6063 hydrochloride), *e.g.*, admixed with an excipient (*e.g.*, a binder, *e.g.*, a polymer, *e.g.*, a precipitation inhibitor, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF); a *e.g.*, polyol (*e.g.*, mannitol-starch (*e.g.*, Pearlitol Flash), mannitol, sorbitol)). In one aspect, there is provided a pharmaceutical composition comprising defactinib or a pharmaceutically acceptable salt thereof and a hydroxypropyl methylcellulose (HPMC) polymer. In some embodiments, the excipient is a binder. In some embodiments, the excipient is a polymer. In some embodiments, the polymer is a precipitation inhibitor. In some embodiments, the precipitation inhibitor is a HPMCAS. In some embodiments, the precipitation inhibitor is HPMCAS-HF. In some embodiments, the excipient reduces precipitation (*e.g.*, of VS-6063 in solution, *e.g.*, in vivo) when administered orally. In some embodiments, the excipient enhances bioavailability (*e.g.*, improves absorption) of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), when administered orally. In some embodiments, the ratio (*e.g.*, relative amount) by weight of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), to the polymer is about 1 to 1, 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, 1 to 7, 1 to 8, or 1 to 9. In some embodiments, the polymer is a precipitation inhibitor, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF). In some embodiments, the VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), is present in the composition in an amount that is about 10, 25, 30, 31, 32, 32.5, 33, 34, 35, 40, 45, 50% or more weight per weight (w/w) relative to an amount of polymer, *e.g.*, a precipitation inhibitor, provided. In some embodiments, the composition is admixed with 5 to 50%, 5 to 30%, 10 to 30%, 10 to 20%, 12 to 15%, or 13% weight of VS-6063, or a pharmaceutically acceptable salt thereof, per weight of the composition. In some embodiments, the polymer is present at 25 to 55%, 35 to 45%, 38 to 43%, or 40% weight of polymer per weight of the oral dosage form. In some embodiments, the polymer is a precipitation inhibitor, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF). In some embodiments, the precipitation inhibitor is a HPMCAS. In some embodiments, the precipitation inhibitor is HPMCAS-HF.

dry weight basis, a pharmaceutically acceptable disintegrant (*e.g.*, starch, *e.g.*, modified starch, *e.g*, sodium starch glycolate) in an amount from about 0 to 5% by weight on a dry weight basis, and a pharmaceutically acceptable lubricant (*e.g.*, magnesium stearate) in an amount from about 0.1 to 2% by weight on a dry weight basis. In one aspect, there is provided an oral dosage form comprising defactinib or a pharmaceutically acceptable salt thereof, wherein the oral dosage form comprises 5 to 50%, 5 to 30%, 10 to 30%, 10 to 20%, 12 to 15% or 13% weight of defactinib, or a pharmaceutically acceptable salt thereof, per weight of the oral dosage form. In some embodiments, the present disclosure comprises an oral dosage form comprising: VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride) in an amount from about 10 to 15% by weight on a dry weight basis, a pharmaceutically acceptable excipient (*e.g.*, a binder, *e.g.*, polymer, *e.g.*, a precipitation inhibitor, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF), in an amount from about 35 to 55% by weight on a dry weight basis, a pharmaceutically acceptable filler (*e.g.*, microcrystalline cellulose, *e.g.*, microcrystalline cellulose PH 102, *e.g.*, Avicel PH102) in an amount from about 15 to 25% by weight on a dry weight basis, a second pharmaceutically acceptable filler (*e.g.*, lactose, *e.g.*, lactose monohydrate, *e.g.*, FastFlo 316) in an amount from about 15 to 25% by weight on a dry weight basis, a pharmaceutically acceptable disintegrant (*e.g.*, starch, *e.g.*, modified starch, *e.g.*, sodium starch glycolate) in an amount from about 2.5 to 3.5% by weight on a dry weight basis, and a pharmaceutically acceptable lubricant (*e.g.*, magnesium stearate) in an amount from about 0.2 to 1.5% by weight on a dry weight basis. In some embodiments, the oral dosage form is a compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet.

