[0005] Problematically, some combinations of drugs, fillers and disintegration agents (to impart rapid release properties) have poor compression characteristics thereby presenting mechanical strength and dissolution issues for tablets prepared by dry granulation and tablet compression methods.

[0006] A need therefore exists for improved tablet compositions containing a drug, a filler and a disintegration agent and related preparation methods that allow for tablets having both (1) sufficient hardness to resist breakage, chipping and abrasion and (2) adequate dissolution and disintegration characteristics required for immediate-release tablets.

SUMMARY

[0007] Disclosed is a process for preparing a pharmaceutical dosage unit tablet core. The process comprises blending a particulate pharmaceutical active drug, an intragranular filler, an intragranular disintegrant and an intragranular lubricant to form a pre-blend, wherein the particulate pharmaceutical active drug has a particle size D[v, 0.5] of from about 25 μm to about 65 μm, from about 25 μm to about 50 μm, or from about 30 μm to about 40 μm. The pre-blend is compacted by application of a roller compaction force of from about 1 kN/cm to about 8 kN/cm, from about 2 kN/cm to about 5 kN/cm, or from about 2 kN/cm to about 4 kN/cm. The compacted pre-blend is milled and screened to form granules. In some particular embodiments of the disclosure, the pre-blend is compacted between at least two rotating rolls having a gap width of from about 2 mm to about 5 mm, from about 2 mm to about 4 mm, from about 3 mm to about 5 mm or from about 4 mm to about 5 mm to form a ribbon, and the ribbon is milled and screened to form granules. The granules are tableted by application of a tableting compression force of from about 5 kN to about 20 kN, from about 14 kN to about 19 kN, from about 14 kN to about 18 kN, or from about 8 kN to about 13 kN to form the pharmaceutical dosage unit tablet core.

[0007a] In a first aspect, there is provided a process for preparing a pharmaceutical dosage unit tablet core, the process comprising: (1) blending a particulate pharmaceutical drug active, an intragranular filler, an intragranular disintegrant and an intragranular lubricant to form a pre-blend, wherein the particulate pharmaceutical drug active has a particle size D[v, 0.5] of from about 25 μm to about 65 μm, from about 25 μm to about 50 μm, or from about 30 μm to about 40 μm; (2) compacting the pre-blend by application of a compaction force of from about 1 kN/cm to about 8 kN/cm, from about 2 kN/cm to about 5 kN/cm, or from about 2 kN/cm to about 4 kN/cm; (3) milling and screening the compacted pre-blend to form granules; and (4) tableting the granules by application of a tableting compression force of from about 5 kN to about 20 kN, from about 14 kN to about 19 kN, from about 14 kN to about 18 kN, or from about 8 kN to about 13 kN to form the pharmaceutical dosage unit tablet core.

[0008] Disclosed is a pharmaceutical dosage unit tablet core. In a second aspect, there is provided a pharmaceutical dosage unit tablet core, the tablet core comprising: (1) about 5 wt.% or

more of a particulate pharmaceutical active drug; (2) a lubricant at a content based on the pharmaceutical dosage unit tablet core weight of from about 0.5 wt.% to about 5 wt.%, from about 0.5 wt.% to about 3 wt.%, from about 1 wt.% to about 3 wt.%, from about 1 wt.% to about 2.5 wt.%, or from about 1.5 wt.% to about 2 wt.%; (3) a disintegrant at a content based on the pharmaceutical dosage unit tablet core weight of from about 2 wt.% to about 7 wt.%, from about 2 wt.% to about 6 wt.%, from about 2 wt.% to about 5 wt.%, from about 3 wt.% to about 6 wt.%, or from about 3 wt.% to about 5 wt.%; (4) a filler at a content based on the pharmaceutical dosage unit tablet core weight of from about 60 wt.% to about 78 wt.%, from about 65 wt.% to about 78 wt.%, from about 65 wt.% to about 77 wt.%, from about 70 wt.% to about 77 wt.%, or from about 71 wt.% to about 75 wt.%; and (5) optionally, up to 10 wt.% of a binder.

