib Form A.

[0021] FIG. 1B shows DSC and TGA thermograms of pralsetinib Form A.

[0022] FIG. 1C shows the DVS thermogram of pralsetinib Form A.

[0023] FIG. 2A is an X-ray powder diffraction pattern (XRPD) pattern of pralsetinib Form B.

[0024] FIG. 2B shows DSC and TGA thermograms of pralsetinib Form B.

[0025] FIG. 2C shows the DVS thermogram of pralsetinib Form B.

[0026] FIG. 3A is an X-ray powder diffraction pattern (XRPD) pattern of pralsetinib Form C.

[0027] FIG. 3B shows DSC and TGA thermograms of pralsetinib Form C.

[0028] FIG. 3C shows the DVS thermogram of pralsetinib Form C.

[0029] FIG. 4A is an X-ray powder diffraction pattern (XRPD) pattern of pralsetinib HCl salt Form I.

[0030] FIG. 4B shows DSC thermogram of pralsetinib HCl salt Form I.

[0031] FIG. 5A is an X-ray powder diffraction pattern (XRPD) pattern of pralsetinib HCl salt Form II.

[0032] FIG. 5B shows DSC and TGA thermograms of pralsetinib HCl salt Form II.

[0033] FIG. 6A is an X-ray powder diffraction pattern (XRPD) pattern of pralsetinib HCl salt Form III.

[0034] FIG. 6B shows DSC and TGA thermograms of pralsetinib HCl salt Form III.

Claims

1. A pharmaceutical composition comprising 1) an amorphous solid dispersion comprising pralsetinib or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable hydrophilic polymer; and 2) an effervescent couple.

2. A pharmaceutical composition comprising 1) an amorphous solid dispersion comprising pralsetinib or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable amphiphilic polymer; and 2) an effervescent couple.

3. The composition of claim 1 or 2, wherein the polymer is selected from the group consisting of hydroxypropyl methylcellulose (hypromellose) , hydroxypropyl methylcellulose acetate succinate (HPMC-AS), vinylpyrrolidone-vinyl acetate copolymer (KOLLIDON VA64 or KOLLIDON K30), dimethylaminoethyl methacrylate-copolymer (EUDRAGIT EPO), poly(ethylene) oxide (POLYOX), and polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (SOLUPLUS).

4. The composition of any one of claims 1-3 wherein the polymer is hydroxypropyl methylcellulose.

5. The composition of any one of claims 1-4, wherein the polymer is hydroxypropylmethylcellulose E3 (HPMC-E3) or hydroxypropylmethylcellulose E5 (HPMC-E5).

6. The composition of any one of claims 1, 3, and 4, wherein the pralsetinib, or an equivalent amount of a pharmaceutically acceptable salt thereof, and the hydrophilic polymer are in a weight percent ratio of about 1:1.

7. The composition of any one of claims 2-4, wherein the pralsetinib, or an equivalent amount of a pharmaceutically acceptable salt thereof, and the amphiphilic polymer are in a weight percent ratio of about 1:1.

8. The composition of any one of claims 1, 3, and 4, wherein the pralsetinib, or an equivalent amount of a pharmaceutically acceptable salt thereof, and the hydrophilic polymer are in a weight percent ratio of from about 1:5 to about 5:1.

9. The composition of any one of claims 2-4, wherein the pralsetinib, or an equivalent amount of a pharmaceutically acceptable salt thereof, and the amphiphilic polymer are in a weight percent ratio of from about 1:5 to about 5:1.

10. The composition of any one of claims 1 to 9, wherein the composition comprises the amorphous solid dispersion from about 25% to about 65% by weight of the composition, based on the total weight of the composition.

11. The composition of any one of claims 1 to 10, wherein the composition comprises the amorphous solid dispersion from about 50% to about 60% by weight of the composition, based on the total weight of the composition.

12. The composition of any one of claims 1 to 11, wherein the amorphous solid dispersion is prepared by hot melt extrusion, lyophilization, spray drying, solvent casting, or melt quenching.

13. The composition of any one of claims 1 to 12, wherein the effervescent couple comprises a water-soluble acid and a water-soluble base.