In some embodiments, the excipient is one or more binders (*e.g.*, polyvinylpyrrolidone (*e.g.*, polyvinylpyrrolidone vinyl acetate copolymer (PVP/VA), Copovidone), other copolymers (*e.g.*, comprising polyethylene glycol, polyvinylcaprolactam, and polyvinylactate (*e.g.*, Soluplus))). In some embodiments, the binder is a polymer, *e.g.*, a precipitation inhibitor. In some embodiments, the binder comprises two binders (*e.g.*, polyvinylpyrrolidone (*e.g.*, polyvinylpyrrolidone vinyl acetate copolymer (PVP/VA), Copovidone), other

In an embodiment, an oral dosage form described herein has a greater C_{max} value than a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF), in an admixture. In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.1 times (*e.g.*, at least 1.25 times, at least 1.5 times, at least 2 times, at least 3 times, at least 5 times) greater than a reference dosage form of the same dosage amount (*e.g.*, a dosage form having 100 mg of VS-6063 relative to a reference dosage form also having 100 mg of VS-6063). In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.6 times greater, at least 1.7 times greater, at least 1.8 times greater, at least 1.9 times greater, at least 2 times greater, at least 3 times greater, or at least 4 times greater than a reference dosage form of the same dosage amount.

In an embodiment, an oral dosage form described herein has a reduced food effect relative to a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture. In an embodiment, the difference between the T_{max} value of the fed and fasted states for subjects administered an oral dosage form described herein is less that the difference between the T_{max} value of the fed and fasted states for subjects administered a reference oral dosage form of the same dosage amount, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture.

In an embodiment, an oral dosage form described herein has consistent exposure when administered to a subject. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 50% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 40%, 30%, 20%, or 10% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount.

The present disclosure also relates to an oral dosage form comprising: VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride) in an amount from about 10 to 15% by weight on a dry weight basis, a pharmaceutically acceptable excipient (*e.g.*, a binder (*e.g.*, polyvinyl pyrrolidone (*e.g.*, polyvinyl pyrrolidone vinyl acetate copolymer

in treating a subject having been identified with a cancer disorder (*e.g.*, mesothelioma (*e.g.*, malignant pleural mesothelioma, *e.g.*, surgical resectable malignant pleural mesothelioma), breast cancer (*e.g.*, triple negative breast cancer), ovarian cancer (*e.g.*, advanced ovarian cancer), lung cancer (*e.g.*, non-small cell lung cancer (NSCLC), *e.g.*, KRAS mutant NSCLC)), or a non-hematolotic malignancy. In one aspect, there is provided the use of the oral dosage form as disclosed herein comprising defactinib in the manufacture of a medicament for treating a cancer disorder in a subject in need thereof.

In the present disclosure, there is provided the use of an oral dosage form comprising 10 to 500 mg of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), in the manufacture of a medicament for treating a disorder in a patient in need thereof. In one embodiment, the present disclosure comprises a method of treating a disorder in a patient in need thereof, the method comprising administering an oral dosage form comprising 10 to 500 mg of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), to thereby treat the disorder. In some embodiments, the disorder is a cancer disorder (*e.g.*, mesothelioma (*e.g.*, surgical resectable malignant pleural mesothelioma), breast cancer (*e.g.*, triple negative breast cancer, ovarian cancer (*e.g.*, advanced ovarian cancer)), lung cancer (*e.g.*, non-small cell lung cancer (NSCLC), *e.g.*, KRAS mutant NSCLC)), or a non-hematolotic malignancy.

In some embodiments, the administration is performed in combination with administration of an additional agent (*e.g.*, an anti-cancer or anti-tumor agent, *e.g.*, taxane, *e.g.*, paclitaxel).

In one embodiment, the present disclosure comprises a method for preparing a direct compressed tablet in unit dosage form, which comprises: (a) admixing (*e.g.*, blending) as a % by weight on a dry weight basis: (i) 5 to 50% by weight on a dry weight basis of VS-6063; (ii) a pharmaceutically acceptable excipient (*e.g.*, a binder, *e.g.*, polymer, *e.g.*, a precipitation inhibitor, *e.g.*, HPMC, *e.g.*, HPMC-AS, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF); and (iii) at least one pharmaceutically acceptable excipient selected from a pharmaceutically acceptable filler, a pharmaceutically acceptable disintegrant, and a pharmaceutically acceptable lubricant; to form a VS-6063 formulation in the form of a tabletting powder, capable of being directly compressed into tablets; and (b) compressing the formulation prepared during step (a) to form the compressed VS-6063 tablet in unit dosage form. In one aspect, there is provided a method for preparing a direct compressed tablet in unit dosage form, which comprises: (a) blending as a % by weight on a dry weight basis: (i) 5 to 50% by weight on a dry weight basis of defactinib or a pharmaceutically acceptable salt thereof; (ii) a hydroxypropyl methylcellulose (HPMC) polymer