[0009] Disclosed is a pharmaceutical dosage unit tablet core. In a third aspect, there is provided a pharmaceutical dosage unit tablet core, the tablet core comprising: (1) 18.5 wt.% cobimetinib hemifumarate polymorph Form A; (2) 45.6 wt.% microcrystalline cellulose; (3) 30.4 wt.% lactose monohydrate; (4) 4 wt.% croscarmellose sodium; and (5) 1.5 wt.% magnesium stearate.

[0010] Disclosed is a coated pharmaceutical dosage unit tablet core. In a fourth aspect, there is provided a coated pharmaceutical dosage unit tablet core, the coated table comprising: (1) 17.79 wt.% cobimetinib hemifumarate polymorph Form A; (2) 43.85 wt.% microcrystalline cellulose; (3) 29.23 wt.% lactose monohydrate; (4) 3.84 wt.% croscarmellose sodium; (5) 1.45 wt.% magnesium stearate; and (6) 3.85 wt.% film coating.

[0011] Disclosed is a process for preparing a coated pharmaceutical dosage unit tablet. In a fifth aspect, there is provided a process for preparing a coated pharmaceutical dosage unit tablet, the process comprising the following steps: (1) combining a particulate filler component, a first particulate disintegrant component and a particulate active drug component in a blender and admixing said components to form a primary pre-blend; (2) combining a particulate first lubricant component with the primary pre-blend in a blender and admixing said first lubricant component and primary pre-blend to form a finished pre-blend; (3) dry granulating the finished pre-blend to form granules; (4) combining the granules and a second particulate disintegrant component in a blender and admixing said granules

and disintegrant component to form a primary final blend; (5) combining a second particulate lubricant component and the primary final blend in a blender and admixing said second lubricant component and primary final blend to form a finished final blend; (6) tableting the final blend to form tablet cores; and (7) coating the tablet cores. In some embodiments of the disclosure, a film-coat solid mixture is suspended in water to form a coating mixture slurry and the tablet cores are coated with the coating mixture slurry to form the coated pharmaceutical dosage unit tablet.

[0012] Disclosed is a pharmaceutical product. The product comprises (1) a first tablet comprising cobimetinib and (2) a second tablet comprising propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4- difluoro-phenyl}-amide (vemurafenib), or a pharmaceutically acceptable salt thereof. The first tablet and the second tablet comprise a combined preparation for concurrent or sequential use in the treatment of BRAFV600 mutation positive unresectable or metastatic melanoma. One or more first tablets are administered to provide a total dose of 60 mg cobimetinib, on days 1-21 of a 28 day cycle, and one or more second tablet are administered to provide a total dose of 960 mg vemurafenib, twice daily each day of the 28 day cycle.

[0012a] In a sixth aspect, there is provided a pharmaceutical product comprising: (1) a first tablet of the second and the fourth aspects; and (2) a second tablet comprising propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4- difluoro-phenyl}-amide (vemurafenib), or a pharmaceutically acceptable salt thereof, wherein the first tablet and the second tablet comprise a combined preparation for concurrent or sequential use in the treatment of $BRAF^{V600}$ mutation positive unresectable or metastatic melanoma, wherein one or more first tablets are administered to provide a total dose of 60 mg cobimetinib, on days 1-21 of a 28 day cycle, and wherein one or more second tablets are administered to provide a total dose of 960 mg vemurafenib, twice daily each day of the 28 day cycle.

[0013] In yet other embodiments of the disclosure, the pharmaceutical product recited above is used in the manufacture of a medicament for treatment of $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma.

[0013a] In a seventh aspect, there is provided the pharmaceutical product as described herein, for use in the manufacture of a medicament for treatment of $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma.

[0014] In other embodiments of the disclosure, a kit is provided. The kit comprises (1) a first tablet comprising cobimetinib and (2) a second tablet comprising vemurafenib, or a pharmaceutically acceptable salt thereof.

[0014a] In an eighth aspect, there is provided a kit comprising: (1) a first tablet as described in the second or the fourth aspect; and (2) a second tablet comprising propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4- difluoro-phenyl}-amide (vemurafenib), or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 depicts a first tableting process of the present disclosure.