14. The composition of any one of claims 1 to 12, wherein the effervescent couple comprises a water-soluble base.

15. The composition of claim 13, wherein the water-soluble acid is selected from the group consisting of citric acid, tartaric acid, fumaric acid, adipic acid, succinic acid, malonic acid, benzoic acid, oxalic acid, malic acid, and glutaric acid.

16. The composition of any one of claims 13-15, wherein the water-soluble base is selected from the group consisting of sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate and magnesium carbonate.

17. The composition of claim 13, wherein the water-soluble acid is citric acid and the water-soluble base is sodium bicarbonate.

18. The composition of any one of claims 13 and 15-17, wherein the composition comprises the water-soluble acid from about 1% to about 20% by weight of the composition, based on the total weight of the composition.

19. The composition of any one of claims 13-18, wherein the composition comprises the water-soluble base from about 1% to about 35% by weight of the composition, based on the total weight of the composition.

20. The composition of any one of claims 1 to 19, wherein the composition further comprises a moisture scavenger.

21. The composition of claim 20, wherein the moisture scavenger is a starch.

22. The composition of claim 21, wherein the starch is pregelatinized starch.

23. The composition of any one of claims 20 to 22, wherein the composition comprises the moisture scavenger from about 0.5% to about 30% by weight of the composition, based on the total weight of the composition.

24. The composition of any one of claims 1 to 23, wherein the composition further comprises a diluent.

25. The composition of claim 24, wherein the diluent is a cellulose.

26. The composition of claim 25, wherein the cellulose is microcrystalline cellulose.

27. The composition of any one of claims 24 to 26, wherein the composition comprises the diluent from about 5% to about 60% by weight of the composition, based on the total weight of the composition.

28. The composition of any one of claims 1 to 27, wherein the composition further comprises a lubricant.

29. The composition of claim 28, wherein the lubricant is magnesium stearate.

30. The composition of any one of claims 28 or 29, wherein the composition comprises the lubricant from about 0.1% to about 5% by weight of the composition, based on the total weight of the composition.

31. The composition of any one of claims 1 to 30, wherein the composition is prepared in an oral dosage form.

32. The composition of claim 31, wherein the oral dosage form is a capsule.

33. The composition of claim 31, wherein the oral dosage form is a tablet.

34. The composition of any one of claims 1 to 33, wherein the composition is an immediate release composition.

35. The composition of any one of claims 1 to 34, wherein the composition comprises about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, or about 200 mg of pralsetinib, or an equivalent amount of a pharmaceutically acceptable salt thereof.

36. An oral dosage form comprising a) an amorphous solid dispersion comprising pralsetinib, or a pharmaceutically acceptable salt thereof and hydroxypropyl methylcellulose (HPMC); b) microcrystalline cellulose (MCC); c) pregelatinized starch; d) sodium bicarbonate; e) citric acid; and f) magnesium stearate.

37. The oral dosage form of claim 36, wherein the oral dosage form comprises the amorphous solid dispersion from about 25% to about 65% percent by weight of the oral dosage form, based on the total weight of the oral dosage form.

38. The oral dosage form of claim 36 or 37, wherein the oral dosage form comprises the microcrystalline cellulose (MCC) from about 5% to about 60% percent by weight of the oral dosage form, based on the total weight of the oral dosage form.

39. The oral dosage form of any one of claims 36 to 38, wherein the oral dosage form comprises the pregelatinized starch from about 0.5% to about 30% by weight of the oral dosage form, based on the total weight of the oral dosage form.

40. The oral dosage form of any one of claims 36 to 39, wherein the oral dosage form comprises the sodium bicarbonate from about 1% to about 35% percent by weight of the oral dosage form, based on the total weight of the oral dosage form.

41. The oral dosage form of any one of claims 36 to 40, wherein the oral dosage form comprises the citric acid from about 1% to about 20% by weight of the oral dosage form, based on the total weight of the oral dosage form.

42. The oral dosage form of any one of claims 36 to 41, wherein the oral dosage form comprises the magnesium stearate from about 0.1% to about 5% by weight of the oral dosage form, based on the total weight of the oral dosage form.