; and (iii) at least one excipient selected from a filler, a disintegrant, and a lubricant; to form a defactinib formulation in the form of a tableting powder, capable of being directly compressed into a tablets; and (b) compressing the formulation prepared during step (a) to form the compressed defactinib tablet in unit dosage form. In some embodiments, a pharmaceutically acceptable filler is present at 30 to 60% by weight on a dry weight basis. In some embodiments, a pharmaceutically acceptable distintegrant is present at 2.5 to 5% by weight on a dry weight basis. In some embodiments, a pharmaceutically acceptable lubricant is present at 0.5 to 2% by weight on a dry weight basis.

In one embodiment, the present disclosure comprises a method of treating a subject having mesothelioma, *e.g.,* malignant pleural mesothelioma, *e.g.,* surgical resectable malignant pleural mesothelioma (*e.g.,* non-metastatic, unresectable), comprising: providing an effective amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); to said subject, thereby treating said subject. In some embodiments, the method comprises providing an effective

Claims

1. A pharmaceutical composition comprising defactinib or a pharmaceutically acceptable salt thereof and a hydroxypropyl methylcellulose (HPMC) polymer.

2. The pharmaceutical composition of claim 1, wherein the HPMC polymer is a hydroxypropylmethylcellulose acetate succinate (HPMCAS).

3. The pharmaceutical composition of claim 2, wherein HPMCAS is HF-grade HPMCAS (HPMCAS-HF).

4. The pharmaceutical composition of claim 1, wherein the ratio by weight of defactinib or a pharmaceutically acceptable salt to the hydroxypropyl methylcellulose (HPMC) polymer is 1 to 1, 1 to 2, 1 to 3, or 1 to 4.

5. The pharmaceutical composition of claim 1, wherein defactinib or a pharmaceutically acceptable salt thereof is present in the composition in an amount that is 25, 30, 31, 32, 32.5, 33, 34, 35, 40, 45, 50% or more than 50% w/w relative to an amount of hydroxypropyl methylcellulose (HPMC) polymer provided.

6. The pharmaceutical composition of claim 1, wherein the composition is configured in an oral dosage form.

7. The oral dosage form of claim 6, comprising defactinib or a pharmaceutically acceptable salt thereof, wherein the oral dosage form comprises 5 to 50%, 5 to 30%, 10 to 30%, 10 to 20%, 12 to 15% or 13% weight of defactinib, or a pharmaceutically acceptable salt thereof, per weight of the oral dosage form.

8. The oral dosage form of claim 6, wherein the defactinib, or a pharmaceutically acceptable salt thereof is present at 13% weight of defactinib, or a pharmaceutically acceptable salt thereof, per weight of the oral dosage form.

9. The oral dosage form of claim 6, wherein the oral dosage form is a tablet.

10. The oral dosage form of claim 9, wherein the tablet is provided by direct compression of a physical blend or mixture.

11. The oral dosage form of claim 9, wherein the physical blend or mixture is provided by a dry granulation process.

12. The oral dosage form of claim 7, wherein the hydroxypropyl methylcellulose (HPMC) polymer is present at 25 to 55%, 35 to 45%, 38 to 43% or 40% weight of hydroxypropyl methylcellulose (HPMC) polymer per weight of the oral dosage form.

13. The oral dosage form of claim 12, wherein the hydroxypropyl methylcellulose (HPMC) polymer is HPMCAS or HPMCAS-HF.

14. The oral dosage form of claim 13, further comprising one or more fillers.

15. The oral dosage form of claim 14, wherein the filler is present at 5 to 80%, 10 to 70%, 20 to 60%, 30 to 60%, 30 to 50% or 42% weight of filler per weight of the oral dosage form.

16. The oral dosage form of claim 14, wherein the filler is a mixture of two fillers.

17. The oral dosage form of claim 16, wherein one filler is microcrystalline cellulose PH 102.

18. The oral dosage form of claim 16, wherein one filler is lactose monohydrate.

19. The oral dosage form of claim 17 or 18, wherein each filler is present at 10 to 30%, 15 to 25% or 20% weight of filler per weight of the oral dosage form.