[0016] Figure 2 depicts a second tableting process of the present disclosure.

WHAT IS CLAIMED IS:

1. A process for preparing a pharmaceutical dosage unit tablet core, the process comprising:

(1) blending a particulate pharmaceutical drug active, an intragranular filler, an intragranular disintegrant and an intragranular lubricant to form a pre-blend, wherein the particulate pharmaceutical drug active has a particle size D[v, 0.5] of from about 25 μm to about 65 μm, from about 25 μm to about 50 μm, or from about 30 μm to about 40 μm;

(2) compacting the pre-blend by application of a compaction force of from about 1 kN/cm to about 8 kN/cm, from about 2 kN/cm to about 5 kN/cm, or from about 2 kN/cm to about 4 kN/cm;

(3) milling and screening the compacted pre-blend to form granules; and

(4) tableting the granules by application of a tableting compression force of from about 5 kN to about 20 kN, from about 14 kN to about 19 kN, from about 14 kN to about 18 kN, or from about 8 kN to about 13 kN to form the pharmaceutical dosage unit tablet core.

2. The process of claim 1 wherein the pre-blend is compacted between at least two rotating rolls having a gap width of from about 2 mm to about 5 mm, from about 2 mm to about 4 mm, from about 3 mm to about 5 mm or from about 4 mm to about 5 mm to form a ribbon, wherein the ribbon is milled and screened to form granules.

3. The process of claim 1 or claim 2 wherein the pharmaceutical drug active has a particle size D[v, 0.9] of from about 45 μm to about 500 μm, from about 45 μm to about 400 μm, from about 45 μm to about 300 μm, from about 45 μm to about 200 μm, from about 45 μm to about 100 μm, from about 50 μm to about 60 μm, from about 65 μm to about 100 μm, from about 45 μm to about 80 μm, or from about 75 μm to about 100 μm.

4. The process of any preceding claim further comprising applying a film coating on the surface of the pharmaceutical dosage unit tablet core.

5. The process of any one of claims 2 to 4 wherein the ribbon has an at-gap density selected from:

(1) from about 0.85 g/mL to about 0.95 g/mL and from about 0.9 g/mL to about 0.95 g/mL;

(2) from about 0.95 g/mL to from about 1.1 g/mL, from about 0.95 g/mL to about 1.05 g/mL, from about 1 g/mL to about 1.10 g/mL and from about 1 g/mL to about 1.05 g/mL; and

(3) from about 1.1 g/mL to about 1.3 g/mL, from about 1.1 g/mL to about 1.25 g/mL, from about 1.1 g/mL to about 1.2 g/mL, from about 1.1 g/mL to about 1.15 g/mL, from about 1.15 g/mL to about 1.3 g/mL, from about 1.15 g/mL to about 1.25 g/mL, and from about 1.15 g/mL to about 1.2 g/mL.

6. The process of any preceding claim further comprising, prior to tableting, blending the granules with extragranular disintegrant and extragranular lubricant to form a final blend wherein the final blend is tableted.

7. The process of any preceding claim wherein the total lubricant content based on pharmaceutical dosage unit tablet core weight is from about 0.5 wt.% to about 5 wt.%, from about 0.5 wt.% to about 3 wt.%, from about 1 wt.% to about 3 wt.%, from about 1 wt.% to about 2.5 wt.%, or from about 1.5 wt.% to about 2 wt.%.

8. The process of claim 6 or claim 7 wherein

(1) the intragranular lubricant content based on tablet core weight is from about 0.1 wt.% to about 1 wt.%, from about 0.2 wt.% to about 0.75 wt.% or from about 0.25 wt.% to about 5 wt.%; and

(2) the extragranular lubricant content based on tablet core weight is from about 0.5 wt.% to about 2.5 wt.%, from about 0.75 wt.% to about 2.25 wt.%, from about 0.75 wt.% to about 2 wt.%, from about 1 wt.% to about 1.75 wt.%, or from about 1.25 wt.% to about 1.5 wt.%.