43. The oral dosage form of any one of claims 36 to 42 wherein the pralsetinib, or an equivalent amount of a pharmaceutically acceptable salt thereof, and the hydrophilic polymer are in a weight percent ratio of about 1:1.

44. The oral dosage form of any one of claims 36 to 43, wherein the amorphous solid dispersion is prepared by hot melt extrusion, lyophilization, spray drying, solvent casting, or melt quenching.

45. The oral dosage form of any one of claims 36 to 44, wherein the oral dosage form is a capsule.

46. The oral dosage form of claim 32 or 45, wherein the size of the capsule is 0.

47. The oral dosage form of any one of claims 36-44, wherein the oral dosage form is a tablet.

48. The oral dosage form of any one of claims 36 to 47, wherein the oral dosage form comprises about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg, or about 200 mg of pralsetinib, or an equivalent amount of a pharmaceutically acceptable salt thereof.

49. The oral dosage form of any one of claims 36 to 48, wherein the oral dosage form is an immediate release oral dosage form.

50. An immediate release oral dosage form comprising:

a) an amorphous solid dispersion comprising: pralsetinib, or a pharmaceutically acceptable salt thereof, and hydroxypropyl methylcellulose E3, wherein the pralsetinib or an equivalent amount of pharmaceutically acceptable salt thereof and the hydroxypropyl methyl cellulose E3 are in about a 1:1 weight ratio;

b) an effervescent couple comprising about 3 to about 13 w/w% citric acid and about 7 to about 30 w/w% sodium bicarbonate; wherein w/w% is based on the total weight of the oral dosage form;

c) a diluent; and optionally

d) moisture scavenger and/or a lubricant.

51. The oral dosage form of claim 50, wherein the amorphous solid dispersion comprises about 30 mg, about 50 mg, about 60 mg or about 100 mg of pralsetinib or an equivalent amount of a pharmaceutically acceptable salt thereof.

52. The composition or oral dosage form of any one of claims 1-51, wherein at least 80% of the pralsetinib is released in 45 minutes using USP) <711> with a Type 2 Apparatus, media containing 900 mL 0.1 M HCl, and a paddle speed of 100 rpm.

53. The composition or oral dosage form of any one of claims 1-51, wherein the dosage form is a capsule, wherein the capsule disintegrates in about 7 to 15 minutes using USP <701>, with Basket Type A and a disc with a maintained temperature at 37 ºC ± 2 ºC.

54. The composition or oral dosage form of any one of claims 1-51, wherein the dosage form is a capsule, wherein at least 80% of the pralsetinib is released in about 120 minutes using USP II apparatus with a media containing 900 mL pH 6.8 sodium phosphate buffer with 0.5% CTAB and a paddle speed of 75 rpm ± 2 rpm.

55. A method for preparing the amorphous solid dispersion according to any one of claims 1 to 54, comprising: mixing the pralsetinib or the pharmaceutically acceptable salt thereof, with the hydrophilic polymer in about a 1:1 ratio; adding a solvent, and removing the solvent by heating.

56. Use of the composition according to any one of claims 1 to 35 or an oral dosage form of any one of claims 36 to 54, in the manufacture of a medicament for treating a RET-altered cancer.

57. Use of the composition according to any one of claims 1 to 35 or an oral dosage form of any one of claims 36 to 54, in the manufacture of a medicament for treating a patient with rearranged during transfection (RET)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

58. The use of claim 57, wherein the (RET)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) is detected by an FDA approved test.

59. Use of the composition according to any one of claims 1 to 35 or an oral dosage form of any one of claims 36 to 54, in the manufacture of a medicament for treating a patient with RET-mutation positive locally advanced or metastatic medullary thyroid cancer (MTC).

60. Use of the composition according to any one of claims 1 to 35 or an oral dosage form of any one of claims 36 to 54, in the manufacture of a medicament for treating a patient with

RET-fusion positive locally advanced or metastatic thyroid cancer who require systemic therapy and have no satisfactory alternative treatment options.

61. The composition according to any one of claims 1 to 35 or an oral dosage form of any one of claims 36 to 54, for use in therapy.