20. The oral dosage form of claim 16, wherein the fillers are present at a 1:1 w/w ratio to one another.

21. The oral dosage form of claim 13, further comprising a disintegrant.

22. The oral dosage form of claim 21, wherein the disintegrant is sodium starch glycolate.

23. The oral dosage form of claim 22, wherein the disintegrant is present at 0 to 5%, 1 to 5%, 2.5 to 5% or 3% weight of disintegrant per weight of the oral dosage form.

24. The oral dosage form of claim 13, further comprising a lubricant.

25. The oral dosage form of claim 24, wherein the lubricant is magnesium stearate.

26. The oral dosage form of claim 24, wherein the lubricant is present at 0.1 to 2%, 0.2 to 1.5%, 1% or 0.5% weight of lubricant per weight of the oral dosage form.

27. The oral dosage form of claim 7 comprising:

defactinib or a pharmaceutically acceptable salt thereof in an amount from 5 to 50% by weight on a dry weight basis,

a first pharmaceutically acceptable filler in an amount from 10 to 30% by weight on a dry weight basis,

a second pharmaceutically acceptable filler in an amount from 10 to 30% by weight on a dry weight basis,

a hydroxypropyl methylcellulose (HPMC) polymer in an amount from 25 to 55% by weight on a dry weight basis,

a pharmaceutically acceptable disintegrant in an amount from 0 to 5% by weight on a dry weight basis; and

a pharmaceutically acceptable lubricant (*e.g.*, magnesium stearate) in an amount from 0.1 to 2% by weight on a dry weight basis.

28. The oral dosage form of claim 27, comprising:

defactinib or a pharmaceutically acceptable salt thereof in an amount from 10 to 15% by weight on a dry weight basis,

a first pharmaceutically acceptable filler in an amount from 15 to 25% by weight on a dry weight basis,

a second pharmaceutically acceptable filler in an amount from 15 to 25% by weight on a dry weight basis,

a hydroxypropyl methylcellulose (HPMC) polymer in an amount from 35 to 55% by weight on a dry weight basis,

a pharmaceutically acceptable disintegrant in an amount from 2.5 to 3.5% by weight on a dry weight basis, and

a pharmaceutically acceptable lubricant in an amount from 0.2 to 1.5% by weight on a dry weight basis.

29. The oral dosage form of claims 27 or 28, wherein the hydroxypropyl methylcellulose (HPMC) polymer is HPMCAS.

30. The oral dosage form of claim 29, wherein the hydroxypropyl methylcellulose (HPMC) polymer is HPMCAS-HF.

31. The oral dosage form of claim 30, wherein:

the first pharmaceutically acceptable filler is microcrystalline cellulose PH 102;

the second pharmaceutically acceptable filler is lactose monohydrate;

the disintegrant is sodium starch glycolate, and;

the lubricant is magnesium stearate.

32. The oral dosage form of claim 31, wherein the oral dosage form is a compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet.

33. Use of the oral dosage form of any one of claims 6-32 comprising defactinib in the manufacture of a medicament for treating a cancer disorder in a subject in need thereof.

34. The use of claim 33, wherein the oral dosage form comprises 10 to 500 mg of defactinib or a pharmaceutically acceptable salt thereof.

35. The use of claim 34, wherein the cancer disorder is selected from mesothelioma, breast cancer, ovarian cancer, lung cancer and other non-hematologic malignancies.

36. The use of claim 34, characterized in that the oral dosage form is to be administered in combination with an additional agent.

37. A method for preparing a direct compressed tablet in unit dosage form, which comprises:

(a) blending as a % by weight on a dry weight basis:

(i) 5 to 50% by weight on a dry weight basis of defactinib or a pharmaceutically acceptable salt thereof;

(ii) a hydroxypropyl methylcellulose (HPMC) polymer; and

(iii) at least one excipient selected from a filler, a disintegrant, and a lubricant;

to form a defactinib formulation in the form of a tableting powder, capable of being directly compressed into a tablets; and

(b) compressing the formulation prepared during step (a) to form the compressed defactinib tablet in unit dosage form.

38. The method of claim 37, wherein a filler is present at 30 to 60% by weight on a dry weight basis.

39. The method of claim 37, wherein a distintegrant is present at 2.5 to 5% by weight on a dry weight basis.

40. The method of claim 37, wherein a lubricant is present at 0.5 to 2% by weight on a dry weight basis.