9. The process of any preceding claim wherein the total disintegrant content based on pharmaceutical dosage unit tablet core weight is from about 2 wt.% to about 7 wt.%, from about 2 wt.% to about 6 wt.%, from about 2 wt.% to about 5 wt.%, from about 3 wt.% to about 6 wt.%, or from about 3 wt.% to about 5 wt.%.

10. The process of any one of claims 6 to 9 wherein the pharmaceutical dosage unit tablet core comprises intragranular disintegrant and extragranular disintegrant, wherein

(1) the intragranular disintegrant content based on tablet core weight is from about 0.1 wt.% to about 3 wt.%, from about 0.25 wt.% to about 2.5 wt.%, from about 0.25 wt.% to about 2 wt.%, from about 0.25 wt.% to about 1.5 wt.%, from about 0.25 wt.% to about 1 wt.%, from about 0.5 wt.% to about 3 wt.%, from about 0.5 wt.% to about 2 wt.%, from about 0.5 wt.% to about 1.5 wt.%, from about 1 wt.% to about 3 wt.%, or from about 1.5 wt.% to about 2.5 wt.%; and

(2) the extragranular disintegrant content based on tablet core weight is from about 0.5 wt.% to about 3 wt.%, from about 1 wt.% to about 3 wt.%, from about 1.25 wt.% to about 3 wt.%, from about 1.25 wt.% to about 2.5 wt.%, from about 1.25 wt.% to about 2 wt.%, from about 1.25 wt.% to about 1.5 wt.%, from about 1.5 wt.% to about 3 wt.%, or from about 1.5 wt.% to about 2.5 wt.%.

11. The process of claim 10 wherein the weight ratio of the intragranular disintegrant to the extragranular disintegrant is about 1:5, about 1:3, about 1:1, or about 2:1.

12. The process of any preceding claim wherein the total filler content based on pharmaceutical dosage unit tablet core weight is from about 60 wt.% to about 78 wt.%, from about 65 wt.% to about 78 wt.%, from about 65 wt.% to about 77 wt.%, from about 70 wt.% to about 77 wt.%, or from about 71 wt.% to about 75 wt.%.

13. The process of any one of claims 6 to 12 wherein the bulk density of the final blend is from about 0.4 g/mL to about 0.75 g/mL, from about 0.45 g/mL to about 0.7 g/mL, or from about 0.5 g/mL to about 0.65 g/mL.

14. The process of any preceding claim wherein the screen size is from about 0.5 mm to about 2.0 mm, from about 0.5 mm to about 1.5 mm, from about 0.5 mm to about 1.25 mm, from about 0.75 mm to about 2.0 mm, from about 0.75 mm to about 1.5 mm, from about 0.75 mm to about 1.25 mm, or about 1 mm.

15. The process of any one of claims 2 to 14 wherein the particulate pharmaceutical active drug has a particle size D[v, 0.5] of from about 27 μm to about 37 μm, the roller compaction gap force is about 2 kN/cm, and the gap width is about 5 mm.

16. The process of any one of claims 2 to 14 wherein the particulate pharmaceutical active drug has a particle size D[v, 0.5] of from about 38 μm to about 65 μm, the roller compaction gap force is from about 2 kN/cm to about 4 kN/cm, and the gap width is from about 4 mm to about 5 mm.

17. The process of any preceding claim wherein the particulate pharmaceutical active drug is cobimetinib hemifumarate polymorph Form A.

18. The process of any preceding claim wherein the filler comprises (1) lactose or (2) lactose and microcrystalline cellulose wherein the weight ratio of lactose to microcrystalline cellulose is from about 1:1.5 to about 4:1, from about 1.25 to about 4:1, from about 1:1 to about 4:1 from about 1:1 to about 3:1, from about 1.5:1 to about 3:1, or from about 2:1 to about 2.5:1.

19. The process of any preceding claim wherein the disintegrant comprises sodium starch glycolate, croscarmellose sodium, or a combination thereof.

20. The process of any preceding claim wherein the lubricant comprises magnesium stearate, sodium stearyl fumarate, or a combination thereof.

21. The process of any preceding claim wherein the pre-blend further comprises a binder at a total binder content based on pharmaceutical dosage unit tablet core weight of from about 1 wt.% to about 10 wt.%, from about 1 wt.% to about 7 wt.%, from about 1 wt.% to about 6 wt.%, or from about 1 wt.% to about 5 wt.%.

22. The process of claim 21 wherein the binder comprises povidone, copovidone, pregelatinized starch, hydroxypropyl methylcellulose, or a combination thereof.

23. The process of any preceding claim wherein the particulate pharmaceutical active drug content based on the weight of the tablet core is at least 5 wt.%, from about 15 wt.% to about 25 wt.%, or about 20 wt.%.

24. The process of any preceding claim wherein the pharmaceutical dosage unit tablet core comprises: (1) from 17.6 wt.% to 19.4 wt.% cobimetinib hemifumarate polymorph Form A; (2) from 43.3 wt.% to 47.9 wt.% microcrystalline cellulose; (3) from 28.9 wt.% to 31.9 wt.% lactose monohydrate; (4) from 3.8 wt.% to 4.2 wt.% croscarmellose sodium; and (5) from 1.4 wt.% to 1.6 wt.% magnesium stearate.

25. A pharmaceutical dosage unit tablet core, the tablet core comprising:

(1) about 5 wt.% or more of a particulate pharmaceutical active drug;

(2) a lubricant at a content based on the pharmaceutical dosage unit tablet core weight of from about 0.5 wt.% to about 5 wt.%, from about 0.5

wt.% to about 3 wt.%, from about 1 wt.% to about 3 wt.%, from about 1 wt.% to about 2.5 wt.%, or from about 1.5 wt.% to about 2 wt.%;

(3) a disintegrant at a content based on the pharmaceutical dosage unit tablet core weight of from about 2 wt.% to about 7 wt.%, from about 2 wt.% to about 6 wt.%, from about 2 wt.% to about 5 wt.%, from about 3 wt.% to about 6 wt.%, or from about 3 wt.% to about 5 wt.%;

(4) a filler at a content based on the pharmaceutical dosage unit tablet core weight of from about 60 wt.% to about 78 wt.%, from about 65 wt.% to about 78 wt.%, from about 65 wt.% to about 77 wt.%, from about 70 wt.% to about 77 wt.%, or from about 71 wt.% to about 75 wt.%; and

(5) optionally, up to 10 wt.% of a binder.

26. The pharmaceutical dosage unit tablet core of claim 25 wherein the particulate pharmaceutical active drug is cobimetinib hemifumarate polymorph Form A.

27. The pharmaceutical dosage unit tablet core of claim 25 or claim 26 wherein the particulate pharmaceutical active drug content based on the weight of the tablet core is from about 15 wt.% to about 25 wt.%, or about 20 wt.%.

28. The pharmaceutical dosage unit tablet core of any preceding claim wherein the particulate pharmaceutical active drug has a particle size D [v, 0.5] of from about 25 μm to about 65 μm, from about 25 μm to about 50 μm, or from about 30 μm to about 40 μm.

29. The pharmaceutical dosage unit tablet core of any preceding claim wherein the particulate pharmaceutical active drug has a particle size D [v, 0.9] of from about 45 μm to about 500 μm, from about 45 μm to about 400 μm, from about 45 μm to about 300 μm, from about 45 μm to about 200 μm, from about 44 μm to about 100 μm, from about 50 μm to about 60 μm, from about 65 μm to about 100 μm, from about 45 μm to about 80 μm, or from about 75 μm to about 100 μm.

30. The pharmaceutical dosage unit tablet core of any one of claims 25 to 29 wherein said tablet core comprises intragranular lubricant and extragranular lubricant, wherein

(1) the intragranular lubricant content based on said tablet core weight is from about 0.1 wt.% to about 1 wt.%, from about 0.2 wt.% to about 0.75 wt.%, or from about 0.25 wt.% to about 5 wt.%; and

(2) the extragranular lubricant content based on said tablet core weight is from about 0.5 wt.% to about 2.5 wt.%, from about 0.75 wt.% to about 2.25 wt.%, from about 0.75 wt.% to about 2 wt.%, from about 1 wt.% to about 1.75 wt.%, or from about 1.25 wt.% to about 1.5 wt.%.

31. The pharmaceutical dosage unit tablet core of any one of claims 25 to 30 wherein the lubricant comprises magnesium stearate, sodium stearyl fumarate, or a combination thereof.

32. The pharmaceutical dosage unit tablet core of any one of claims 25 to 31 wherein said tablet core comprises intragranular disintegrant and extragranular disintegrant, wherein

(1) the intragranular disintegrant content based on said tablet core weight is from about 0.1 wt.% to about 3 wt.%, from about 0.25 wt.% to about 2.5 wt.%, from about 0.25 wt.% to about 2 wt.%, from about 0.25 wt.% to about 1.5 wt.%, from about 0.25 wt.% to about 1 wt.%, from about 0.5 wt.% to about 3 wt.%, from about 0.5 wt.% to about 2 wt.%, from about 0.5 wt.% to about 1.5 wt.%, from about 1 wt.% to about 3 wt.%, or from about 1.5 wt.% to about 2.5 wt.%; and

(2) the extragranular disintegrant content based on said tablet core weight is from about 0.5 wt.% to about 3 wt.%, from about 1 wt.% to about 3 wt.%, from about 1.25 wt.% to about 3 wt.%, from about 1.25 wt.% to about 2.5 wt.%, from about 1.25 wt.% to about 2 wt.%, from about 1.25 wt.% to about 1.5 wt.%, from about 1.5 wt.% to about 3 wt.%, or from about 1.5 wt.% to about 2.5 wt.%.

33. The pharmaceutical dosage unit tablet core of claim 32 wherein the weight ratio of the intragranular disintegrant to the extragranular disintegrant is about 1:5, about 1:3, about 1:1, or about 2:1.

34. The pharmaceutical dosage unit tablet core of any one of claims 25 to 33 wherein the disintegrant comprises sodium starch glycolate, croscarmellose sodium, or a combination thereof.

35. The pharmaceutical dosage unit tablet core of any one of claims 25 to 34 wherein the filler comprises (1) lactose or (2) lactose and microcrystalline cellulose wherein the weight ratio of lactose to microcrystalline cellulose is from about 1:1.5 to about 4:1, from about 1.25 to about 4:1, from about 1:1 to about 4:1 from about 1:1 to about 3:1, from about 1.5:1 to about 3:1, or from about 2:1 to about 2.5:1.

36. The pharmaceutical dosage unit tablet core of any one of claims 25 to 35 wherein the particulate pharmaceutical active drug has a particle size D [v, 0.5] of from about 25 μm to about 40 μm.

37. The pharmaceutical dosage unit tablet core of any one of claims 25 to 35 wherein the particulate pharmaceutical active drug has a particle size D [v, 0.5] of from about 40 μm to about 65 μm.

38. The pharmaceutical dosage unit tablet core of any one of claims 25 to 37 wherein the tablet core further comprises a binder at a total binder content based on said tablet core weight of from about 1 wt.% to about 10 wt.%, from about 1 wt.% to about 7 wt.%, from about 1 wt.% to about 6 wt.%, or from about 1 wt.% to about 5 wt.%.

39. The pharmaceutical dosage unit tablet core of claim 38 wherein the binder comprises povidone, copovidone, pregelatinized starch, hydroxypropyl methylcellulose, or a combination thereof.

40. The pharmaceutical dosage unit tablet core of any one of claims 25 to 39 wherein said tablet core comprises:

(1) from about 17.6 wt.% to about 19.4 wt.% cobimetinib hemifumarate polymorph Form A;

(2) from about 43.3 wt.% to about 47.9 wt.% microcrystalline cellulose;

(3) from about 28.9 wt.% to about 31.9 wt.% lactose monohydrate;

(4) from about 3.8 wt.% to about 4.2 wt.% croscarmellose sodium; and

(5) from about 1.4 wt.% to about 1.6 wt.% magnesium stearate.

41. The pharmaceutical dosage unit tablet core of any one of claims 25 to 40 further comprising a film-coating on the surface of said tablet core, wherein the coated pharmaceutical dosage unit tablet core is characterized by:

(1) a dissolution profile such that 80% of the tablet dissolves in 20 minutes;

(2) a minimum hardness of 45 N;

(3) a disintegration time of no more than 300; and

(4) an abrasion of less than 1.0%.

42. The pharmaceutical dosage unit tablet core of claim 41 wherein the coated pharmaceutical dosage unit tablet core comprises from about 2 wt.% to about 6 wt.%, or from about 3 wt.% to about 5 wt.% of the film-coating based on the weight of said tablet core, and wherein the film-coating comprises:

(1) from about 38 wt.% to about 42 wt.% polyvinyl alcohol;

(2) from about 23.8 wt.% to about 26.3 wt.% titanium dioxide;

(3) from about 19.2 wt.% to about 21.2 wt.% macrogol/PEG3350; and

(4) from about 14.1 wt.% to about 15.5 wt.% talc.

43. A pharmaceutical dosage unit tablet core, the tablet core comprising:

(1) 18.5 wt.% cobimetinib hemifumarate polymorph Form A;

(2) 45.6 wt.% microcrystalline cellulose;

(3) 30.4 wt.% lactose monohydrate;

(4) 4 wt.% croscarmellose sodium; and

(5) 1.5 wt.% magnesium stearate.

44. The pharmaceutical dosage unit tablet core of claim 43 comprising:

(1) 2 wt.% intragranular croscarmellose sodium and 2 wt.% extragranular croscarmellose sodium; and

(2) 0.25 wt.% intragranular magnesium stearate and 1.25 wt.% extragranular magnesium stearate.

45. The pharmaceutical dosage unit tablet core of claim 43 or claim 44 wherein the microcrystalline cellulose is Avicel®PH101 or equivalent.

46. A coated pharmaceutical dosage unit tablet core, the coated tablet comprising:

(1) 17.79 wt.% cobimetinib hemifumarate polymorph Form A;

(2) 43.85 wt.% microcrystalline cellulose;

(3) 29.23 wt.% lactose monohydrate;

(4) 3.84 wt.% croscarmellose sodium;

(5) 1.45 wt.% magnesium stearate; and

(6) 3.85 wt.% film coating.

47. The coated pharmaceutical dosage unit tablet of claim 46 comprising:

(1) 1.92 wt.% intragranular croscarmellose sodium and 1.92 wt.% extragranular croscarmellose sodium; and

(2) 0.24 wt.% intragranular magnesium stearate and 1.21 wt.% extragranular magnesium stearate.

(1) the particulate filler component is selected from lactose, microcrystalline cellulose, and combinations thereof;

(2) the first particulate disintegrant and second particulate disintegrant are each selected from sodium starch glycolate, croscarmellose sodium, and combinations thereof;

(3) the active drug component is cobimetinib hemifumarate polymorph Form A; and

(4) the first lubricant component and the second lubricant component are each selected from magnesium stearate, sodium stearyl fumarate, and combinations thereof.

52. A pharmaceutical product comprising:

(1) a first tablet of any one of claims 41, 42, and 46 to 48; and

(2) a second tablet comprising propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4- difluoro-phenyl}-amide (vemurafenib), or a pharmaceutically acceptable salt thereof,

wherein the first tablet and the second tablet comprise a combined preparation for concurrent or sequential use in the treatment of $BRAF^{V600}$ mutation positive unresectable or metastatic melanoma,

wherein one or more first tablets are administered to provide a total dose of 60 mg cobimetinib, on days 1-21 of a 28 day cycle, and

wherein one or more second tablets are administered to provide a total dose of 960 mg vemurafenib, twice daily each day of the 28 day cycle.

53. The pharmaceutical product of claim 52, wherein the first tablet is administered sequentially with the second tablet.

54. The pharmaceutical product of claim 52, wherein the first tablet is administered concurrently with the second tablet.